Women's Issues in Pulmonary Medicine

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Objectives:

1. To review the normal respiratory and cardiovascular physiology of pregnancy.
2. To review the management of asthma in pregnancy.
3. To review the management of venous thromboembolism in pregnancy.
4. To review the management of tuberculosis and other respiratory infections in pregnancy.
5. To review the causes and management of acute respiratory failure in pregnancy.
6. To discuss the statistics regarding smoking and the epidemiology of lung cancer in women.

Key words: women; pregnancy; asthma; venous thromboembolism; acute respiratory failure; lung cancer

This chapter will focus on pulmonary diseases unique to women, including issues surrounding pregnancy, as well as diseases that may have different epidemiology and/or prognosis in women. Common pulmonary problems with different treatment plans in the pregnant or lactating woman, and causes and management of acute respiratory failure in the pregnant patient will be reviewed. Other diseases that occur exclusively or are more prevalent in women, such as lymphangioleiomyomatosis, are covered elsewhere in this course.

Table 1—*Normal Respiratory Physiologic Changes in Pregnancy*

Pulmonary Function	
Expiratory reserve volume	Decreased
Residual volume	Decreased
Functional residual capacity	Decreased
Total lung capacity	Mildly decreased
Inspiratory capacity	Increased
Vital capacity	No change
Tidal volume	Increased
Respiratory rate	No change – mild increase
Minute ventilation	Increased
Peak flow	No change
FEV_1	No change
Lung compliance	No change
Total respiratory compliance	Decreased
Diffusion capacity	Increased followed by decrease
Gas Exchange	
$PaCO_2$	Decreased to 28-32 mm Hg
PaO_2	Increased followed by decrease
pH	Increased to 7.40-7.45
Serum bicarbonate	Decreased to 18-21 mEq/L
Alveolar-arterial gradient	Mildly increased
O_2 consumption	Increased
CO_2 production	Increased

Physiology of Pregnancy

During pregnancy, the body undergoes anatomic and physiologic changes affecting both the respiratory and cardiovascular systems. It is important that the pulmonologist be familiar with these normal physiologic changes (Tables 1 and 2).

Respiratory

The upper respiratory tract undergoes changes during pregnancy, including hyperemia of the airway mucosa, increased secretion production, and mucosal edema, particularly accentuated in the third trimester. Patients can experience upper respiratory tract symptoms secondary to the above, including epistaxis, nasal stuffiness, hoarseness, and voice changes. Nasal polyposis and allergic rhinitis can begin or become exacerbated during pregnancy. These changes are primarily due to estrogen production. The healthcare provider should be aware of these changes when performing procedures such as endotracheal intubation and/or nasopharyngeal tube placement.

The thoracic cage also undergoes anatomic changes during pregnancy. The diaphragm becomes elevated up to an average of 4 cm above normal at full-term pregnancy. However, diaphragmatic

Table 2—*Normal Cardiovascular Physiologic Changes in Pregnancy*

Cardiac output	Increased
Heart rate	Increased
Stroke volume	Increased
Systemic vascular resistance	Decreased
Pulmonary vascular resistance	Decreased
Blood pressure	Decreased
Blood volume	Increased
Red blood cell volume	Increased, but less than blood volume
Hematocrit	Dilutional decrease
Serum protein levels	Decreased

dysfunction due to pregnancy is unusual because concurrent with these changes, there is a widening of the lower rib cage and alteration of the abdominal muscles, and thus diaphragmatic excursion is actually maintained or increased.

Pulmonary Function Tests. The major change in pulmonary function testing in pregnancy is a progressive decrease in the expiratory reserve volume by 8% to 40% and a decrease in residual volume by 7% to 22%, both changes due to the enlarging uterus and diaphragmatic elevation. Because of these changes, functional residual capacity is, in turn, decreased by 10% to 25% by the third trimester of pregnancy. Total lung capacity may decrease slightly, inspiratory capacity increases, and vital capacity does not change significantly during pregnancy. The decrease in residual volume with a relatively maintained total lung capacity results in a low ratio of residual volume to total lung capacity. Closure of the small airways during normal tidal breathing due to the reduction in functional residual capacity can result in changes in ventilation perfusion matching and gas exchange discussed below.

Tidal volume increases significantly during pregnancy by 150 mL to a final value of 450-600 mL, or a 30% to 50% increase in the average patient. This is most likely due to a direct progesterone-mediated increase in central respiratory drive and enhancement of the hypercapnic ventilatory drive. There is little or no change in respiratory rate during pregnancy, and tachypnea is an unusual finding. Because of the increase in tidal volume, there is a significant increase in resting minute ventilation from 6 L in the nonpregnant state to 9 L at full term (or 20%-50% above baseline).

There are no significant changes in peak flow rates, FEV_1, airway resistance, or maximum voluntary ventilation during pregnancy. Although lung compliance does not change significantly during pregnancy, there is a reduction in total respiratory compliance due to a reduction in chest wall compliance because of an elevated diaphragm caused by uterine enlargement by the third trimester. DLCO may increase slightly in the first trimester followed by a slight decrease later in pregnancy, likely due to alterations in pulmonary vascular volume.

Gas Exchange. Gas exchange in pregnancy is characterized by a mild compensated respiratory alkalosis secondary to an increase in minute ventilation out of proportion to maternal needs. Thus, normal $PaCO_2$ values are lower, 28-32 mm Hg, and serum bicarbonate is compensatorily decreased to 18-21 mEq/L. Normal pH is slightly alkalemic at 7.40-7.45. PaO_2 is slightly elevated, 100-105 mm Hg, with a slight decrease at term to 100 mm Hg. There is normally a 5-10 mm Hg elevation in alveolar-arterial (A-a) gradient above baseline, especially in the supine position. Oxygen consumption increases by 20% to 30% during pregnancy, with a concomitant increase in CO_2 production by 30% to 35%. These changes are due to increased maternal and fetal metabolic requirements and increases in work of breathing and cardiac output. During delivery, oxygen consumption can increase to 40% to 100% above baseline.

