Influenza and Pneumonia in Pregnancy

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Influenza is a significant cause of morbidity and mortality from febrile respiratory illness worldwide. Influenza in pregnant women has historically been associated with a higher rate of morbidity and mortality. Pneumonia is the sixth leading cause of death in the United States, and it is the number one cause of death from an infectious disease. Although pregnant women do not get pneumonia more often than nonpregnant women, it can result in greater morbidity and mortality because of the physiologic adaptations of pregnancy. Pregnant patients who have either of these conditions require a higher level of surveillance and intervention.

Influenza

Influenza is caused by two RNA viruses in the family Orthomyxoviridae, influenza A and influenza B. First identified in 1933, they remain a significant cause of morbidity and mortality from febrile respiratory illness worldwide [1]. Influenza A is subtyped using two surface antigens: hemagglutinin (H) and neuraminidase (N). Both viruses are further grouped based on antigenic characteristics. Antigenic drift, the yearly variation in the surface antigens caused by point mutations, results in the need for annual revaccination. Because immunity to surface antigens reduces the chance of becoming infected as well as the severity of symptoms if infected [2], vaccines are developed with subtle alterations each year in anticipation of viral variation. Antigenic shift, seen only in influenza A, occurs when mutations accumulate in the N or H antigens, replacing

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the current antigen with a new subtype. The years associated with antigenic shift report much higher morbidity and mortality rates. Between 1990 and 1999, influenza caused an average of 36,000 deaths per year [3]. The H3N2 strain of influenza A has caused the most hospitalizations during epidemic years since 1968, at approximately 142,000 per year [4]. A patient's response to influenza is multifactorial and cannot be predicted based on viral properties alone [5]. It is this uncertainty that has continued to make influenza a formidable opponent.

Historical perspective

Influenza in pregnant women has historically been associated with a higher rate of morbidity and mortality. The course of influenza in pregnancy was first reported 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 [6]. 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 the deaths of women of childbearing age [7]. During the same epidemic, 11 pregnant women died in Minnesota. All deaths were attributed to respiratory insufficiency secondary to pulmonary edema and pneumonia [8]. Mullooly and colleagues [9] reviewed influenza complicating pregnancy from 1975 to 1979. There were four epidemics in that 5-year time period. Pregnant women sought outpatient medical attention for acute respiratory disease during the influenza season significantly more often than nonpregnant women; however, unlike the previously reported epidemics, there were no maternal deaths attributable to influenza, and the hospitalization rate was low at 2 per 1000.

Risk factors

It is recommended that high-risk groups be vaccinated annually, because the severity of the season will only be known in retrospect. High-risk groups include children aged 6 to 23 months; people aged 65 or older; residents of long-term care facilities; adults and children who have chronic illnesses, including asthma, diabetes, and immunosuppression; and pregnant women. In 2000, 73 million people in the United States were considered high-risk [4]. Unfortunately, up to 50% of these high-risk patients do not receive annual vaccination.

Pregnant women are felt to be at increased risk for influenza. This risk is higher if they have an underlying medical condition, are of advanced age, or are exposed in the third trimester [10]. In a study by Neuzil and coworkers [10], women in the third trimester were three to four times more likely than postpartum women to be hospitalized for an acute cardiopulmonary illness during influenza season. Asthma in pregnant women increased the rate of hospitalizations for a respiratory illness during influenza season 10-fold [11].

Clinical presentation

The virus is spread from person to person via respiratory droplets. Particles are created when a person coughs, sneezes, or speaks. These particles are filtered by the recipient's nose and pharynx and then reach the alveoli [12].

The clinical presentation of influenza does not appear to be altered by pregnancy. The incubation period for influenza is 1 to 4 days, with an average of 2 days [13]. Patients are generally infectious the day before the onset of symptoms and for 5 days thereafter; however, young children and immunocompromised adults can shed virus for much longer periods of time [4]. Infants infected while in the hospital can shed virus for up to 21 days [12].

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. Fever in adults generally lasts for 3 days, with resolution of symptoms normally within 1 week; however, the cough and malaise may persist for greater than 2 weeks [5].

