27 Pulmonary diseases in pregnancy

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INTRODUCTION

Pregnancy induces significant changes in normal pulmonary physiology while also causing increased susceptibility to the effects of certain respiratory diseases. In the following chapter, the changes in pulmonary function and respiratory physiology that occur during normal pregnancy will be described, followed by a review of specific pulmonary disorders during pregnancy. Obstructive and restrictive lung diseases, pulmonary vascular disease, pulmonary infections, respiratory failure, and other topics will be reviewed in the context of pregnancy. In addition, the challenge of distinguishing between the normal physiologic dyspnea of pregnancy and an underlying pulmonary or cardiac disease will be discussed.

Respiratory disorders account for a small, but significant percentage of maternal morbidity and mortality (1,2). These are sometimes due to preexisting conditions that may be exacerbated by pregnancy such as pulmonary hypertension (PH), cystic fibrosis (CF), or restrictive lung disease or due to acute illnesses such as pulmonary embolism (PE), pneumonia, or adult respiratory distress syndrome. Particularly with respect to chronic progressive pulmonary diseases, physicians must be familiar with the potential maternal and fetal complications that can occur and be prepared to counsel women regarding these issues.

Changes in Lung Function During Pregnancy

Chest Wall and Diaphragm

Early in pregnancy, the overall diameter of the chest wall increases, possibly due to relaxation of the ligamentous attachments between the ribs and the sternum. More specifically, the subcostal angle increases by approximately 35°, the transverse diameter of the chest increases by approximately 2 cm, and the chest circumference expands by 5 to 7 cm. In later pregnancy, as the uterus enlarges, the level of the diaphragm rises approximately 4 cm, but this does not affect diaphragmatic excursion (3).

Pulmonary Function

Overall, respiratory muscle function is not altered by pregnancy. Maximum inspiratory and expiratory pressures remain unchanged. However, due to the changes in chest wall configuration as noted above, static lung volumes are altered. The total lung capacity is minimally reduced and the functional residual capacity (the amount of air remaining in the lungs at end expiration) is more significantly reduced due to elevation of the diaphragm in later stages of gestation. By contrast, due to the decrease in functional residual capacity, the inspiratory capacity (the maximum amount of air that can be inspired at end expiration in the resting state) is increased, and steady-state tidal volumes may be increased up to 30% to 40% (Table 1).

Airway function remains unaffected by pregnancy, with no change in forced expiratory volume in one second, forced vital capacity (FVC), or peak expiratory flow rates. Therefore, the use of a peak flowmeter in pregnant asthmatics that are experiencing respiratory symptoms can be invaluable in distinguishing between worsening of underlying airway disease and alternative causes for their symptoms, including the normal dyspnea of pregnancy. However, it is important that peak flows be performed in the upright position, as lying supine can result in small alterations in peak flow rates.

Gas Exchange

As gestation progresses, a state of chronic hyperventilation ensues. This is probably due to progressively increasing levels of progesterone, which is a known stimulant of respiratory drive, from approximately 25 ng/mL at 6 weeks to 150 ng/mL at term (4). By 8 weeks of gestation, there is already an increase in tidal volume as noted above. This increased tidal volume results in increased alveolar ventilation, with subsequent decreased arterial carbon dioxide (PaCO_2). PaCO_2 levels typically decrease from normal levels of 37 to 40 mmHg to 27 to 32 mmHg. This decrease in maternal PaCO_2 creates a favorable gradient for CO_2 transfer from the fetus across the placenta. The maternal pH is maintained within the normal range through increased renal excretion of bicarbonate with a subsequent mild metabolic acidosis, with typical serum bicarbonate levels of 18 to 21 mEq/L.

Maternal oxygenation (PaO_2) usually increases early in pregnancy (106–108 mmHg) as a result of decreased PaCO_2 , but as the uterus enlarges in the third trimester, the PaO_2 decreases slightly (101–104 mmHg), with a slight increase in alveolar to arterial oxygen gradient from 14 to 20 mmHg. This decrease in PaO_2 is even more pronounced in the supine position.

Oxygen consumption increases by approximately 20% during pregnancy to meet the increased metabolic demands of maternal organs, the fetus, and the placenta (5). These oxygen requirements are more pronounced during exercise and labor (6). Due to the decreased functional residual capacity, maternal oxygen reserve is lower, and pregnant women can develop a more rapid onset of hypoxia during periods of apnea or during attempted endotracheal intubation.

In the setting of slightly elevated maternal pH and elevated 2,3 DPG during pregnancy, the oxygen–hemoglobin dissociation curve is shifted to the right, resulting in a decreased affinity of hemoglobin for oxygen (Fig. 1). This not only favors an increased transfer of oxygen to the fetus, but also results in a decreased oxygen saturation of hemoglobin for any given level

Table 1 Pulmonary Function Changes During Pregnancy		
Measurement	Definition	Change in pregnancy
Respiratory rate	Number of breaths per minute	None
Tidal volume	Amount of air inspired and expired with normal breathing	Increased 30–40%
Total lung capacity	Amount of air in lungs at maximal inspiration	Decreased 5%
Vital capacity	Amount of air that can be forcibly expired after maximal inspiration	none
Residual volume	Amount of air remaining in lungs after maximal expiration	Decreased 20–25%
Functional residual capacity	Amount of air remaining in lungs at resting expiratory level	Decreased 20%
Inspiratory capacity	Amount of air that can be inspired from resting expiratory level	Increased 5–10%
Inspiratory reserve volume	Amount of air that can be inspired at the end of normal inspiration	none
Expiratory reserve volume	Amount of air that can be expired from resting expiratory level	Decreased 15–20%

Figure 1 Oxygen dissociation curves for human maternal and fetal blood, indicating the physiologic range of PO₂ and O₂ for mother and fetus. Source: From Ref. 7.

of PaO₂ (8). This also causes the pregnant women to be more susceptible to hypoxemia. Although fetal partial pressure of oxygen is much lower (25–35 mmHg), the saturation is relatively higher than that in the adult due to displacement of the fetal oxygen–hemoglobin dissociation curve to the left. The fetus can be very sensitive to a small decrease in maternal PaO₂ due to the steep slope of the fetal oxygen dissociation curve in the 50% saturation range (9).