Cardiovascular

The cardiovascular system probably undergoes the most significant changes during pregnancy, including an increase in cardiac output, beginning in the first trimester and peaking at about the 25th to 32nd week at 30% to 50% above normal. This is due to both a change in heart rate as well as stroke volume, and a decrease in systemic vascular resistance, partially due to shunting of blood to the low resistance placental bed and perhaps due to increased levels of vasodilator mediators. Pulmonary vascular resistance also decreases. Both systolic and particularly diastolic pressures are reduced. Postural hypotension may be apparent, particularly in the third trimester when the uterus can compress the inferior vena cava, impeding venous return to the heart. During delivery, the cardiac output may be further augmented by an additional 10% to 15% due to catecholamine release.

Total blood and plasma volume increases up to 35% to 50% of normal, peaking in the mid-third trimester with a lesser increase in red cell volume (about 20% to 40%). The result is hemodilution with a relative decrease in hemoglobin, hematocrit (about a 12% decrease), and relative red blood cell volume, *ie*, the anemia of pregnancy. There is also a dilutional decrease in serum protein levels, resulting in a 5 mm Hg decrease in plasma oncotic pressures, predisposing patients to edema formation, including pulmonary edema. There is an approximate total body fluid expansion of 6-8 L of water divided among the fetus, amniotic fluid, and intracellular and extracellular spaces, and an increase in plasma volume of 1-1.5 L. These

changes in fluid status are likely due to increased mineralocorticoid production and/or hormonally mediated vasodilation.

Dyspnea During Pregnancy

Up to two thirds of pregnant women report dyspnea during pregnancy. Although the etiology of this normal physiologic dyspnea is not clearly defined, it is most commonly reported in the first and second trimesters with improvement toward the end of the third trimester. These findings support the fact that dyspnea is not purely related to mechanical enlargement of the uterus. Marked progesterone elevation early in pregnancy, resulting in direct brainstem stimulation and hyperventilation, and alteration in the sensitivity to carbon dioxide likely contribute to the sensation of dyspnea. The normal anemia of pregnancy may also contribute to the sensation of dyspnea.

One must also be aware of concomitant heart disease manifested in pregnant women. Mitral stenosis and other stenotic lesions may become apparent during pregnancy, particularly in the third trimester when blood volume is at its maximum, and right-to-left shunts tend to worsen.

Treatment of Specific Pulmonary Diseases in the Pregnant Patient

Asthma, pulmonary embolism, and infections such as tuberculosis are not uncommon in the pregnant patient. It is important that the pulmonologist be aware of the management of these conditions in pregnancy, including the acceptable pharmacologic treatments.

Food and Drug Administration Drug Classification

Acceptable pharmaceutical agents in pregnancy have been classified by the Food and Drug Administration (FDA). A category A drug means that well controlled drug studies in pregnant women have failed to demonstrate any risk to the fetus, and the possibility of fetal harm appears remote. A category B drug indicates that animal drug studies have shown that there was no demonstrated fetal risk, but controlled drug studies have not been performed in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in studies conduced in pregnant women. A category C agent is a drug for which studies in animals have revealed adverse effects on the fetus, including teratogenicity, and there are no controlled studies in women; or that studies in women and animals are not available. These drugs can be used if the potential benefit of the drug outweighs the potential risk to the fetus. A category D agent is where drug studies have shown positive evidence of human fetal risks, but in certain situations these drugs may be of benefit if the risk is outweighed by potential gain. Category X agents are where drug studies in animals or humans have demonstrated fetal abnormalities and/or there is evidence of fetal risks based on human experience and clearly the risk outweighs the benefit of the drug (e.g., thalidomide).

Asthma

Of the approximate 10 to 12 million asthmatics in the United States, a significant number are of childbearing age. Asthma affects up to 7% of pregnant women.[1] Poorly controlled asthma can result in small but increased risks of preterm labor and birth, pre-eclampsia, congenital anomalies, and intrauterine growth retardation, as well as increased maternal morbidity, such as placenta previa. General medical teaching states that one third of asthmatics get worse during pregnancy, one third improve and have less frequent asthma exacerbations, and approximately one third have no change in the frequency or severity of asthma. The best predictor of asthma severity in pregnancy is the severity of asthma in the nonpregnant state and the course of asthma in prior pregnancies. Asthma tends to be less severe in the first and latter third trimesters and worse in the middle of pregnancy (gestational weeks 29-36). Asthma may also worsen during delivery and in the postpartum period. Gastroesophageal reflux leading to worsening asthma should be carefully evaluated in the pregnant asthmatic.

The treatment of chronic asthma in pregnancy is similar to that of the nongravid asthmatic. In 1993, the National Asthma Education Program sponsored by the National Heart, Lung and Blood Institute developed guidelines for the treatment of the pregnant asthmatic.[2] A more recent consensus statement on this subject was published jointly by the American College of Allergy, Asthma, and Immunology and the American College of Obste-

tricians and Gynecologists.[3] In general, asthmatic patients well controlled on an appropriate medical regimen prior to pregnancy can remain on this regimen if control is acceptable during pregnancy.