Diagnosis

Influenza is usually diagnosed using clinical features during the influenza season. Rapid testing by either immunofluorescence or immunoassay has the advantage of providing same-day diagnosis; however, it does not have the same sensitivity as culture. There are various rapid tests on the market. Some detect influenza but cannot distinguish influenza A from B. Others detect both and can distinguish them. Nasal samples provide a higher level of sensitivity than do throat samples when performing rapid testing. The positive and negative predictive value of the rapid tests depends on the level of influenza activity in the population being tested. Patients who have a clinical picture highly suggestive of influenza but with a negative rapid test should still be cultured, because false negatives do occur [4,12]. Viral culture is necessary to subtype influenza as well as to perform drug sensitivities.

Complications

Pneumonia, either viral or superimposed bacterial, is a well-recognized complication of influenza. Patients initially 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. Superimposed bacterial pneumonia typically occurs 2 to 14 days after symptoms of influenza have resolved. Local consolidation is seen on chest radiograph with superimposed bacterial pneumonia. Myopathy is another complication that has been associated with influenza. Patients may develop rhabdomyolysis and myoglobinuria. In adults, myopathy is more commonly found with influenza A. It has been suggested that a genetic predisposition exists for this

complication. Pathology slides of muscle biopsies taken from patients who had suspected influenza-associated myopathy showed lysis of muscle fibers. Carditis has also been reported. The influenza virus has been isolated from the myocardium of patients who died of influenza complications. With carditis there are often EKG changes, including ST changes, inverted T waves, and rate disturbances. Carditis can occur at the same time as the initial respiratory manifestations. Finally, encephalopathy is a rare complication of influenza. The virus has been isolated from cerebrospinal fluid (CSF) and brain tissue at autopsy. Encephalopathy is also thought to be genetically linked [5].

Fetal effects

There is a paucity of prospective data on the effects of intrapartum, laboratory-confirmed influenza on fetal outcome. Irving and colleagues [14] found no significant difference between women who had serum-confirmed influenza and controls in the incidence of congenital malformations. Widelock and coworkers [15] studied the influenza epidemics of 1957 to 1960. They too found no increased incidence of fetal death or malformations in pregnant women who had influenza. Influenza has been associated with limb reduction and neural tube defects, including anencephaly [16–18]. Other investigators have not found an association between influenza and anencephaly [19]. Several studies have noted an increased incidence of schizophrenia in people who were born 2 to 3 months after an influenza epidemic, implying that maternal exposure to influenza in the second trimester, when fetal neurons are migrating, is a risk factor [20,21]. There have also been reports of an increased incidence of cleft lip [22,23]. Unfortunately, many studies are limited by recall and selection bias, making it unclear if there truly is an association.

Treatment

There are four antiviral agents approved for the treatment and prevention of influenza. These medications are no substitute for vaccination, especially in high-risk groups. The adamantanes, M2 ion-channel inhibitors, include amantadine and rimantadine. These drugs have activity only against influenza A [24]. Given as chemoprophylaxis, they are 70% to 90% effective at preventing influenza. They also can 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 3 to 5 days. Most notable side effects are of the central nervous system and include confusion, insomnia, and difficulty concentrating [25]. The neuraminidase inhibitors are effective in the treatment of influenza A and B. Oseltamivir, given orally, is approved for both treatment and chemoprophylaxis. It is reported to be 70% to 90% effective at preventing influenza [26]. The most commonly reported side effects are nausea and vomiting [27]. Zanamivir is an inhaled medication approved for treatment only. It should be noted that there have been several reports of bronchospasm in patients who

have asthma and who take this drug. Both shorten the duration of symptoms by, on average, 1 day. There are limited data on safety in pregnancy. All four drugs are US Food and Drug Administration category C, and therefore should be used only when the benefits outweigh the risks [28].