Dyspnea of Pregnancy

The increasing levels of progesterone throughout the course of gestation as well as the changes in lung function noted above are thought to be the main mechanisms responsible for the physiologic dyspnea of pregnancy. During the course of normal pregnancy, 60% to 70% of women experience a sensation of dyspnea (10). This sensation of breathlessness usually begins during the first trimester and gradually increases throughout the second and third trimesters. At 28 weeks of gestation, approximately 50% of women experience dyspnea walking up hills or climbing stairs, and 20% have dyspnea walking on flat ground (11). Distinguishing between the physiologic dyspnea of pregnancy and the presence of underlying cardiac or pulmonary disease can be a diagnostic challenge. The dyspnea of pregnancy is typically gradual in onset, is not associated with cough, wheezing, or chest pain, and is characterized by a clear lung exam and normal spirometry.

AIRWAY DISEASES

Asthma

Epidemiology

Asthma is the most common pulmonary disorder in pregnancy, affecting 8% of pregnant women (12). The National Asthma Education Program Working Group on Asthma in Pregnancy estimated that 10% of pregnant asthmatics have an acute exacerbation of asthma during labor, and 0.2% experience status asthmaticus during the course of their pregnancy (13,14). Approximately one-third of asthmatics have an improvement in asthma control during pregnancy, one-third have worsening during pregnancy, and one-third experience no change (13).

Maternal and Fetal Effects

Over the last 30 years, multiple studies have investigated the effect of asthma on maternal and fetal outcomes, with varying results. There have been reports of adverse outcomes, including low infant birth weight, congenital malformations, increased incidence of preterm labor, and increased incidence of maternal pre-eclampsia and hypertension, particularly in poorly controlled asthmatics (15). A recent case-control study of over 3000 women over 10 years showed only an increase in pre-eclampsia and maternal hypertension in poorly controlled asthmatic patients (16).

Symptoms and Triggers

Asthma is characterized by either partial or completely reversible airway obstruction, with airway inflammation, bronchospasm, and mucous hypersecretion. Typical symptoms of asthma include dyspnea, cough, wheezing, and chest tightness. These may be worse at night and, with exercise, may occur in the setting of an upper respiratory tract infection or after exposure to environmental triggers such as hot or cold air, dust or pollen, house dust mites, cockroach antigens, pets, or other inhaled irritants. Asthma symptoms can also be triggered by gastroesophageal reflux that is estimated to occur in up to 50% of pregnant women (17) or by postnasal drip that is precipitated by hyperemia and glandular hyperactivity in the upper respiratory mucosa during pregnancy.

Diagnosis and Monitoring

The diagnosis of asthma is made based on the clinical history as noted above with or without supporting physical exam findings of expiratory wheezing or rhonchi. The diagnosis is confirmed by spirometry demonstrating a reduced forced expiratory volume in one second (FEV1) with a reduced ratio

Table 2 Assessing Asthma Severity

	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Symptoms	≤2 days/wk	>2 days/wk	Daily	Continuous
Nocturnal Awakenings	≤2 times/month	3–4 times/month	>1 time/wk	Nightly
Use of rescue inhaler	≤2 days/wk	>2 days/wk, but not >1 time/day	Daily	Several times/day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal	FEV1>80% predicted FEV1/FVC normal	FEV1>60% but <80% FEV1/FVC reduced 5%	FEV1<60% predicted FEV1/FVC reduced >5%
Recommended step for initiating treatment	Step 1	Step 2	Step 3	Step 4 or 5 and consider short course of systemic corticosteroids

of FEV1 to FVC, with further confirmation if airway reversibility is shown by an improvement by 12% and 200cc in either the FEV1 or the FVC after the administration of an inhaled bronchodilator. The sensitivity, however, of spirometry in the diagnosis of asthma is limited (18). Methacholine challenge testing, which can be used to diagnose asthma in patients with normal spirometry, is contraindicated in pregnant women due to a lack of safety data (19).

Once the diagnosis of asthma has been established, the cornerstone of asthma assessment is patient self-monitoring with a portable peak flowmeter. Patients should be instructed to measure their peak expiratory flow on a regular basis at different times of day to establish a baseline, and then to use the meter when experiencing new or changing respiratory symptoms, in order to facilitate early detection of an acute asthma exacerbation. The peak flowmeter is a particularly helpful objective assessment of pulmonary function in distinguishing between the normal dyspnea of pregnancy and worsening of asthma symptoms.

Physician assessment of asthma control involves tracking the frequency and severity of asthma symptoms, including the presence of nocturnal awakenings due to asthma and the use of short-acting inhaled beta-agonist rescue therapy. Most importantly, patients should be asked about their consistent use of controller medications and avoidance of environmental triggers. Pregnant asthmatics requiring regular controller medications should undergo monthly physician visits.

Treatment

The first step in the treatment of asthma is to identify and counsel patients on the avoidance of asthma triggers. In addition, assessment should be performed for the presence of other conditions that can exacerbate asthma such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease and these conditions should be treated if present.

It is important to note that the risks of uncontrolled asthma far outweigh any risks from the medications used to control asthma (20).

Airway inflammation is treated with inhaled corticosteroids and bronchial hyper-responsiveness is treated with short- or long-acting bronchodilators. In addition, leukotriene receptor antagonists, theophylline, and cromolyn appear to be safe during pregnancy and may be considered in select patients (21). Most data on the safety of asthma medications in

pregnancy are observational, with the most extensively studied being albuterol and inhaled budesonide (21–23). Albuterol appears to be safe based on a review of six published studies including 1599 women and a prospective study including 1828 women, in whom no significant relationship was found between the use of inhaled beta-2 agonists and adverse pregnancy outcomes (21,24). The National Asthma Education and Prevention Program Working Group reviewed 10 studies, including 6113 patients who were treated with inhaled corticosteroids during pregnancy and found no increases in congenital malformations or adverse perinatal outcomes in these patients (24).