Short-acting selective β_2-agonists are indicated for intermittent asthma. These are category C agents. Cromolyn is the preferred recommended agent for initiating treatment for mild persistent asthma in the pregnant patient. Patients managed on nedocromil can remain on this agent. Both are category B agents. Inhaled corticosteroids can be substituted if these agents are not adequate. Beclomethasone and budesonide are the best studied and, therefore, are the preferred agents. The former is a category C and the latter is a category B agent. Patients with moderate persistent asthma should be placed on inhaled beclomethasone or budesonide with salmeterol or oral theophylline added if not well controlled despite a regimen of medium-dose inhaled corticosteroids. Patients already maintained on other inhaled corticosteroids can be continued on those agents. All other inhaled corticosteroids are category C agents. Patients maintained on salmeterol for control of moderate persistent asthma prior to pregnancy can remain on this agent. Salmeterol has not been well studied in pregnancy and is listed as category C.

Systemic corticosteroids (category C) can be used for control of severe and acute asthma. Earlier studies raised the concern of increased risk of prematurity and low-birth-weight infants with the use of systemic corticosteroids, but this may have been related to the severity of asthma in these patients rather than the medications used. Other studies have shown a 3.5% incidence of congenital malformations, an increased incidence of cleft palate, and increased risk of pre-eclampsia with the use of systemic corticosteroids. Patients on systemic corticosteroids require careful evaluation for gestational diabetes. In the steroid-dependent asthmatic, stress-dose corticosteroids should be administered during labor and delivery.

Theophylline (category C) has been used safely in pregnancy, although clearance in the third trimester may be reduced, and there is decreased protein binding of the drug. There are little data examining the use of leukotriene receptor antagonists during pregnancy, but montelukast and zafirlukast can be used in patients demonstrating prior response to these agents. Both are listed as category B agents. Zileuton (category C) has been associated with teratogenicity in animals and should be avoided. Terbutaline and other parenteral β-agonists given near term can cause tocolytic pulmonary edema and are often avoided, although terbutaline is a category B agent. Prostaglandin F2α used for uterine atony should be avoided in asthmatics since it can cause bronchoconstriction.

Management of acute asthma and status asthmaticus is the same as in the nonpregnant asthmatic. For acute asthma, anticholinergic agents are also permissible (category B). Based on the normal compensated respiratory alkalosis of pregnancy, when evaluating the pregnant asthmatic in the midst of an acute episode, a $PaCO_2$ of 35 mm Hg could indicate fatigue and impending ventilatory failure. Intubation should be considered with a $PaCO_2$ in the range of 42 mm Hg consistently, as this relative acidosis places the fetus at risk. Heliox has been used for the treatment of status asthmaticus. Epinephrine is not recommended for use during pregnancy because of concern for uteroplacental vasoconstriction.

Venous Thromboembolism in Pregnancy

Pulmonary embolism (PE) is a leading cause of non-obstetric maternal mortality. Some studies have suggested that PE can account for 20% to 50% of maternal deaths. The spectrum of venous thromboembolism (VTE) can affect 0.05% to 0.1% of pregnancies. Although earlier studies suggested an increased incidence of deep venous thrombosis (DVT) in the third trimester and postpartum period, subsequent studies have supported an equal distribution of DVT throughout pregnancy and suggest that DVT may be as common or more common antepartum as postpartum.

Pregnant women are at increased risk of VTE during pregnancy due to a combination of all three components of Virchow's triad. There is increased venous stasis, hypercoagulability, and endothelial disruption of pelvic and uteroplacental vessels during delivery. The hypercoagulability in pregnancy is due to alterations in levels of clotting factors (increases in fibrinogen, factors I, II, VII, VIII, IX, X, and XII), possibly decreased fibrinolytic activity, and a progressive increase throughout pregnancy of activated protein-C resistance. The increase in venous stasis is mechanical, due to reduced venous flow in the lower extremity and pelvic vessels from the compression of the inferior vena

cava (IVC) by the gravid uterus, and there is an interesting predominance of left lower extremity DVT (~90%), likely due to greater compression of the left iliac vein by the right iliac artery. There is also a predominance of iliofemoral DVT that are more likely to embolize. Other risk factors for VTE in pregnancy include prolonged bed rest, caesarean delivery, pre-eclampsia, advanced maternal age, obesity, multiparity, prior VTE, and thrombophilia. Despite the increased risks of VTE, an episode of thrombosis during pregnancy should still prompt a thrombophilic evaluation.

The most commonly used diagnostic test for determining DVT in pregnancy is Doppler ultrasound, although test results may be impaired, and false-positive results can occur. Additionally, problems such as difficulty in detecting iliac, pelvic, and calf thromboses exist. The sensitivity and specificity of this study may be improved when performed in the left lateral decubitus position. Impedence plethysmography in pregnancy is associated with a high false-positive rate. Venography (<50 mrads fetal exposure) remains the gold standard test for the diagnosis of DVT, but is rarely used.

The diagnosis of a suspected PE in pregnancy is similar to that in the nonpregnant individual. Ventilation/perfusion scanning can be used (6-30 mrads fetal exposure); however, a smaller dose of radioisotope is recommended, and when possible, the perfusion scan should be performed without the ventilation scan to further minimize radiation exposure. There are limited data evaluating the role of CT angiogram for the diagnosis of PE in the pregnant patient, but it appears safe when conducted with abdominal shielding. Pulmonary angiography should be used when indicated as the gold standard test for the diagnosis of PE (<50 mrads fetal exposure for a brachial approach and 220-375 mrads for a femoral approach).

