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The Management of Respiratory Infections During Pregnancy

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Respiratory infections that complicate pregnancy are encountered frequently, and they encompass a broad range of disorders. Although respiratory infections usually are not seen more commonly in pregnancy, they often result in greater morbidity and mortality secondary to the physiologic adaptations that occur during pregnancy. Pregnant patients who have one of these disorders require a higher level of surveillance and intervention.

Pulmonary physiologic adaptations during pregnancy

Pulmonary physiologic changes during pregnancy are discussed in detail elsewhere in this issue. As with many of the other organ systems, the respiratory system undergoes several adaptations during pregnancy. Tidal volume increases although the respiratory rate remains unchanged which results in an increase in minute ventilation that up to 50% higher than in nonpregnant women [1–5]. Minute oxygen uptake also increases, and allows for the increasing oxygen requirements as the pregnancy advances. There is no change in forced vital capacity, lung compliance, or diffusing capacity; however, functional residual capacity decreases by 15% to 20% at term. Total pulmonary resistance also decreases during pregnancy, possibly because of an increase in progesterone levels. Although overall hemoglobin amount increases and allows for an increase in total oxygen-carrying capacity, the increase in blood volume—which is disproportionate to the increase in hemoglobin concentration—results in a physiologic anemia that

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decreases the arterial oxygen content by a small amount in the third trimester [6]. Finally, the diaphragm is elevated as much as 4 cm in pregnancy, and the transverse chest diameter increases 2.1 cm [7].

Sinusitis

Acute bacterial sinusitis is an infection of the mucosa of the paranasal sinuses and nasal cavity, and it develops most commonly as a complication of a viral upper respiratory infection. It is one of the most common diseases in the outpatient clinical setting, with annual costs of more than $2 billion in the United States [8]. Acute viral sinusitis is common and usually resolves without treatment; however, bacterial sinusitis complicates viral sinusitis in 0.5% to 2% of cases [9,10], and requires antimicrobial therapy to prevent complications. Distinguishing between viral and bacterial sinusitis can be difficult.

Sinusitis develops when there is inflammatory edema of the sinus mucosa, obstruction of the sinus ostia, and decreased mucociliary activity [9]. This stasis provides a milieu that is conducive to bacterial growth. Common bacterial pathogens that are associated with acute bacterial sinusitis include *Streptococcus pneumoniae*, *H influenzae*, *Streptococcus pyogenes*, *Neisseria* species, *Moraxella catarrhalis* (more common in children), *Staphylococcus aureus*, and some anaerobic bacteria. Fungal sinusitis, primarily aspergillosis, also should be considered, particularly in women who have a history of immunoincompetence. Risk factors for the development of acute bacterial sinusitis include a history of allergic disorders; dental infections; anatomic abnormalities, such as a deviated septum, nasal polyps, or cleft palate; nasogastric or nasotracheal intubation; barotrauma; chemical irritants; cystic fibrosis; and immunodeficiency. Although one older study suggested an increase in the incidence of sinusitis during pregnancy [11], no recent data are available that address this issue.

Acute viral and bacterial sinusitis often present with nasal congestion, purulent nasal or postnasal discharge, sinus pain or pressure over the affected sinus, cough, sinus headache, fever, and malaise. To distinguish bacterial from viral sinusitis—a challenging, yet important, distinction because management varies—a person must have persistence of symptoms for longer than 7 to 10 days. A common finding when bacterial infection develops in the setting of viral sinusitis is a report of two phases with improvement in between—a ‘‘double sickening’’ sign. A change in color of nasal discharge from clear/yellow to greenish also is an indicator of progression to bacterial sinusitis. Transillumination of the sinuses and plain radiographs of the sinuses may help to confirm sinusitis, but they cannot distinguish between viral and bacterial sinusitis [12]. CT or MRI should be reserved for evaluation of complicated sinus cases.

Although uncommon, complications of acute bacterial sinusitis can be severe. Local extension of infection into the sinus bones, orbits, and intracranial cavity can occur as can central nervous system involvement (ie, meningitis, brain abscess, and cavernous sinus infection). Appropriate antimicrobial therapy

has decreased the incidence of these complications markedly over the last few decades.