The pharmacologic treatment of asthma depends on the severity of the asthma symptoms and degree of physiologic impairment. Patients with mild, intermittent asthma (symptoms ≤2 days/wk and ≤2 nights/month with normal FEV1) do not require daily controller medications and can be managed with a short-acting inhaled bronchodilator as needed. Patients with persistent asthma (symptoms >two times/wk or >2 nights/month) require daily treatment with inhaled corticosteroids at increasing dosages depending on the severity and frequency of their asthma symptoms, with the addition of inhaled long-acting beta agonists in steps 4 to 6 (19,24,25) (Tables 2, 3, and 4).

Pregnant patients who had good asthma control prior to pregnancy should generally be instructed to continue on their prepregnancy regimen. In nonpregnant patients, it is recommended that if their asthma has been well controlled for 3 months, then they be considered for a step-down in their therapy. This may also be considered in pregnant patients requiring high-dose inhaled corticosteroids with long-acting inhaled beta agonists, with the goal of first eliminating the long-acting beta agonist if possible, as data are lacking regarding the safety of long-acting beta agonists during pregnancy. The safety of short-acting beta agonists and the accumulating clinical experience with these medications during pregnancy are reassuring. Therapy should be increased by one step (Table 3) in patients with poorly controlled asthma. Patients using their rescue inhalers more than twice a week should be considered for a step-up in therapy. If patients have very poor asthma control, therapy should be increased by two steps or a short course of systemic corticosteroids should be prescribed. A typical regimen would be oral prednisone 40 to 60 mg daily for 1 week, followed by a taper over 7 to 10 days.

Table 3 Steps of Asthma Therapy During Pregnancy		
Step	Preferred controller medication	Alternative controller medication
1	None	-
2	Low-dose inhaled corticosteroid	LTRA, cromolyn, theophylline
3	Medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid plus LABA, LTRA, or theophylline
4	Medium-dose inhaled corticosteroid plus LABA	Medium-dose inhaled corticosteroid plus either LTRA or theophylline
5	High-dose inhaled corticosteroid plus LABA	-
6	High-dose inhaled corticosteroid plus LABA plus oral prednisone	-
Abbreviations: LTRA, leukotriene receptor antagonist; LABA, long-acting beta-2 agonist.		

Table 4 Controller Medications for the Management of Asthma During Pregnancy		
Inhaled corticosteroids	Usual dose	FDA pregnancy class
Budesonide	Low: 180–600µg/day Medium: 600–1200µg/day High: >1200µg/day	B
Beclomethasone	Low: 80–240µg/day Medium: 240–480µg/day High: >480µg/day	C
Fluticasone	Low: 100–300µg/day Medium: 300–500µg/day High: >500µg/day	C
Long-acting beta agonists (add-on therapy to medium- or high-dose inhaled corticosteroids)		
Salmeterol	1 puff BID	C
Formoterol	1 puff BID	C
Leukotriene receptor antagonists		
Montelukast	10mg daily	B
Zafirlukast	20mg BID	B
Theophylline	400–600mg/day (adjusted to level 8–12µg/mL)	C
Cromolyn	2 puffs QID	B

Labor and Delivery Management

Acute exacerbations of asthma are rare during labor and delivery. Adequate analgesia with the use of epidural anesthesia may reduce the risk of bronchospasm and has the added benefit of reducing oxygen consumption and minute ventilation during labor. The ultimate goal of asthma management during labor and delivery is maintaining adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother.

Cystic Fibrosis

Cystic Fibrosis occurs in about 1 in 1500 whites and 1 in 17,000 blacks (26). With improved therapy, median survival is now 33.4 years (26,27). The Cystic Fibrosis Foundation found that in 2004, 191 American women with CF were pregnant. Though many women with CF, particularly those with more mild disease, are able to undergo pregnancy without significant problems, pregnancy in CF patients has been associated with adverse fetal and maternal outcomes. Close management by a multidisciplinary team is required throughout the pregnancy. Overall, 25% of patients had preterm delivery, and the 2-year perinatal death rate was 14%. The mortality risk appears to be associated with more severe

disease, with the suggestion that an FEV1<60% of predicted, colonization with Burkholderia cepacia, poor nutrition, and diabetes mellitus are poor prognostic factors for both maternal and fetal outcomes (28–30). Women with CF with good pulmonary function prior to pregnancy do develop an increased frequency of pulmonary exacerbations and hospitalizations throughout the course of gestation, but there is no change in long-term survival compared with controls (30).

Bronchiectasis

There is little information known about the impact of bronchiectasis on pregnancy. Based on case reports in the literature, it appears that there is no change in pulmonary function during pregnancy and no significant effects on fetal outcomes if normal oxygenation is maintained (31,32). In cases in which maternal hypoxia was present, fetal growth retardation has been reported (31).

DISORDERS OF THE PULMONARY VASCULATURE

Pulmonary Hypertension

Pulmonary Hypertension is defined as an elevated mean pulmonary artery pressure of greater than 25mmHg and a pulmonary capillary wedge pressure of greater than

15 mmHg, measured with a right heart catheter at rest (33). It can be primary, caused by a vasculopathy in the pulmonary arteries, or secondary, due to diseases affecting the lungs such as pulmonary emboli, interstitial lung diseases of many etiologies, emphysema, cardiac disease, or extra pulmonary diseases such as HIV, liver failure, or sleep apnea, with resultant hypoxemia (34).

It becomes relevant for obstetricians to learn about PH because women of childbearing age are more likely to suffer from primary pulmonary arterial hypertension (PAH) or congenital heart disease, and the hemodynamic demands of pregnancy can lead to increased cardiac output and hemodynamic or respiratory decompensation. With maternal mortality estimated between 30% and 50%, historically, the recommendation has been, for women with PAH, to avoid pregnancy with effective contraception and to terminate pregnancy should it occur (35). More recently, medications have become available that can lower pulmonary artery pressures, thereby improving exercise tolerance, quality of life, and survival. These medications, however, do not cure the condition (35,36). Use of these therapies, such as IV epoprostenol, inhaled nitric oxide, inhaled iloprost, oral calcium channel blockers, endothelin receptor antagonists (bosentan, ambrisentan), and sildenafil, have been tried and, in review, have resulted in lower but still high mortality, over 25% (37–40).