There are several important caveats to treating VTE during pregnancy, and this topic is included in the recent ACCP consensus conference on anticoagulation.[4] Heparin is the anticoagulant agent of choice for both treatment and prophylaxis during pregnancy since it does not cross the placenta, and unfractionated heparin (UFH)(category C) or low-molecular-weight heparin (LMWH) (category B) can be safely used. For treatment of VTE, UFH can be begun intravenously for 5 days, followed by adjusted dose UFH subcutaneously to maintain the APTT in therapeutic range, or low-molecular-weight heparin at full weight-adjusted doses can be used. Some authors suggest that anti-Xa levels, rather than APTT, should be used to monitor full dose heparin anticoagulation due to alterations in fibrinogen and Factor VIII that can make APTT results less reliable. High doses of unfractionated heparin may be required. Anticoagulation should be continued throughout pregnancy and 4-6 wks postpartum to complete a total of 3 months of anticoagulation. Warfarin can be safely used in the postpartum period.

One should be aware of the significant complications with prolonged heparin use, including heparin-induced thrombocytopenia. Osteoporosis can also be a complication in patients on long-term therapy with heparin. LMWH may be associated with a lower incidence of osteoporosis and heparin-induced thrombocytopenia. Heparinoids can be used in cases of heparin-induced thrombocytopenia.

Warfarin (category X) crosses the placental barrier, particularly between 6-10 gestational weeks and is associated with poor fetal epiphyseal cartilage formation, chondrodysplasia, and fetal nasal hypoplasia. CNS abnormalities have also been described, including malformations, optic atrophy, and microhemorrhages, with warfarin use at any time during pregnancy. The use of warfarin is permissible during lactation. Following an episode of VTE, anticoagulation should be continued with warfarin for 4-6 wks after delivery or to complete 3 months of anticoagulation.

Thrombolytic agents are relatively contraindicated during pregnancy, especially near term and within 2 wks postpartum due to the risk of hemorrhage. However, published case reports of successful use exist. Inferior vena caval filter placement can be performed, although suprarenal placement is recommended, because the left ovarian vein empties into the left renal vein.

The management of labor and delivery in the fully anticoagulated patient can be difficult. Epidural anesthesia should be used with caution in fully anticoagulated patients since epidural hematomas may result. High-risk patients for VTE should be switched to UFH at least 24 h prior to expected induced delivery in order to safely discontinue anticoagulation 6-8 h prior to expected delivery. Those patients at lower risk of VTE on LMWH or UFH should have their anticoagulation stopped 24 h prior to elective induction.

The indications for prophylaxis for VTE in pregnancy are the same as those in the nonpregnant individual with some of the following specific recommendations.[4] Those patients with a history of a single prior VTE related to a clear transient risk factor, but not with additional risk factors other than pregnancy currently, should undergo close surveillance during pregnancy and anticoagulation in the 4- to 6-wk postpartum period. Those patients with a prior history of idiopathic VTE, and those with thrombophilia with or without a prior VTE, should undergo close surveillance or prophylaxis with UFH or LMWH during pregnancy and anticoagulation in the 4- to 6-wk postpartum period. Those patients with any type of thrombophilia are at increased risk for VTE in pregnancy, but patients with antithrombin deficiency are particularly at risk for VTE and should undergo active prophylaxis and postpartum anticoagulation. Many authors suggest that patients with a history of VTE in a prior pregnancy should be prophylaxed for VTE in subsequent pregnancies, as the recurrence rate can be as high as 12%. Patients with a history of two or more episodes of VTE should be anticoagulated during pregnancy and converted to long-term anticoagulation postpartum. Patients requiring long-term warfarin anticoagulation prior to pregnancy should be converted to UFH or LMWH when pregnancy is planned or as early in pregnancy as possible if not planned. Reference 4 contains specific recommendations for unique situations, such as mechanical heart valve patients.

UFH or LMWH heparin is the agents of choice for prophylaxis, used at prophylactic doses of mini-dose UFH (5,000 U subcutaneously q 12 h) or moderate dose UFH (subcutaneously q 12 h following anti-Xa levels) or prophylactic LMWH (subcutaneously q 24 h following peak anti-Xa levels).

Tuberculosis in Pregnancy

With increases in the rates of tuberculosis (TB) in the United States, largely due to increases in HIV infection and increases in foreign-born immigrants, there has been an increase in TB cases in childbearing adults and children. The actual incidence of TB in pregnancy is not completely clear, but can be in the range of 1% in poverty-stricken inner city areas with poor access to prenatal health care. The prognosis of TB in pregnant females has been debated. At one time, it was thought that TB had an increased incidence of dissemination in the pregnant female. Most recent data support that there is no difference in the susceptibility to infection, course of disease, obstetrical outcome, prognosis, and incidence of TB in nonpregnant or pregnant individuals, unless immunosuppression coexists.

Treatment of active tuberculosis in pregnancy is similar to that of treatment in the nonpregnant individual with a few caveats.[5] Drugs approved in pregnancy include isoniazid (INH), rifampin, and ethambutol. These drugs all cross the placenta but have not been shown to have teratogenic effects. In general, pyrazinamide, streptomycin, and ethionamide should be avoided in pregnancy. There are situations in which treatment with these other drugs may outweigh the potential risks of using these agents. The teratogenicity of streptomycin is primarily fetal ototoxicity due to nerve damage, congenital auditory malformations, and/or congenital deafness. Pyrazinamide has been avoided traditionally since it has not been well studied in pregnancy. Thus, standard treatment for active TB in an area without suspected INH resistance should include INH and rifampin for 9 months. If in a potentially INH-resistant area, then INH, rifampin, and ethambutol should be begun for at least 9 months or longer, depending on results of susceptibility testing. These same drugs can be continued during lactation without compromise to the infant. INH resistant cases can be treated with rifampin and ethambutol. Multidrug-resistant cases may have to consider therapeutic abortion. It is standardly recommended that pyridoxine always be administered with INH during pregnancy to decrease the incidence of INH neurotoxicity (optic and peripheral neuropathy).