After a diagnosis of acute bacterial sinusitis is made, antimicrobial therapy and systemic relief should be initiated. Analgesics and antipyretics; decongestants; and moisturization techniques, including nasal irrigation, steam inhalation, and warm packs are useful in providing relief. Recommended antimicrobial therapy to eradicate the bacterial pathogen varies among countries, depending on the common pathogens and patterns of antimicrobial resistance. In the United States [13], the American Academy of Otolaryngology-Head and Neck Surgery's Guidelines first line of treatment regimens include amoxicillin, amoxicillin–clavulanic acid, or a second-/third-generation cephalosporin. These are acceptable regimens in pregnancy and should be given for 10 to 14 days. In penicillin-allergic patients, a course of one of the macrolides, particularly azithromycin, is warranted. Macrolide resistance has become a major problem in many European countries and it is not recommended in these areas. Surveillance in the United States shows a lower rate of resistance, and macrolides remain an alternative first-line therapy for patients who have penicillin allergy. In penicillin-allergic patients, a course of trimethoprim–sulfamethoxazole also may be considered. Telithromycin, a new antibacterial ketolide with a low propensity for drug resistance, is as effective as any first-line agent and has limited side effects [14]. Listed as pregnancy Category C, no data are available regarding its use during pregnancy in humans. Alternative regimens for bacterial sinusitis listed in the American Academy of Otolaryngology—Head and Neck Surgery's Guidelines include the fluoroquinolones, but fluoroquinolones are not recommended during pregnancy and should be avoided if possible.

Bronchitis

Bronchitis is inflammation of the bronchial mucous membranes. Chronic bronchitis, defined as a productive cough for more than 3 months per year for at least 2 years, is a major part of chronic obstructive pulmonary disease and rarely complicates pregnancy. Acute bronchitis is associated with cough that develops during an upper respiratory tract infection that usually is viral in origin. Most cases of acute bronchitis are caused by rhinovirus, influenza, and adenovirus. Other causative organisms include *Mycoplasma pneumoniae* and *C pneumoniae*. Cigarette smoking is the predominant risk factor for chronic bronchitis, and may play a role in acute disease.

During an acute upper respiratory infection, a cough with occasional sputum production and low-grade fever may be present. Dyspnea is an uncommon symptom of acute bronchitis. Antibiotics are indicated rarely for acute disease, although they are prescribed frequently; symptomatic relief is paramount. Antibiotic use should be reserved for suspected bacterial etiology or for women who do not respond to symptomatic relief. Symptoms should resolve within a few days, al-

though the cough may persist for months. The management of chronic bronchitis is outside the scope of this article because it rarely complicates pregnancy.

Pneumonia

Pneumonia and influenza combined are the seventh leading cause of death in the United States, and the number one cause of death from an infectious disease [15]. More than 5 million cases occur annually, more than 1.3 million persons require hospitalization, and there were 22 deaths per 100,000 population in 2002 [15]. Although women of reproductive age have much lower mortality, they are susceptible to pneumonia from bacterial, viral, and fungal sources. Overall, pneumonia is the primary diagnosis for 4.2% of the antepartum admissions for nonobstetric causes [16]. Although pregnant women do not acquire pneumonia more often than do nonpregnant women, it can result in greater morbidity and mortality because of the physiologic adaptations of pregnancy.

Thus, pregnant patients require a higher level of surveillance and intervention. In a study by Jin and colleagues [17], the hospitalization rate for community-acquired pneumonia in pregnant women was 1.51 per 1000 pregnancies. Another recent report noted a prevalence of 1 per 660 deliveries [18] for community-acquired pneumonia.

Bacterial pneumonia

Some of the organisms that cause bacterial pneumonia include *Streptococcus pneumoniae*, *H influenzae*, *C pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila.* The American Thoracic Society notes that even with extensive diagnostic testing, the etiology cannot be identified in at least 50% of cases. A gram stain and culture of sputum can be helpful in focusing therapy, but its use is controversial. Bacterial cultures of sputum have poor sensitivity and specificity [19]. Of strains identified, *Streptococcus pneumoniae* is the most common, although the overall incidence is decreasing in women of reproductive age because of the improved use of pneumococcal conjugate vaccine. Drug-resistant strains of *Streptococcus pneumoniae*, particularly β-lactamase–resistant strains, are increasing in prevalence [20].