We would continue the recommendation to avoid pregnancy, but should the woman wish to proceed, consultation with expert cardiologists, pulmonologists, and anesthesiologists with experience with these new therapies and complications during delivery should be obtained. Termination of pregnancy should be considered if PH worsens, which is reported most often between 20 and 24 weeks, when most hemodynamic changes have occurred (37,40).

Pulmonary Embolism

Overview

Deep venous thrombosis and its manifestation, pulmonary embolism, (DVT/PE) are the leading cause of maternal death in the developed world. Estimated deaths in the United States and Europe are 1.1 to 1.5 per 100,000 deliveries, with 5 to 12 events of DVT/PE per 100,000 pregnancies, which is 7 to 10 times higher than age-matched nonpregnant women (41).

Two-thirds of DVT occur antepartum and are equally distributed among the trimesters. PEs occur more commonly post delivery, 43% to 60%, and the risk of DVT/PE is elevated for 6 weeks following delivery. Pregnancy is thus considered a hypercoagulable or thrombophilic state, increasing the risk of DVT/PE (42).

Pregnancy is associated with hypercoagulable changes in blood, venous stasis with decreased blood flow, compression of iliac veins by the uterus, the crossing of the right iliac artery over the left iliac vein, and immobilization. Trauma from the delivery or from interventions to aid in delivery can lead to vascular damage and therefore all variables of Virchow's triad: hypercoagulability, venous stasis, and vascular damage (41–43).

Other factors increasing the risk for DVT/PE include underlying thrombophilias (found in approximately 50% of episodes in pregnancy), previous DVT or family history of

DVT/PE, elevated BMI, immobilization, assisted reproduction, hemorrhage, infection, Caesarean delivery (especially emergent multiple pregnancies), age over 35, and pre-eclampsia (42).

Diagnosis

The diagnosis of DVT/PE in pregnancy is more complicated than that in the nonpregnant population, as the symptoms are nonspecific, overlap with those of normal pregnancy, and require the use of radiation-associated imaging, which patients and physicians wish to avoid due to negative effects on the fetus. Recommendations are extrapolated from studies in nonpregnant populations from which pregnant women were specifically excluded (41–45).

Most patients with DVT/PE will complain of shortness of breath, pleuritic chest pain, hemoptysis, syncope, or leg swelling occurring over minutes to hours. They may have tachypnea, tachycardia, hypotension, and shock. While these symptoms and signs are sensitive, they are not specific to confirm the diagnosis, and further objective testing, such as imaging, is required.

Consideration of the possibility of DVT/PE is the most important factor leading to a correct diagnosis and requires that one recognize the signs and symptoms while screening for risk factors in addition to pregnancy. Examination of the patient should focus on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, the presence of jugular venous distention, wheezing, rales, pleural rubs, heart murmurs or gallops, leg swelling, tenderness, and/or warmth. The differential diagnosis often includes pulmonary congestion, heart failure, atelectasis, asthma, pneumonia, and pneumothorax in addition to DVT/PE. A clinical probability for DVT/PE should be made. Clinical prediction rules and algorithms exist and have been evaluated in the nonpregnant population, but have not been similarly developed for the pregnant group. Therefore, if DVT/PE is suspected, further studies are required (41–43).

Electrocardiograms and arterial blood gases have not been demonstrated to be useful in excluding or making the diagnosis of PE, although they can aid in the evaluation of other conditions, such as myocardial infarction. d-Dimer testing remains problematic, as the levels increase in the blood through each trimester and often exceed the upper range of normal, which has been established in nonpregnant subjects (46). Furthermore, levels have not been developed to allow the treating physician to discriminate DVT/PE from normal pregnancy. By contrast, however, threshold levels have been developed in the nonpregnant patient. Therefore, the combination of a low suspicion for DVT/PE and a normal level of d-dimer in the blood effectively rules out the diagnosis. However, in those who have an intermediate or high clinical suspicion, a d-dimer study will neither diagnose nor exclude DVT and, therefore, it is not recommended.

Once the diagnosis is considered, and further testing is in progress, treatment should begin. The next test should be compression ultrasonography of the lower extremities. It is noninvasive and does not require radiation. If DVT is seen, PE can be diagnosed and treatment continues as it is the same for DVT and PE. Limitations to this study are its decreased accuracy in those without symptoms or signs of DVT or with isolated calf, iliac vein, or pelvic vein thromboses. If DVT is

not seen, further testing is indicated. Available studies include chest radiography, ventilation-perfusion scintigraphy (V/Q), computed tomography pulmonary angiography, pulmonary angiography, and CT or conventional venography (41,42,45).

While chest radiography can suggest an alternate diagnosis, such as fluid overload, pneumonia, or pneumothorax, it cannot definitively exclude or make a diagnosis of DVT/PE. V/Q scanning has been validated in the diagnosis of PE, in combination with pretest clinical probability determinations. A normal or near-normal scan and low clinical probability practically excludes the diagnosis in nonpregnant patients. A high clinical suspicion with a high probability scan confirms the diagnosis. All other combinations of clinical probability and scan interpretation do not confirm or exclude the diagnosis. The radiation dose from a complete V/Q scan is from 0.00028 to 0.00051 Gy; doses in humans of 0.01 Gy during gestation are estimated to be a threshold above which increased congenital abnormalities are seen. Fetal exposure to radiation of 0.01 Gy above normal background radiation may increase the probability of cancer before age 20 by 0.017 (41).

Results of V/Q scanning show that 70% are interpreted as normal and 25% are non-diagnostic. These results suggest that V/Q scanning may be a good first test to exclude PE, but many patients will require further testing (47).