Chemoprophylaxis for latent tuberculous infection (LTBI) is somewhat more controversial.[6] Since it appears that pregnancy does not increase the risk of developing active TB in patients with LTBI, many healthcare workers would delay prophylactic treatment until after delivery in a patient with a clear chest radiograph, and who is HIV-negative, not a recent converter, and not in another high-risk group. However, most authorities recommend 9 months INH prophylaxis, if the patient falls in a high-risk LTBI group. Routine PPD testing during pregnancy has fallen out of favor at most medical centers, unless in an endemic TB area, or unless the patient is in a high-risk group such as those with HIV infection.

Children <5 years of age with LTBI are at high risk of progression to disease and/or developing more severe and/or disseminated disease, and require 9 months of INH prophylaxis. If a child is exposed to a mother with active TB, then the child should be separated from the mother (only until the mother is deemed noncontagious) undergo PPD skin testing, and a chest radiograph, and be placed on INH therapy for 8-12 wks even if the skin test is negative. At that time, the PPD should be repeated. If the PPD remains negative, then INH can be discontinued and, if positive, then 9 months of INH prophylaxis should be completed.

Pneumonia in Pregnancy

In general, the incidence of bacterial pneumonia in the pregnant woman is similar to that in the nonpregnant individual. Pneumonia may complicate 1.2 to 2.7 per 1000 deliveries and may be more frequent in inner cities. Preterm labor, preterm delivery, and respiratory failure can result. Maternal mortality can be as high as 4%.

Several small epidemiologic studies examining the bacterial organisms responsible for community-acquired pneumonia in the pregnant patient show the spectrum to be similar to that in the nonpregnant woman and similar empiric therapies can be used. The cephalosporins and penicillins can be safely used in pregnancy (all are category B). Quinolones are category C agents. The macrolides are category B and C agents. The tetracyclines are category D agents and should be avoided. The sulfonamide drugs are category C agents and are usually reserved for infections such as Pneumocystis pneumonia.

A few specific organisms responsible for pneumonia in pregnancy deserve mention. In pregnancy, cell-mediated immunity may be altered and, thus, infections with fungal and viral organisms can be more severe and life-threatening. The risk of dissemination with coccidioidomycosis, as well as mortality, is likely increased during pregnancy (20% vs 0.2% in the nonpregnant individual), although this has not been borne out consistently in all studies.[7] It is generally thought that dissemination is more likely if the infection is acquired in the third trimester. Treatment includes amphotericin or a liposomal derivative. Both agents are category B agents. The majority of the azoles are classified as category C.

Of the viral agents, *Varicella zoster* is the most feared during pregnancy. Although this illness is usually self-limited and benign in children, in the nonexposed adult pregnant patient, the mortality rate associated with varicella pneumonia may approach 35%. Infection is most severe in the third trimester. Patients present with fever and rash, and can rapidly progress to pneumonia. A typical chest radiograph shows miliary and nodular infiltrates, usually resolving within 14 days. The end radiographic result of such pneumonia is often calcified, but physiologically insignificant, nodules. Acyclovir (category B) can be safely used during pregnancy and should be begun with the first sign of Varicella infection.

Influenza virus can also be more severe during pregnancy, although more recent data support the fact that mortality associated with influenza during pregnancy is similar to that of the nonpregnant woman. The anti-influenza drugs are category C agents. Influenza vaccine is made from inactivated virus. Women at high risk should be immunized for influenza during pregnancy regardless of the stage of pregnancy. All other pregnant women should be vaccinated after the first trimester.

Acute Respiratory Failure in Pregnancy

Hemodynamics

As pregnancy progresses, cardiac output can become positionally dependent due to the gravid uterus potentially obstructing the inferior vena cava (IVC) and reducing venous return. This is particularly true in the third trimester and is most notable in the supine position. Severe hypotension can result. This effect is reduced in the full or partial left lateral decubitus position, allowing the uterus to be displaced from the IVC. This can be an important factor in the resuscitation of the hypotensive pregnant patient. Due to low colloid oncotic pressure, invasive monitoring with pulmonary artery pressures may have to be interpreted with caution and pulmonary edema can result at a lower pulmonary artery occlusion pressure.

Sepsis

In addition to nonobstetrical-related causes of sepsis in the pregnant patient, sepsis can re-

sult from endometritis, pelvic thrombophlebitis, and septic abortion and from procedures such as amniocentesis, and/or infection of caesarean or episiotomy incisions. It is important to recall that baseline hemodynamic parameters in a nonseptic pregnant individual, *ie*, high cardiac output and low systemic vascular resistance, can be confused with the hemodynamics of sepsis.

Mechanical Ventilation

The principles of mechanical ventilation in the pregnant patient are similar to those in the nonpregnant individual. Intubation may be more difficult due to edema of the upper airway, a reduced airway caliber, and an increased risk for aspiration and bleeding, and smaller endotracheal tubes may be required. Tidal volumes may have to be reduced due to reduced chest wall compliance from the gravid uterus, and higher peak pressures may be required to overcome chest wall stiffness. Gas exchange goals should be to maintain $PaCO_2$ in the pregnant eucapnic range of 28-32 mm Hg with a PaO_2 >90 mm Hg to prevent fetal hypoxemia. A further reduction in $PaCO_2$ can lead to reduced uterine blood flow and fetal hypoxemia. The fetus is very sensitive to hypoxemia and attempts to compensate for maternal hypoxia by divergence of maternal blood flow to essential tissues, a leftward shift in the oxyhemoglobin dissociation curve, and high avidity of fetal hemoglobin for oxygen.