Mycoplasma pneumoniae is another major cause of bacterial pneumonia in young adults, and outbreaks are common in institutional-type settings (eg, college). Persistent cough is common but the disease rarely is fatal. The incidence of *C pneumoniae* pneumonia is unknown, although it is most common in school-aged children. Reinfection throughout life is common and occasionally it presents in pregnancy.

Risk factors for pneumonia include asthma and other chronic respiratory diseases, HIV/AIDS, smoking, and drug use [21]. Signs and symptoms of bacterial pneumonia in pregnancy are the same as in nonpregnant individuals. Symptoms include cough (>90%), sputum production (66%), dyspnea (66%),

and pleuritic chest pain (50%) [22]. Signs include fever, crackles, and abnormal breath sounds. A chest radiograph should be performed in patients who have the aforementioned findings and in whom pneumonia is suspected. The chest radiograph will confirm pneumonia, rule out other diagnoses, suggest a possible cause, and aid in determining the severity of illness. Multilobar pneumonia is considered a more severe process than is single lobar involvement [19]. Generally, all pregnant women who have pneumonia are hospitalized for observation and initial therapy. Work-up should include a complete blood count, electrolytes, assessment of oxygenation, and blood cultures; however, blood cultures are positive only 7% to 15% of the time [18,21].

Maternal mortality was reduced greatly with the advent of antibiotics [23,24]. Intravenous antibiotic therapy should be started empirically. Erythromycin monotherapy is an acceptable initial choice for treatment because it is considered safe in pregnancy [25]. Treatment success rates of up to 99% have been reported [18]. If aspiration, gram-negative organisms, or complications that are noted in Box 1 are suspected or identified, cefotaxime or ceftriaxone should be added to the erythromycin regimen. In endemic areas that are known to harbor drug-resistant *Streptococcus pneumoniae*, a course of fluoroquinolones may be required [26], although little information regarding the possible human teratogenicity is avail-

Box 1. Complicating factors that are associated with pneumonia

- Coexisting chronic conditions (eg, asthma, diabetes, heart disease)
- Altered mental status
- Vital sign abnormalities
  - Respiration $\geq$30/min
  - Temperature $\geq$39°C or $\leq$35°C
  - Hypotension
  - Pulse $\geq$125 beats per minute
- Laboratory abnormalities
  - White blood cell count <4000/uL or $\geq$30,000/uL
  - Room air Pa_{O_2} <60 mm Hg
  - Room air Pa_{CO_2} >50 mm Hg
  - Serum creatinine >1.2 mg/dL
- Multiorgan dysfunction or sepsis
- Radiologic abnormalities
- Multilobe involvement
- Cavitation
- Pleural effusion

Data from American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2001;163:1730–54.

able [24]. Most patients have a clinical response within 3 days. Therapy should not be changed in the first 72 hours unless there is a marked clinical deterioration [19].

Many different complications of bacterial pneumonia have been reported. Infections at other sites can occur; meningitis, arthritis, endocarditis, empyema, and pericarditis have been noted in association with pneumonia. Severe cases of pneumonia can be complicated by sepsis, heart failure, renal failure, and acute respiratory distress syndrome and require intensive care admission. Obstetric complications include fetal distress secondary to poor oxygenation and preterm birth. Munn and colleagues [27] found that women who had pneumonia were significantly more likely to deliver before 34 weeks. Preterm birth was reported to be more common when the woman who had pneumonia has some underlying comorbid condition [28]. Anemia also was reported in several studies of pneumonia during pregnancy [18,21,27]. The birth weight of infants who were born to women who had antepartum pneumonia was significantly less than that of controls [18,21].

With the increasing number of pregnant women who are infected with HIV, *Pneumocystis carinii* pneumonia (PCP) deserves specific mention. This is the leading cause of AIDS-related death among pregnant women in the United States [29]. Symptoms include dry cough, dyspnea, and tachypnea. A diffuse infiltrate is seen on chest radiograph. Ahmad and colleagues [30] reported 22 cases of PCP in pregnancy. The mortality was extremely high (50%). Fifty-nine percent required mechanical ventilation. These numbers may be inflated because none of the patients was on antiretroviral therapy; all were diagnosed with HIV when diagnosed with PCP. Treatment is with trimethoprim–sulfamethoxazole or pentamidine. HIV-infected patients with a $CD4^+$ T lymphocyte count of less than 200/μL, a history of oropharyngeal candidiasis, or an AIDS-defining illness should receive prophylaxis [31]. The preferred prophylactic regimen is trimethoprim–sulfamethoxazole, one double-strength tablet per day. Prophylaxis is 90% to 95% effective [32] in nonpregnant individuals and is expected to be similarly effective in pregnancy.