CT scanning delivers 0.00003 to 0.00013 Gy to the fetus, similar to V/Q scanning; however, more radiation is received by the mother's breasts than the fetus. The incidence of breast cancer may be increased with chest CT. CT scans are reported either as positive or negative and are accurate in lobar vessels (97% accurate). In smaller segmental and subsegmental vessels, accuracy declines and both false-positive (reported clot where none exists) or false-negative results are noted. However, a negative scan can reliably exclude the diagnosis, and follow-up of those with negative scans show good outcomes without treatment. An advantage of CT is that other diagnoses may be made. The problem of isolated pelvic vein thrombosis can be associated with abdominal and back pain, and swelling of the leg may require CT scanning of the iliac veins and pelvis (41,48,49).

In studies of nonpregnant patients who undergo full diagnostic testing for DVT/PE, up to 25% of patients will have the diagnosis confirmed. In pregnant women, 10% to 15% will be found to have DVT/PE. Despite studying many patients who do not have DVT/PE, it is felt that with a mortality of 30% when untreated, compared with 8% when treated, evaluation leading to a diagnosis is required if a pregnant patient presents with signs or symptoms suggestive of possible DVT/PE (41).

If the V/Q scan and chest CT are non-diagnostic, conventional angiography can be done. This choice requires trained personnel both to perform and to interpret the study. It delivers more radiation than other studies, but offers the most certain diagnosis. However, with the widespread availability of CT scans, this test is less frequently done.

A suggested approach to the evaluation of DVT/PE is to consider the diagnosis in those who complain of acute dyspnea, pleuritic chest pain, hemoptysis, or syncope. A chest

radiograph, electrocardiogram, and ultrasound of the lower extremities should be obtained. Blood studies can include a blood count and d-dimer. If an alternative diagnosis is not made, or the ultrasound does not reveal DVT, then further imaging is needed. We recommend a CT angiogram, as this will be diagnostic in most cases. A CT angiogram requires informed consent from the patient and should include a discussion of radiation exposure to the patient and fetus, including a possible slightly elevated risk of cancer. If available, a discussion with radiology personnel and the application of breast shields can be attempted (41,50).

Therapy

The initial treatment of DVT/PE in both pregnant and nonpregnant patients is heparin. Low-molecular weight heparin (LMWH) (enoxaparin 1mg/kg up to 100mg twice daily, dalteparin using weight-based dosing of 5000–10,000 units twice daily, or tinzaparin 175units/kg once daily at all weights) is preferred (41,44). Unfractionated heparin, given intravenously, was the standard historically, but studies have shown that the subcutaneous use of LMWH has therapeutic equivalence, better bioavailability and predictable dose response, a reduced risk of bleeding, weight-based dosing without the need for monitoring of coagulation, reduced risk of heparin-induced osteoporosis and fractures, and reduced risk of heparin-induced thrombocytopenia. Heparins neither cross the placenta nor are they excreted in breast milk. Allergic reactions are uncommon and include itching, urticaria, and erythematous plaques (44).

Full anticoagulation in the absence of other factors, such as an underlying thrombophilia or prior DVT/PE, must continue for at least 6 months, throughout the pregnancy, and at least 6 weeks postpartum.

In patients with massive PE, mortality with aggressive therapies exceeds 50%. These patients are hemodynamically unstable, with a large clot burden causing obstructive shock, right ventricular failure, hypoxemia, and hypotension. In the nonpregnant patient, the use of thrombolytics, such as tissue plasminogen activating factor, or streptokinase, are used. Thrombolysis, as well as surgical embolectomy, has been used in pregnant patients with successful outcomes (41,44,51).

For patients receiving heparin, some clinicians have recommended a reduction in dose to 75% of a full treatment dose after 30 days, extrapolating from studies in nonpregnant patients. This approach has not been confirmed with studies in pregnant patients but is not unreasonable (44).

If pregnant patients are receiving anticoagulation therapy and are approaching delivery, they can be switched from subcutaneous LMWH to IV unfractionated heparin 24 to 36 hours prior to elective induction of labor or caesarean section. If, however, spontaneous labor begins while the patient is receiving subcutaneous LMWH, epidural anesthesia cannot be administered.

A special situation involves women with a recent (less than 1 week previously) DVT/PE receiving full anticoagulation therapy near delivery. There is a higher rate of recurrence during this period. Options include insertion of an inferior vena cava filter and induction of labor with reinstitution of anticoagulation following delivery when hemostasis is

obtained, or switching from LMWH heparin subcutaneously to IV unfractionated heparin and cessation 4 to 6 hours prior to expected delivery (44).

Prevention

If a patient with known risk factors for DVT/PE, such as a history of prior idiopathic or pregnancy-associated DVT/PE or a known thrombophilia, becomes pregnant, their risk for recurrent DVT/PE during pregnancy will be increased. As a preventative strategy, low-dose subcutaneous LMWH should be given throughout the pregnancy and postpartum for 6 weeks. If women with known thrombophilia have not had DVT in the past, with the exception of antithrombin deficiency, they should receive low-dose prophylactic therapy throughout the pregnancy and for 6 weeks after delivery (34,44).

AMNIOTIC FLUID EMBOLISM SYNDROME

A rare but catastrophic situation is amniotic fluid embolism syndrome (also called anaphylactoid syndrome of pregnancy). It is rare, unpredictable, unpreventable, and has a high mortality rate between 20% and 90%. Survivors are often left with anoxic encephalopathy. After pulmonary thromboembolism, it is the next leading cause of unexpected maternal death. Women who undergo a difficult labor, who are older, who have a caesarean or instrumental delivery, and who have placenta previa or abruptio are at an increased risk (52).

The clinical presentation is the sudden onset of hypoxemia, hypotension, seizures, and coagulopathy during labor or within 30 minutes of delivery. The condition appears as a systemic process with hypoxemia due to ventilation perfusion mismatching followed by non-cardiac pulmonary edema, hypotension, decreased left ventricular function, and, within minutes, disseminated intravascular coagulation with bleeding. Occasional cases are reported following abortion, amniocentesis, or trauma. There are no specific tests that confirm the diagnosis. The differential diagnosis includes sepsis, acute PE, anaphylaxis, air embolism, anesthetic complications, transfusion reactions, eclampsia, heart failure, hemorrhage, or aspiration and all of these must be considered (52,53).