Noninvasive mechanical ventilation has not been well studied in pregnancy, but its utility may be limited by the increased risk of aspiration and narrow airway caliber in this population.

Amniotic Fluid Embolism

Amniotic fluid embolism (AFE) is a rare but catastrophic complication of pregnancy. The incidence of AFE ranges between 1 in 8,000 and 1 in 80,000 pregnancies, with an associated 80% to 90% mortality. AFE is responsible for 10% to 20% of maternal deaths in the peripartum period. Risk factors for AFE include advanced maternal age, multiparity, premature rupture of membranes, and meconium staining of amniotic fluid. The use of uterine stimulants and tumultuous labor may also be risk factors. The risk of AFE extends 48 h into the immediate postpartum period and has also been reported to develop during abortions and placental abruption. The pathophysiology of AFE is not completely known, but postulated mechanisms include true mechanical obstruction of the pulmonary vasculature with fetal squamous cells and other debris, alveolar capillary leak due to a release of mediators during delivery, pulmonary edema due to left ventricular failure, and an anaphylactic reaction to exposure of the mother to fetal antigens.

Amniotic fluid embolism presents catastrophically with the acute onset of tachypnea, dyspnea, tachycardia, cyanosis, hypotension, hypoxemia likely due to ventilation/perfusion abnormalities, and hemodynamic collapse. Seizures can occur. Disseminated intravascular coagulation can develop in 40% to 80% of patients, and hemorrhage can be the initial presentation. The majority (70%) of those patients who survive the initial event will develop the acute respiratory distress syndrome (ARDS). This is often followed by some transient left ventricular dysfunction, as supported by studies using pulmonary artery catheters.

The diagnosis of AFE is one of exclusion, but can be supported in the appropriate clinical setting with the presence of fetal squamous cells and lanugo hairs in the maternal circulation, although these can also be present under normal conditions and are not pathognomonic for this diagnosis. Treatment is supportive with intubation, mechanical ventilation, vasopressors, sedation, neuromuscular blockade, and pulmonary artery catheter placement. Factor replacement may be required for hemorrhage.

Venous Air Embolism

Venous air embolism can occur during normal delivery, with placenta previa, and during abortion. It has also been reported during oral genital sex and during gynecological procedures using air insufflation. One percent of maternal deaths are thought to be from venous air embolism. The usual sites of air entry are at the subplacental venous sinuses, during the antepartum or peripartum period, followed by entry into the venous circulation. In the right ventricle, air can obstruct the pulmonary blood flow, resulting in cardiopulmonary collapse. In general, it is thought that 100 mL of air can lead to mortality. Recruitment and activation of neutrophils, protein aggregation at the turbulent air blood interface and obstruction of pulmonary arterial vessels by microemboli also contribute to the pathophysiology of venous air embolism.

Patients with venous air embolism present with profound hypotension, as well as nonspecific signs of coughing, dizziness, tachypnea, dyspnea, tachycardia and diaphoresis. Respiratory arrest soon follows, and mortality can rise to 90%. The classic but rarely heard cardiac mill-wheel murmur audible over the precordium is supportive of the diagnosis of venous air embolism. ARDS may develop. Other findings include mental status changes, coma, seizures, stroke, myocardial infarction, and thrombocytopenia. Bubbles may be visualized in the retinal arterioles and subdermal air may be present. Air in the heart or great vessels is occasionally seen on chest radiograph.

Treatment includes recognition of the syndrome, followed by placing the patient in the left lateral decubitus position so that the air bubble is removed from the entrance to the right ventricular outflow tract. Cases of aspiration of air from the right heart using a pulmonary artery or central venous catheter have been reported. Patients should be ventilated with 100% oxygen to facilitate removal of nitrogen, which comprises a significant (up to 80%) of gas content in the embolus. There are anecdotal reports of using heparin to treat microemboli and corticosteroids to decrease pulmonary edema in this syndrome.

Tocolytic Pulmonary Edema

Until recently, β-adrenergic agents were widely used in obstetrics for inhibition of preterm labor often administered in combination with corticosteroids to promote fetal lung development. The most common agents used were β_2 selective agents such as terbutaline, ritodrine, and isoxsuprine, and as many as 4% to 5% of patients receiving these agents developed tocolytic pulmonary edema. Currently, many obstetricians use magnesium for treatment of preterm labor, which has resulted in a decrease in this problem.

Usually, symptoms of tocolytic pulmonary edema develop within 24 h, but occur more commonly 48 h after initiation of therapy, and can also develop within 24 h after discontinuation of the drug. Those patients who receive prolonged tocolytic therapy with concomitant infusions of crystalloid volume, those with multiple gestations, and those with pre-eclampsia are more at risk for development of tocolytic pulmonary edema. The mechanisms of tocolytic pulmonary edema include possible fluid overload, direct cardiac toxicity, alterations, and reductions in colloid oncotic pressure and/or increased pulmonary capillary permeability.

Tocolytic pulmonary edema presents typically with dyspnea, tachycardia, tachypnea, chest pain, crackles and the presence of pulmonary edema on chest radiograph. This syndrome reverses quickly, usually 12-24 h after recognition and discontinuation of the offending agent. The prognosis is excellent. Transient use of oxygen and diuretics may be needed.