Viral pneumonia

Viral pneumonia is caused most commonly by influenza and varicella-zoster virus (VZV). Influenza is caused by two RNA viruses in the family Orthomyxoviridae, influenza A and influenza B. Historically, influenza in pregnant women has been associated with a higher rate of morbidity and mortality. The course of influenza in pregnancy was reported first during the epidemic of 1918, when 1350 cases in pregnant women who had an influenza-like illness were evaluated. Pneumonia complicated 585 (43%) of the cases. In 52% of these patients, the pregnancy was interrupted. There were 308 (23%) maternal deaths. Mortality was highest in the last 3 months of pregnancy, and increased if complicated by pneumonia [33]. During the influenza epidemic of 1957, 22 pregnant women in New York City died from complications of the flu. Pregnant

women accounted for nearly half of the deaths of women of child-bearing age [34]. During the same epidemic, 11 pregnant women died in Minnesota. All deaths were attributed to respiratory insufficiency secondary to pulmonary edema and pneumonia [35]. Mullooly and colleagues [36] reviewed influenza complicating pregnancy from 1975 to 1979. There were four epidemics in that 5-year period. Pregnant women sought outpatient medical attention for acute respiratory disease during the influenza season significantly more often than did nonpregnant women.

Influenza infection is epidemic in winter months, and is spread by aerosolized droplets. Particles are created when a person coughs, sneezes, or speaks. These particles are filtered by the recipient's nose and pharynx and reach the alveoli [37].

The clinical presentation of influenza does not seem to be altered by pregnancy. The incubation period for influenza is 1 to 4 days with an average of 2 days [38]. Generally, patients are infectious the day before the onset of symptoms and for 5 days thereafter. Young children and immunocompromised adults can shed virus for much longer periods of time [39]. Infants who are infected while in the hospital can shed virus for up to 21 days [37].

Symptoms of influenza include cough, fever, malaise, rhinitis, myalgias, headache, chills, and sore throat. Less common symptoms include nausea and vomiting, otitis, and conjunctival burning. Signs of influenza include fever, tachycardia, facial flushing, clear nasal discharge, and cervical adenopathy. In adults, fever generally lasts for 3 days with resolution of symptoms normally within 1 week; the cough and malaise may persist for longer than 2 weeks.

Pneumonia, either viral or superimposed bacterial, is a well-recognized complication of influenza. Initially, patients present with respiratory distress in the case of viral pneumonia. On chest radiograph, diffuse bilateral infiltrates are seen. Signs of pneumonia include course rales and rhonchi, wheezing, dyspnea, and tachypnea. Typically, superimposed bacterial pneumonia occurs 2 to 14 days after symptoms of influenza have resolved. Local consolidation is seen on chest radiograph with superimposed bacterial pneumonia. Pregnant women who have influenza pneumonia should be evaluated, and may be treated with one of the antiviral agents that are approved for the treatment of influenza. The adamantines, M2 ion-channel inhibitors, include amantadine and rimantadine and have activity only against influenza A. They may be given within the first 48 hours of symptoms to reduce symptom duration. To minimize drug resistance, therapy should be discontinued within 24 to 48 hours after symptoms resolve, or within 3 to 5 days. The neuraminidase inhibitors are effective in the treatment of influenza A and B. Oseltamivir, given orally, is approved for treatment and chemoprophylaxis. Zanamivir is an inhaled medication that is approved for treatment only. There have been several reports of bronchospasm in patients who had asthma who took this drug. Both shorten the duration of symptoms by an average of 1 day. There are limited data on safety in pregnancy. All four drugs are U.S. Food and Drug Administration category C, and therefore, should be used only when the benefits outweigh the risks [25].