Treatment is supportive with supplemental oxygen, most likely with intubation and mechanical ventilation, trying to maintain a maternal PO₂ greater than 65 mmHg. Blood pressure should be maintained with norepinephrine or dopamine and fluids, while central access is obtained, and evaluation of fluid status is undertaken. Blood and blood products may be necessary, and delivery might be necessary as well, but bleeding must be controlled first (20,21).

The etiology of this syndrome is unknown, but it is felt to be inflammatory—a response to antigens in amniotic fluid in susceptible hosts (52–54).

RESTRICTIVE LUNG DISEASES

There are a number of chronic lung diseases affecting women of childbearing years that are characterized by reduced lung volumes and normal expiratory airflow. Their physiology is described as restrictive, as compared with the “obstructive” diseases such as asthma and CF. These diseases can cause increased respiratory distress in pregnant women, as the

normal physiology of pregnancy progresses with its increase in minute ventilation and oxygen consumption, changes in rib cage displacement, and intravascular volume, which add to baseline pulmonary dysfunction. We will discuss some of the more common disorders and their response to pregnancy (55,56).

Kyphoscoliosis

Kyphoscoliosis is a deformity of the spine with excessive curvature either posterior (kyphosis) or lateral (scoliosis). Women are more commonly affected than men, with a prevalence of 10.7% in women 25 to 74 years, documented in one study. Kyphoscoliosis, by causing a reduction in lung volumes, can lead to respiratory failure and death. The deformity of the chest wall compresses the lungs and leads to ventilation perfusion mismatching, hypoxemia, and, occasionally, hypercarbia. PH and heart failure can occur (57).

Despite these findings, and worsening respiratory function, reported outcomes of pregnancies appear to be good. Patients should have their pulmonary function tests measured, and oxygen saturation followed throughout pregnancy, at rest and with exercise, and should be supplemented when oxygen saturations drop below 95% (58).

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare lung disease more common in women. It can occur sporadically or can be associated with tuberous sclerosis. Pathologically, cysts and a multifocal nodular proliferation of immature smooth and perivascular epithelioid cells are found. Women may complain of shortness of breath, cough, or hemoptysis and can be found to have a pneumothorax or a chylous effusion in the chest or abdomen. The condition is associated with angiomyolipomas of the kidneys and meningiomas.

In the lungs, chest CT scanning shows multiple (more than 10) thin-walled air-filled cysts with preserved lung volumes and no other lung involvement. Pulmonary function tests may show expiratory airflow obstruction and/or restrictive abnormalities with hypoxemia and normal PCO₂. Prognosis is variable with median survival of 8 to 10 years following diagnosis and has been reported to be up to 20 years. No treatment is of proven benefit. Treatment is supportive with oxygen, bronchodilators, and occasionally lung transplantation.

It is believed that estrogens are related to the progression of the disease and should therefore be avoided. Pregnancy in these patients has been associated with an increased risk of pneumothorax and chylothorax. Those who are pregnant prior to the diagnosis of LAM appear to do well, while those whose diagnosis is made during pregnancy have an increased incidence of premature births and can have greater progression of the disease.

Therefore, women with LAM should be evaluated prior to pregnancy and advised of possible complications. Should they elect to become pregnant, or proceed with pregnancy, they should be evaluated for the progression of disease and pneumothoraces (59).

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that results in noncaseating granulomas in involved organs. It most commonly affects people under 40 years of age and, while affecting all races, is more common in blacks than whites. The lung is the most commonly involved organ (over 90%), and patients present with dyspnea, cough, fever, malaise, and weight loss. Other organs such as the heart, eyes, and skin are frequently involved. The diagnosis is made with a consistent clinical picture and a consistent biopsy. Many patients will spontaneously improve, while others will require treatment, usually glucocorticoids. Patients can progress to respiratory failure due to interstitial lung disease and fibrosis.

Sarcoidosis does not seem to affect fertility or increase the incidence of maternal or fetal complications. Corticosteroids may be administered before and during pregnancy. However, with the use of systemic steroids during pregnancy, there is a reported increase in the incidence of cleft palate in fetuses and women should be made aware of this possible side effect. Some women improve during pregnancy as endogenous steroid levels rise. If respiratory function deteriorates, supplemental oxygen might be needed (60).

INFECTIOUS DISEASES

Allergy and Upper Respiratory Tract Infections

Upper respiratory tract infections are common disorders for which patients, pregnant and nonpregnant, seek therapy. These disorders can be challenging in the pregnant patient because many of the relieving medications must be avoided and because noninfectious rhinitis is a common symptom during normal pregnancy.

Rhinitis of pregnancy occurs in 20% to 30% of women, and although it does not appear to affect outcome, it can certainly affect sleep, nutrition, and increase stress (61). Rhinitis of pregnancy is defined as nasal congestion and/or rhinorrhea lasting more than 6 weeks in the absence of signs of infection or a known allergen. Usually it is not necessary to treat pharmacologically and measures such as exercise (nasal vasoconstriction), saline spray or irrigation, and head of the bed elevation can be very effective (62). Intranasal glucocorticoid sprays do not seem to be beneficial, and when necessary, pseudoephedrine can be used after the first trimester and if there is no maternal hypertension (63).

Much like asthma, allergic rhinitis that is present prior to pregnancy may remain stable, worsen, or improve (64). Skin testing to identify an allergen is avoided during pregnancy given the possibility of a severe systemic allergic response during testing. Intranasal cromolyn sodium is safe and efficacious, and unlike in non-allergic rhinitis of pregnancy, intranasal glucocorticoids are effective and considered safe (65). Antihistamines are generally less effective and the intranasal formulations should be avoided. Second-generation antihistamines such as loratadine and cetirizine are the formulations of choice if more than topical therapy is needed. Decongestants have the added benefit of having vasoconstrictive properties, but because of this effect, they should be avoided in the first trimester. Nasal oxymetolazone, as in nonpregnant patients, should be used only for a short duration of 2 to 3 days to avoid rebound symptoms. If necessary,

pseudoephedrine can be used after the first trimester and if there is no maternal hypertension (65,66). Allergen immunotherapy is often successful in controlling symptoms of allergy—both rhinitis and asthma. While it is not recommended to start immunotherapy during pregnancy, for fear of systemic allergic reaction, patients who are tolerating a stable dose and who are benefiting from the therapy prior to pregnancy should continue their injections throughout pregnancy (67).