Aspiration

Aspiration historically has been a significant problem in obstetrics and is estimated to account for 2% of maternal mortality in the United States. The classic description was made by Mendelson (in 1946) who described large volumes of gastric contents entering the tracheobronchial tree in women undergoing labor and delivery. Because of this large volume of aspiration of low pH containing gastric contents, ARDS and chemical pneumonitis subsequently developed. Immediate asphyxia was also described.

The obstetrical patient is at risk for aspiration for many reasons including progesterone-induced relaxation of lower esophageal sphincter tone, an increase in intragastric pressure due to mechanical compression by the gravid uterus, as well as by frequent exams, a decrease in gastric emptying during parturition, and being in the supine position. In some cases, alterations in mental status due to sedation, and a reduction in vocal chord closure possibly related to analgesia used during labor, may also contribute to an increased risk of aspiration.

There is a correlation between the volume of gastric contents aspirated, the acidity of the aspirate, the presence of particulate matter, the bacterial load, and the host resistance on the progression and severity of clinical symptoms. It is thought that the low pH (<2.5) of the aspirate is the major inciting pathogenic process for disease due to a chemical pneumonitis, although large volumes, particularly those containing food particles, can be clinically significant even with higher pH levels. ARDS can result. A small subgroup of patients will have immediate respiratory arrest and death following aspiration due to uncorrectable hypoxemia. In those cases in which small volumes of gastric contents

are aspirated, symptoms may be delayed until 6-24 h following the event. Bacterial pneumonia can develop 24-72 h after the aspiration.

Treatment is supportive. As in the nonpregnant patient, there is no role for prophylactic antibiotics or corticosteroids when treating this aspiration syndrome. Resolution usually occurs over the next 4-5 days unless secondary superinfection develops. Bronchoscopy may be indicated when witnessed aspiration with large food particles has developed. The chances of aspiration can be reduced by the use of regional anesthesia, restricting oral intake at the time of delivery and cricoid pressure if endotracheal intubation is required.

Acute Respiratory Distress Syndrome

ARDS is defined similarly in the pregnant as in the nonpregnant individual. In addition to the causes of ARDS discussed elsewhere in this course, there is a long list of ARDS etiologies unique to or associated with pregnancy. These include: placental abruption, air embolism, amniotic fluid embolism, aspiration, eclampsia, septic abortion, and the dead fetus syndrome.

Pulmonary Edema

Pulmonary edema can accompany pre-eclampsia/eclampsia in about 3% of cases. Pulmonary edema may develop more frequently in the immediate postpartum period. Risk factors include advanced age and multigravity. Mechanisms for preeclampsia-related pulmonary edema include: increased left ventricular afterload, myocardial dysfunction, the alterations in colloid oncotic pressure discussed earlier, as well as fluid overload. There may also be a component of increased pulmonary capillary permeability. Management is approached in the standard manner with oxygen, diuresis, control of hypertension, and mechanical ventilation, if required. Invasive hemodynamic monitoring may be required.

Peripartum Cardiomyopathy

Pregnancy-related cardiomyopathy can develop in 1 in 1300 to 1 in 4000 deliveries and usually presents in the third trimester or up to 6 months postpartum. Risk factors include advanced age, multiple gestations, pre-eclampsia, and African-American race. Patients typically present with dyspnea, orthopnea, peripheral edema, pulmonary edema, tachycardia, and a cardiac gallop. The chest radiograph shows cardiomegaly and pulmonary edema, and echocardiography demonstrates global hypokinesis. Prognosis is variable and approximately 30% of these patients recover, 30% may have residual cardiac damage, and 30% may require heart transplantation. The cause of death is often thromboembolism from left ventricular thrombus. The recurrence of cardiomyopathy with subsequent pregnancies is common.

Primary Pulmonary Hypertension

Patients with pulmonary hypertension (PH), either secondary or primary, are at increased risk for maternal (35%-50%) and fetal mortality during pregnancy. The risk appears to be greatest in the immediate peripartum period when a large amount of blood volume is "autotransfused" from the uteroplacental bed back to the maternal circulation. Acute right heart failure can result. Patients with primary pulmonary hypertension should be counseled against pregnancy and encouraged to seek termination of pregnancy and permanent forms of birth control. Those patients wishing to continue with their pregnancy should be managed with medications such as inhaled nitric oxide and/or intravenous or inhaled prostacyclin during the peripartum period. Placement of a pulmonary artery catheter should be strongly considered during delivery.

Tobacco and Lung Disease in Women

Tobacco

At the end of the 19th century and beginning of the 20th century, cigarette smoking and tobacco use were limited primarily to males and were thought to be socially unacceptable for women. However, in the early 20th century with the advent of suffragism, numerous ad campaigns promoted the use of tobacco by women, including well known advertisements by brands such as Virginia Slims with the famous slogan "You've come a long way, baby." Tobacco smoking began to be associated with the educated and/or liberated American woman, a concept further promoted by the advertising of the tobacco industry. The use of tobacco products

by women increased dramatically following World War II and peaked in 1965 when the prevalence of smoking among women approached 35%. Currently, 21.3% of women and 25.5% of men smoke.