VZV is a DNA virus that affects 0.7 per 1000 pregnancies [40]. Pneumonia is the most common complication in adults, and it occurs in 10% of cases [41]. Before the availability of antiviral therapy, mortality in pregnant women who had VZV pneumonia was as high as 35% to 40% [42,43]. The mortality in the era of antiviral therapy is approximately 14% [43,44]. Risk factors for varicella pneumonia include smoking and the presence of more than 100 skin lesions [41]. Pulmonary symptoms begin 2 to 5 days after the onset of rash and fever. Symptoms include cough, hemoptysis, dyspnea, tachypnea, and pleuritic chest pain. Chest radiograph shows diffuse miliary or nodular infiltrates. Treatment is with intravenous acyclovir, although the value of this has not been proven in rigorous scientific studies.

Varicella pneumonia has been associated with preterm labor in some studies, although recent reports have not substantiated this [41,45]. If varicella-zoster immunoglobulin is given within 96 hours of exposure to varicella, it can attenuate or prevent infection in susceptible individuals. It is not contraindicated in pregnancy. The varicella vaccine is contraindicated in pregnancy because it is a live-attenuated vaccine.

Severe acute respiratory syndrome (SARS) is caused by a novel coronavirus. Since 2002, this atypical pneumonia has affected more than 8000 people and has resulted in more than 800 deaths worldwide [46]. Transmission is by respiratory droplets or close personal contact. The virus can live in urine and stool for 1 to 2 days. Symptoms are the same in pregnant and nonpregnant women and include fever, chills, rigors, malaise, and myalgias [47]. Patients are most infectious during the second week of illness. Most often, chest radiograph findings are generalized, patchy, interstitial infiltrates [46]. Patients have been noted to have lymphopenia as well as thrombocytopenia [46,47].

Diagnosis can be made by culture, polymerase chain reaction, ELISA, and immunofluorescence assay. Guidelines and protocols for diagnostic tests are available on the World Health Organization web site. Complications of SARS pneumonia include respiratory failure, superimposed bacterial infections, and disseminated intravascular coagulation. The largest case series of pregnant women who had SARS was reported by Wong and colleagues [48] from China. Twelve pregnant women were infected with SARS between February 1, 2003 and July 31, 2003. High rates of morbidity and mortality were noted. The case fatality rate was 25%. A large portion of the cases was complicated by first-trimester spontaneous abortions, preterm births, and intrauterine growth restriction. No case of vertical transmission has been reported. Treatment includes broad-spectrum antibiotics to cover superimposed bacterial infections, high-dose steroids, and possibly, ribavirin. Ribavirin was shown to have teratogenic effects in animals [25], and its use in pregnancy has not been established.

Fungal pneumonia

Fungal pneumonia is usually seen in women who are immunocompromised (eg, HIV infection). Histoplasmosis and blastomycosis are the most common

fungal pneumonias that complicate pregnancy and usually are mild and self-limited. Cryptococcosis also may present during pregnancy, although meningitis is more common than pneumonia. Coccidioidomycosis also may cause pneumonia in pregnancy and is associated with erythema nodosum. It occurs frequently in endemic areas. Most fungal pneumonias present similarly to bacterial and viral pneumonias, with cough, dyspnea, fever, and chest pain as common complaints. Pregnant women who have complicated fungal infections, including disseminated disease, are treated with amphotericin B or ketoconazole [49–52], although the safety data of long-term use in pregnancy are limited [25].

Summary

Regardless of the type of pneumonia, it is important to be aggressive with monitoring and treatment for the sake of the mother and fetus. Oxygen supplementation should be provided to prevent fetal acidemia. Broad-spectrum empiric antibiotics should be started before identification of the etiologic agent, and antibiotic therapy should be tailored to specific organisms as laboratory tests return. Given that most pregnant women are young and healthy, intense, early treatment is likely to result in a good outcome.

Tuberculosis

Tuberculosis is a pulmonary infection that is caused by the acid-fast bacillus, *Mycobacterium tuberculosis*. Although *Mycobacterium bovi*s, *M africanum*, and *M microti* can cause human disease, *M tuberculosis* is encountered most commonly. It is estimated that eight to nine million new cases of tuberculosis occurred worldwide in 2000; more than half occurred in Asia [53]. During 2004, 14,517 cases of tuberculosis in the United States were reported to the Centers for Disease Control and prevention (4.9 per 100,000); this represented a 2.3% decrease from 2003 [54]. Most cases (54%) occurred in foreign-born persons.