The practitioner must have a low threshold for suspecting bacterial sinusitis, as this entity is a common upper respiratory tract complication of pregnancy. Often the symptoms of fever and purulent discharge are absent. Radiologic evaluation with X-ray, computed tomography, or magnetic resonance imaging should be reserved for those not improving on antibiotics. Pathogens are identical to those in all bacterial sinusitis: *Haemophilus influenza*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. Treatment should be initiated with high-dose amoxicillin, amoxicillin–clavulanate, or one of the oral second- or third-generation cephalosporins. A penicillin allergic patient may receive trimethoprim–sulfamethoxazole or azithromycin but the fluoroquinolones, tetracycline, and doxycycline should all be avoided (68).

Just as in the nonpregnant host, it is estimated that 90% of acute bronchitis—productive cough due to airway inflammation with a clear X-ray—is viral in origin. Rhinovirus, influenza, parainfluenza, respiratory syncytial virus, and adenovirus are the usual implicated viral pathogens. Without a chest radiograph, it can be difficult to determine whether a lower respiratory tract infection is bronchitis or pneumonia. The presence of high fever, lack of upper respiratory tract viral symptoms, and leukocytosis might suggest pneumonia, and a chest X-ray and/or a course of antibiotics is probably warranted (69). Humidified steam can be more helpful than prescription or over-the-counter cough medication and should be encouraged.

Bacterial Pneumonia

Pneumonia in pregnant patients is rarely fatal and has the same incidence as in non-gravid individuals. However, there is both maternal and fetal morbidity associated with the condition such as hypoxemia and low birth weight (69). While a young, otherwise healthy pregnant woman may not have a classic presentation, fever, rigors, dyspnea, productive cough, and occasionally pleurisy are common presenting signs and symptoms of bacterial pneumonia. A chest radiograph is required and the risk of an undiagnosed pneumonia far outweighs the risk of fetal radiation if the usual shielding precautions are taken. Causative organisms are those common in community acquired pneumonia such as *S. pneumoniae*, *H. influenza*, *Staphylococcus aureus*, *Legionella*, *Mycoplasma*, and *Chlamydia*. Treatment with azithromycin and, in severe cases, ceftriaxone, is recommended. As with sinusitis, doxycycline, clarithromycin, and the fluoroquinolones should be avoided. Aspiration is common during pregnancy, and when pneumonia develops around the time of delivery or after an aspiration event, anaerobic organisms should be considered and treated (70).

Influenza

There have been three major influenza pandemics in the past 100 years—1918, 1957, and the H1N1 pandemic of 2009. In all three pandemics, there was higher morbidity and mortality among pregnant women. Seasonal influenza also takes a toll on the gravid patient with smokers, asthmatics, and women with other comorbid medical conditions having a higher rate of serious complications and hospitalization. This is especially true in the third trimester. Why influenza infection affects this pregnant group of young patients more seriously than their nonpregnant peers is unclear – theories suggest some difference in the immune system, the propensity of pregnant patients to have pulmonary edema due to hypoalbuminemia, and decreased oncotic pressure or their higher baseline oxygen consumption. Pregnant patients with known or suspected seasonal influenza should be observed closely so that if respiratory symptoms appear, they can be hospitalized. Otherwise, the usual treatment of rest, fluids, and acetaminophen for fever and myalgias applies (71).

The 2009 pandemic H1N1 influenza virus caused serious disease requiring hospitalization in many pregnant patients. Especially in the third trimester, infected women experienced respiratory failure, miscarriage, and preterm births. This led to the gravid patient being a priority for vaccination that season. In fact, influenza vaccination is recommended for all pregnant patients as experience has shown no risk to the fetus and a favorable benefit (72). Oseltamivir should be given to all hospitalized gravid patients with the H1N1 strain even if the conventional 48 hours of symptoms has passed. As with most viral respiratory infections, the bacterial superinfection rate is high and concomitant antibiotics should be considered (73).

Tuberculosis

Over 11,000 active cases of tuberculosis were reported in the United States in 2009 (74). Pregnancy does not appear to change the pathogenesis or disease progression of tuberculosis (75). Skin testing is safe and the results are not altered by pregnancy. However, routine testing for latent tuberculosis is not recommended unless the woman has a specific risk of quick progression from latent to active disease such as HIV infection or a recent significant exposure. Skin testing during pregnancy indicates that the practitioner has an intention to treat during pregnancy. In that setting, a positive skin test warrants a chest X-ray and evaluation to rule out active disease and then prophylactic therapy with isoniazid. In everyone other than those with immunosuppression or a recent exposure, testing and/or latent tuberculosis therapy should be deferred until at least the third month postpartum, since the risk of isoniazid hepatotoxicity is increased during pregnancy and the early postpartum period (76–78).

Active tuberculosis occurring during pregnancy may be initially hard to diagnose, as fatigue and malaise might be misinterpreted and weight loss can be mild. The workup for tuberculosis is the same in a pregnant patient as for a nonpregnant patient, and a new diagnosis of active tuberculosis should always prompt an HIV test. Active disease should be treated, as the risk of untreated disease is certainly higher than that of antituberculosis drug therapy

(77). First-line therapy is isoniazid, rifampin, and ethambutol, but pyrazinamide should be avoided because of limited safety data in pregnancy. However, in those patients with HIV, drug resistance, or extensive disease, its use should be considered. Streptomycin is a known teratogen and causes congenital deafness, so it should be avoided. Kanamycin, amikacin, and capreomycin are to be avoided because all cause eighth nerve damage and can cause renal toxicity. Generally any patient with multidrug resistant disease or who fails first-line therapy should be seen by an expert in tuberculosis. All patients are monitored using directly observed therapy and for hepatotoxicity (78).