The initial 1964 landmark U.S. Public Health Surgeon General's Report on Smoking and Health primarily addressed smoking and respiratory health in men. However, in 1980, the Surgeon General's Report on the Health Consequences for Smoking for Women was released. This report concluded that women demonstrate the same dose-response relationships with cigarette smoking as do men, and that the risk of lung cancer increases with the increasing number of cigarettes smoked per day; earlier ages of cigarette smoking; longer duration of smoking; higher tar and nicotine content of cigarettes, and inhalation of cigarette smoke. The study predicted that mortality rates in women from lung cancer may be comparable to that experienced by men, that there would be a rapid increase in lung cancer rates in women similar to that seen in men 25 years previously, and that lung cancer death rates in women would surpass those of breast cancer by the early 1980s. The study also found that the incidence of other respiratory conditions such as influenza was 20% higher in ever smoking than in nonsmoking women, that there was an increase in death rates due to chronic obstructive pulmonary disease (COPD) in smoking women compared to nonsmoking women, and that this death rate correlated with the number of cigarettes smoked. Finally, the study concluded that women smokers had worse pulmonary function than ex-smokers or never smokers and that the severity of decrease in pulmonary function was dose-related to the number of cigarettes smoked.

The follow-up 2001 Surgeon General Report on Women and Smoking[8] found the following: a) that in 1998, 22% of women smoked cigarettes, b) lung cancer is the leading cause of cancer deaths in women, and 90% of these are related to smoking, and c) in 2000, 25% of cancer deaths in women were due to cancer of the lung. The study also stated that the risk of lung cancer increases with quantity, duration, and intensity of smoking.

Lung Cancer

Lung cancer has become the leading cause of cancer deaths in both men and women in the United States, surpassing death rates in women due to breast cancer in 1987. Twenty-five percent of cancer deaths in women are due to cancer of the lung. Although breast cancer affects a large number of women per year, lung cancer has a significantly worse prognosis with higher mortality rates. In 1998-1999, 68,000 women died of cancer of the lung and bronchus as compared to 43,300 deaths due to breast cancer. Lung cancer incidence rates in women appear to be leveling off from the mid-1990s to early 2000; however, death rates in women from lung cancer continue to rise and have not yet reached the plateau seen in men in the 1980s. Over 80% to 90% of lung cancers in women are related to tobacco use and are thus preventable.

Of the different cell types, adenocarcinoma is the most common cell type of lung cancer in both smoking and nonsmoking women. A possible increase in the susceptibility of tobacco carcinogens in women has been a highly debated topic. Some studies have indicated that there is an increase in the relative risk of developing lung cancer in smoking women than in men; other studies have not been able to support this. Yet, other studies have shown that there is an increased odds ratio of tobacco-related lung cancer in women only for some certain types of lung cancer. For example, it appears that smoking women have a higher odds ratio of developing small cell carcinoma than do men. There are many postulated reasons as to why women may have an increased susceptibility to tobacco carcinogens, including the fact that there may be an increased frequency of mutations in the P53 tumor suppressor gene in women than in men, and a higher pro-mutagenicity DNA level has been observed in women. In addition, hormonal replacement may play a role in the variable susceptibility to tobacco carcinogens, particularly with adenocarcinoma. Other risk factors for lung cancer in women include a family history of lung cancer, occupational exposures to compounds such as asbestos, cadmium, beryllium, silicosis, radon, and prior lung disease as are found in men.

Chronic Obstructive Pulmonary Disease

Cigarette smoking is the major cause of COPD in women, and the risk increases with the amount and duration smoked. Ninety percent of mortality among women in the United States is attributable to smoking. Mortality rates attributable to COPD among men now appear to be plateauing, whereas

COPD mortality rates among women continue to rise. This parallels the trends previously discussed in lung cancer. Because the slope of this curve is steeper than that seen in men, it is possible that women are more vulnerable to tobacco-induced COPD. Studies in these regards have been conflicting; some indicating women with exposure to tobacco smoke develop more severe COPD with fewer pack years of tobacco use than do men.

In children who have prenatal exposure to environmental tobacco smoke from a smoking mother, studies have shown that fetal lung development is affected. These children have more airway obstruction, increased airway hyperresponsiveness, and alterations in lung maturation and lung growth. There is a small decrement in birth weight and increased risk of intrauterine growth retardation and other obstetrical complications. Those children exposed to environmental tobacco smoke in the postnatal period have an increased incidence of cough, wheezes, respiratory illnesses, and infection. Pulmonary function is decreased slightly and there is an increase in airway responsiveness. These children tend to have an increase in childhood asthma, develop asthma earlier, and may develop more severe asthma. Other studies have shown that children exposed to environmental tobacco smoke tend to develop atopy that can result in worsening asthma. There have also been correlations found between environmental tobacco smoke and obstructive apnea in children and sudden infant death syndrome in infants.

Catamenial Pneumothorax and Hemoptysis

Catamenial complications by definition develop during menstruation. Catamenial pneumothorax occurs very rarely and is usually recurrent. Patients are usually in their late 20s to over 30 years of age when they initially present. Symptoms develop within 24-48 h of the onset of menstrual flow. The pneumothoraces are often on the right side and are often associated with pelvic endometriosis. The mechanisms of air entry into the pleural space may be due to a defect at the site of pleural or diaphragmatic endometriosis or may be by air gaining access to the peritoneal cavity during menstruation and then subsequently entering the pleural cavity through a diaphragmatic defect. The diagnosis is fairly straightforward when a pneumothorax develops during the first 48 h of menstrual flow. Treatment includes ovulation-suppressing drugs. Patients wishing to conceive or who do not want ovulation suppressed should undergo thoracotomy with repair of diaphragmatic defects, if present, followed by pleurodesis.

Catamenial hemoptysis is thought to occur due to endometriosis in the lung parenchyma. It is usually a cause of scant hemoptysis but can, in some cases, be severe. Treatment includes hormonal suppression and/or resection of lung parenchyma involved with endometriosis.

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Notes