Several factors were implicated in the resurgence of tuberculosis in the United States that occurred in the late 1980s and early 1990s. These included increased immigration from countries with a high prevalence of tuberculosis, HIV infection, emergence of resistant strains, poverty, homelessness, drug abuse, and a decline in tuberculosis-related health services [55]. This increase was accompanied by an increased frequency of tuberculosis in pregnant women. With appropriate therapy, pregnancy does not affect the course of tuberculosis adversely; however, tuberculosis may affect pregnancy outcome adversely. Low birth weight, preterm delivery, and increased perinatal mortality rates have been reported in the setting of incomplete treatment and advanced or extrapulmonary tuberculosis [56,57].

Transmission

Transmission and infection during pregnancy are believed to be the same as in nonpregnant women. *Mycobacterium tuberculosis* is transmitted most commonly from person to person by respiratory droplets that are aerosolized during coughing, sneezing, singing, or speaking. The droplets dry rapidly and may remain suspended in the air for several hours. Factors that are associated with the likelihood of transmission include the intimacy and duration of contact, the degree of infectiousness of the case, and the shared environment of the contact. Patients who have sputum smear–negative/culture-positive tuberculosis are less infectious, and those who have culture-negative pulmonary disease and extrapulmonary tuberculosis are noninfectious.

Droplets gain direct access to the terminal air passages when inhaled; approximately 10% reach the alveoli. There, activated alveolar macrophages ingest the bacilli. If the bacilli multiply, their growth quickly kills the macrophages, which lyse. Usually, these initial stages of infection are asymptomatic. Two to 4 weeks after infection, two additional host responses develop—a tissue-damaging response and a macrophage-activating response. Large numbers of activated macrophages accumulate at the site of the primary lesion, and granulomatous lesions are formed [58,59]. These lesions consist of lymphocytes and activated macrophages. Macrophages that contain bacilli travel to the lymph nodes and then to the rest of the body.

Many patients are infected with *Mycobacterium tuberculosis*, but do not have the active form of disease. In patients who go on to have active disease, the macrophage-activating response is weak, and, therefore, mycobacterial growth only can be inhibited by an intensified tissue-damaging response. Because the surrounding tissue is damaged progressively, the lesion enlarges. Most infected individuals who develop active disease do so within 1or 2 years after infection. Clinical illness shortly after infection is termed primary tuberculosis. Dormant bacilli may persist for years and then become reactivated. This is referred to as secondary or postprimary tuberculosis [60].

It is estimated that approximately 10% of infected persons eventually develop active tuberculosis. Groups who are at risk for infection and progression to active disease are listed in Box 2. Factors that place patients at high risk for developing active disease include age, HIV coinfection (suppressed cellular immunity), silicosis, malignant neoplasms, hemophilia, chronic renal failure, and insulin-dependent diabetes mellitus [61–65]. Among infected persons, the incidence of tuberculosis is highest during late adolescence and early adulthood. The incidence among women peaks at 25 to 34 years of age [60].

Clinical course

Clinical manifestations of tuberculosis usually include fever, night sweats, cough, weight loss, anorexia, general malaise, and weakness. Massive hemoptysis can occur as a result of erosion into a pulmonary vessel in the wall of a

Box 2. Groups at high risk for tuberculosis

Increased risk for exposure

- Immigrants from areas that are endemic for tuberculosis
- Residents of long-term care facilities and nursing homes
- Healthcare workers
- Incarcerated persons
- Homeless persons
- Intravenous drug users
- People living in crowded conditions

Increased risk for active disease

- Immunocompromised patients, including those who have
  - HIV infection
- Infants
- Elderly
- Patients who have:
  - Diabetes mellitus
  - Hemophilia
  - Chronic renal failure
  - Malignancy
  - Silicosis

tuberculin cavity. Other findings include wasting, rales, rhonchi, and clubbing of fingers because of hypoxia. On chest radiograph, the classic finding is that of an upper lobe infiltrate or cavity; however, the film may be normal or have other findings, such as nodules or diffuse infiltrates. Cavitation or mediastinal lymphadenopathy also may be seen.

Although any organ system can be affected, the extrapulmonary sites that are involved most commonly in tuberculosis include lymph nodes, pleura, genitourinary tract, bones and joints, meninges, and peritoneum. Extrapulmonary tuberculosis is being seen more often because of HIV coinfection. Five to 10% percent of pregnant women who have tuberculosis have extrapulmonary disease.