Pneumocystis Jiroveci Pneumonia due to the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

With the implementation of highly active antiretroviral therapy, the last decade has seen a remarkable decrease in both the morbidity and the mortality associated with HIV and AIDS. However, the percentage of AIDS cases in women continues to grow annually. By 2007, 27% of adult AIDS patients were woman, and of these, 83% were women from communities of color (79). Heterosexual contact is the most common mode of acquisition in women and therefore issues surrounding the management of HIV/AIDS during pregnancy have become increasingly important.

In addition to an increased rate of viral and bacterial infections of the upper and lower airway, AIDS patients with a CD4 count <200 are susceptible to infection with *P. jiroveci*. Limited review of pregnant patients with *P. jiroveci* pneumonia during pregnancy suggests that mortality is higher in this group (50%) than in nonpregnant subjects and that risk is higher in the second and third trimesters of gestation (80). However, only a small number of cases have been reported in the literature and the women reported were almost all unaware of their HIV/AIDS status at the time of pneumonia diagnosis. Therefore, they were not receiving prophylaxis against this infection. Trimethoprim–sulfamethoxazole prophylaxis should be initiated using the same guidelines as for nonpregnant women (CD4 count less than 200). Generally, pentamidine should be used during the first trimester rather than trimethoprim–sulfamethoxazole. While the fetus is most susceptible to drug teratogenicity during the first 10 weeks of gestation, if the mother's health is poor, the benefit of therapy during this early gestational period likely outweighs the risk to the fetus (81–85). For active *P. jiroveci* infection at any time during pregnancy, trimethoprim–sulfamethoxazole remains the standard of care and steroid therapy should be considered in severe cases (80).

MISCELLANEOUS DISORDERS

Pulmonary Edema

Cardiogenic pulmonary edema is uncommon during pregnancy, but can occur late in pregnancy and early postpartum, usually due to heart disease, valvular problems such as mitral stenosis, or idiopathic cardiomyopathy. Patients complain of dyspnea and chest tightness, and may have bilateral infiltrates on chest radiograph. Therapy is similar to nonpregnant patients and includes diuresis and oxygen. However,

non-invasive positive pressure ventilation via mask is best not used due to the increased incidence of aspiration (86).

Non-cardiogenic pulmonary edema occurs in women receiving beta sympathomimetic agents for tocolysis. Usually, this condition occurs during administration of the drug, but can occur within 24 hours after discontinuation. Women complain of dyspnea and chest tightness, and rales may be present, as well as bilateral alveolar infiltrates on chest radiograph. Therapy is supportive with discontinuation of the beta agonist, oxygen, and diuresis. Resolution is expected within 24 hours (87).

Pleural Effusion

While there has been no specific study that identifies the disease processes causing pleural effusion in pregnancy, likely up to 25% of pregnant patients have small, asymptomatic pleural effusions visible on ultrasound. When pleural effusions are symptomatic, they cause dyspnea, cough, and possibly chest pain—if significant, there may be room air hypoxia due to shunting through underlying atelectatic lung. Symptomatic effusions in early pregnancy are either due to ovarian hyperstimulation syndrome or the same processes that cause effusions in nonpregnant patients: infection, cardiomyopathy, and PE. Neither pre-eclampsia nor the HELLP syndrome is associated with pleural effusion. Thoracentesis with drainage is indicated for diagnosis and/or the relief of symptoms due to a significant amount of pleural fluid. The small bilateral effusions described above that are asymptomatic generally are self-limiting and do not require intervention (88).

Sleep Disorders

Sleep-disordered breathing is prevalent in the general population and sleep disturbance is one of the most common complaints during pregnancy. However, there are limited data to elucidate the causes for sleep disturbance during pregnancy—difficulty lying in the supine position, nasal congestion, weight gain, and decreased time spent in rapid eye movement sleep have all been implicated (89,90). There is a suggestion that obese women who become pregnant have more sleep-disordered breathing, even in the first trimester, and this may be important if there is nighttime hypoxia that can affect the growth of the fetus. More work is needed in this area of sleep medicine (90).

Aspiration

Aspiration into the lung of stomach contents occurs most often during or immediately after labor. The combination of delayed gastric emptying, a relaxed lower esophageal sphincter, and increased intra-abdominal pressure with recumbency and sedation or analgesia increase the risk of vomiting and aspiration. Acutely, aspiration can lead to a chemical pneumonitis or bronchospasm, and aspiration of upper airway organisms such as anaerobes and streptococci can ultimately lead to a bacterial pneumonia. Chemical pneumonitis, while hard to distinguish from pneumonia, generally has an acute onset with dyspnea, cough, and low-grade fever. Radiographs reveal multifocal infiltrates with basilar predominance and treatment is supportive. Bronchospasm can be indistinguishable from

asthma with dyspnea and wheezing and is treated with bronchodilators (91,92).

Respiratory Failure and Mechanical Ventilation

Respiratory failure, defined as a PaO_2 of $<60\text{mmHg}$ or $\text{pCO}_2 > 50\text{mmHg}$, is a rare complication of pregnancy. The patient in respiratory failure will be distressed, tachypneic, and with shallow breaths despite the use of accessory muscles. If supplemental oxygen by nasal cannula or face mask fails to keep the oxyhemoglobin saturation above 95% (required for adequate fetal oxygenation), intubation and mechanical ventilation should be considered (93). Oral intubation of the pregnant patient can be difficult, with the decreased functional residual capacity and increased oxygen consumption causing more rapid hypoxia and upper airway edema obscuring adequate visualization during direct laryngoscopy. Intubation should be performed by experts in airway management. While receiving treatment tailored to the cause of the respiratory failure, mechanical ventilation should be managed to maintain a pCO_2 in the 27 to 32 range, as this is the usual pCO_2 during pregnancy. Severe respiratory alkalosis (potentially causing decreased uterine blood flow), hypoxia, and acidosis should be avoided (93).

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