Miliary tuberculosis is due to hematogenous spread of the bacilli. It may occur with recent infection or reactivation of old disseminated foci. Common symptoms include weakness, fever, and weight loss. Miliary tuberculosis can be a difficult diagnosis to make because there may be no radiographic findings [66]. If present, radiologic findings may include large infiltrates, interstitial infiltrates, and pleural effusions. A sputum smear for acid-fast bacilli is negative in 80% of cases. Hematologic abnormalities that are seen with miliary tuberculosis include anemia, leukopenia, neutrophilic leukocytosis, and polycythemia [67]. Dissemi-

nated intravascular coagulation may be present. In patients who have severe hepatic involvement, abnormal liver enzymes can be seen. A purified protein derivative (PPD) test is negative in up to half of cases. Often, bronchoalveolar lavage, transbronchial biopsy, or tissue biopsy is necessary to confirm the diagnosis.

Congenital and neonatal tuberculosis

Congenital tuberculosis is a rare and often fatal disease; it usually is acquired by way of hematogenous spread to the fetus through the placenta and umbilical cord. Bacilli have been retrieved from the decidua, amnion, and chorionic villi [68]. A fetus also may become infected with *Mycobacterium tuberculosis* by ingesting amniotic fluid [69,70]. Hematogenous acquisition commonly results in granulomatous complexes within the liver. Acquisition by way of aspiration results more often in complexes in the lungs or gastrointestinal tract [71]. Beitzke [68] detailed criteria for congenital tuberculosis: (1) firm diagnosis of tuberculosis in the newborn, (2) primary complex in the newborn's liver, or (3) if no primary complex is identified in the liver, tuberculous lesions must be documented in the first few days of life to exclude extrauterine infection. In many cases, the newborn is diagnosed before the mother. Hageman and colleagues [72] reviewed cases of congenital tuberculosis. The most common signs and symptoms, in descending order, were respiratory distress, fever, liver/spleen enlargement, poor feeding, lethargy, and lymphadenopathy. In this review, neonatal mortality was 46%; however, in three quarters of the deaths, there was no treatment because the diagnosis was made post mortem. Initially, tuberculin testing may be negative and may remain so for several months. Neonatal tuberculosis is far more common, and occurs when the newborn is infected after exposure to the infected mother or other family member.

Diagnosis

Current guidelines for screening for tuberculosis include skin testing of women who are in high-risk groups (Box 3). The PPD tuberculin skin test is the only test that can detect *Mycobacterium tuberculosis* infection reliably in asymptomatic persons. The test becomes positive 2 to 12 weeks after infection [73]. Sensitized $CD4^+$ lymphocytes travel to the site, proliferate, and produce cytokines; consequently, a raised, erythematous area forms. The size of the reactive area determines whether the test is positive. The size of the reactive area that is used to define a positive test varies with risk factors. Induration of at least 5 mm is used for patients who have HIV infection, recent contact with a person with active tuberculosis, organ transplant, or fibrotic changes on chest radiograph that are consistent with old tuberculosis. An induration of at least 10 mm is used in patients who are recent immigrants (within 5 years) of high prevalence countries, intravenous drug users, residents or employees of high-risk settings (eg, jails, nursing homes, shelters, hospitals), or who have conditions that are associated with a high risk of disease after infection. An induration of

Box 3. High-risk groups that should undergo tuberculosis screening

HIV-infected persons
Persons who have medical risk factors that are known to increase the risk of disease if infection has occurred
Close contacts of a person who is known or suspected to have tuberculosis
Foreign-born persons from areas where tuberculosis is common
Residents and employees of high-risk congregate settings
Health care workers who serve high-risk clients
Medically underserved, low-income populations (eg, Asian, Hispanic, African, and Native American)
Persons who inject illicit drugs
Persons who have a history of inadequately treated tuberculosis

Data from Centers for Disease Control and Prevention. Interactive core curriculum on tuberculosis: what the clinician should know. Available at: http://www.cdc.gov/nchstp/tb/webcourses/CoreCurr/index.htm.

at least 15 mm is used for low-risk people [74]. The test has low sensitivity and specificity in the case of active tuberculosis. In addition, false negative results are common in immunocompromised patients. Patients who have received the bacille Calmette-Guérin vaccine can have a false-positive test, although the skin induration rarely exceeds 20 mm in false positive results [75].

All pregnant women who have a positive test should undergo a chest radiograph with abdominal shield to assess for evidence of disease. Hematologic findings include anemia, leukocytosis, and occasionally, hyponatremia. In patients who have suspected active pulmonary tuberculosis, three sputum specimens—collected early in the morning—should be taken for acid fast bacillus (AFB) smear and mycobacteriology culture. If tissue is obtained for culture, it is important that it not be put in formaldehyde because this compromises test accuracy. Definitive diagnosis depends on the isolation and identification of *Mycobacterium tuberculosis* from a diagnostic specimen, such as sputum or tissue. Culture is a time-consuming process because *Mycobacterium tuberculosis* can take 4 to 8 weeks to grow; however, it is important because drug susceptibilities can be determined and treatment can be optimized for the individual patient [76].

Treatment

The treatment of tuberculosis in pregnancy varies, depending on disease status (ie, PPD positive alone versus active disease) and drug resistance testing in

endemic areas. If a pregnant woman has a positive PPD that indicates infection but no evidence of active disease, treatment with isoniazid (INH) may be withheld until after delivery because of the increased risk for hepatotoxicity [77,78]. Pregnant women who are infected with HIV should start therapy immediately, because there is an 8% annual risk for progression to active disease. Pregnant women who have other risk factors for progression, including known recent skin-test convertors, also should not delay initiation of therapy [74].

Management of active pulmonary tuberculosis during pregnancy is similar to that in nonpregnant women. INH, rifampin, and ethambutol (EMB) should be used in initial treatment regimens. If local prevalence of isolates that are resistant to INH is high, pyrazinamide should be added to this regimen until the results of susceptibility testing are available. These medications cross the placenta, but were not shown to have teratogenic effects [25]. Women who are being treated can breastfeed. Although these medications are found in breast milk, the amount of drug does not reach therapeutic levels, and is not sufficient for treatment of the newborn [79]. Pregnant and postpartum women should receive pyridoxine.

Table 1 lists the medications that are used in the treatment of tuberculosis. INH dosing can be daily or two to three times per week. Side effects include aminotransferase elevations, hepatitis, peripheral neurotoxicity, and a lupuslike syndrome. Hepatitis seems to be more common in pregnant patients who take INH; thus, liver enzymes should be evaluated frequently and pyridoxine should be administered. The dose of pyridoxine in prenatal vitamins can vary, and generally, the dose is inadequate for this purpose. Rifampin also is a first-line agent with dosing once daily or two to three times per week. Side effects include rash, nausea/vomiting, and hepatitis. Patients must be warned that rifampin will turn urine, sweat, sputum, and tears orange [80,81]. EMB is a first-line drug for treating all forms of tuberculosis. It is included in initial treatment regimens, primarily to prevent emergence of rifampin resistance when primary resistance to INH may be present. Adverse effects include retrobulbar neuritis, peripheral neuritis (rare), and skin reactions that require discontinuation of the drug. EMB is considered safe for use in pregnancy [25]. Pyrazinamide is a first-line agent that is highly active against dormant and semidormant bacterial populations [82].

Table 1
Medications for the treatment of tuberculosis in pregnant women

Drug	Interval and duration	Side effects and warnings
Isoniazid	Daily or 2–3×/wk 6 or 9 months	Hepatitis, GI distress, seizures, peripheral neuropathy
Rifampin	Daily or 2–3×/wk 2–4 months	Hepatitis, GI distress, purpura, febrile reactions, orange secretions
Ethambutol	Daily or 2–3×/wk 2 months	Retrobulbar neuritis, peripheral neuritis, skin reactions
Pyrazinamide	Daily or 3×/wk 2 months	GI distress, rash, arthralgias

Abbreviation: GI, gastrointestinal.

Hepatotoxicity that is attributable to standard doses of pyrazinamide (PZA) occurs in approximately 1% of cases [83]. Mild anorexia and nausea are common. Transient morbilliform rash also can occur but usually is self-limited. There is little information about the safety of PZA in pregnancy. The benefits of PZA may outweigh the possible risks in areas in which drug-resistant tuberculosis is endemic [84,85]. Streptomycin should be avoided in pregnancy because of an increased risk of congenital deafness.

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