Prevention/vaccination

The primary method of influenza prevention is vaccination. Vaccination is most effective when performed in October or November, although unvaccinated patients should not be denied vaccination later in the season. The recommendation of the Advisory Committee on Immunization Practices (ACIP) is that all women who will be pregnant during the influenza season should receive the vaccine. Vaccination can be performed safely in any trimester of pregnancy [29,30]. Breast feeding is not a contraindication to vaccination [4]. There are two different vaccines available. One is a live-attenuated vaccine (LAIV), whereas the other is inactivated. The inactivated vaccine is used for pregnant women as well as all other high risk groups. The LAIV is recommended only for healthy persons ages 5 to 49. The inactivated vaccine is less expensive. Both vaccines are contraindicated in people who have an anaphylactic hypersensitivity to eggs or other components of the vaccine, people who have an acute febrile illness, and people who have a history of Guillain-Barré syndrome within 6 weeks of a previous influenza vaccination. Peak antibody protection develops 2 weeks after vaccination [31,32]. Inactivated vaccine in the United States that is distributed in single-dose syringes is preservative-free and contains only trace amounts of thimerosal, a mercury-containing compound. Thus, there is little concern for mercury exposure because it is limited to less than 0.5 mcg mercury/0.25-mL dose [33]. Vaccine efficacy in healthy adults less than 65 years of age is 70% to 90% if circulating and vaccine viruses are antigenically similar [4].

Secondary prevention strategies should also be implemented. These include hand washing, respiratory and contact isolation, and contact prophylaxis.

Pneumonia

Overall, pneumonia is the sixth leading cause of death in the United States, and it is the number one cause of death from an infectious disease. Over 5 million cases occur annually, with more than 1 million persons requiring hospitalization [34,35]. Although associated with far less mortality, women of reproductive age susceptible to pneumonia from a bacterial, viral, or fungal source. Although pregnant women do not get pneumonia more often than nonpregnant women, it can result in greater morbidity and mortality because of the physiologic adaptations of pregnancy. These include a decrease in pulmonary functional residual capacity as well as alterations in cell-mediated immunity. Thus, pregnant patients require a higher level of surveillance and intervention. In a study by Jin and colleagues [36] the hospitalization rate for community-acquired pneumonia

in pregnant women was 1.51 per 1000 pregnancies. Several recent articles have reported an incidence of 1 per 660 deliveries [36,37].

Bacterial pneumonia

Some of the organisms found to cause bacterial pneumonia include *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. *S pneumoniae* is the most commonly identified bacterial cause, though Richey and coworkers [38] found that in only 27% of cases could the causative organism be identified. The American Thoracic Society notes that even with extensive diagnostic testing, in 50% or more of cases the etiology cannot be identified. A Gram's 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 [39].

Risk factors for pneumonia include asthma and other chronic respiratory diseases, HIV/AIDS, smoking, and drug use [40]. 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%) [41]. Signs include fever, crackles, and abnormal breath sounds. In patients who have the above findings and in whom pneumonia is suspected, a chest radiograph should be performed. The chest radiograph will confirm pneumonia, rule out other diagnoses, suggest a possible etiology, and aid in determining the severity of illness. Multilobar pneumonia is considered a more severe process than single lobar involvement [39]. 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 have been found to be positive only 7% to 15% of the time [37,40].

Maternal mortality was greatly reduced with the advent of antibiotics [42,43]. Intravenous antibiotic therapy should be started empirically. Erythromycin is an acceptable initial choice for treatment, because it is considered safe in pregnancy [28]. Treatment success rates up to 99% have been reported [37]. If aspiration, gram-negative organisms, or drug-resistant *S pneumoniae* is suspected, a beta-lactam such as ceftriaxone or ampicillin should be added. Most patients will have a clinical response within 3 days. Therapy should not be changed in the first 72 hours unless there is a marked clinical deterioration [39].

Many different complications of bacterial pneumonia have been reported. Infections at other sites can occur. Meningitis, arthritis, endocarditis, empyema, and pericarditis have all been reported. Severe cases of pneumonia can be complicated by sepsis, heart failure, renal failure, and acute respiratory distress syndrome (ARDS), requiring intensive care admission. Obstetric complications include fetal distress secondary to poor oxygenation and preterm birth. Munn and coworkers [44] found that women who had pneumonia were significantly more likely to deliver before 34 weeks. Preterm birth has been reported to be more common when the woman who has pneumonia also has some underlying co-

morbid condition [45]. Anemia has also been reported in several studies of pneumonia during pregnancy [37,40,44,46]. Birthweights of infants born to women who have antepartum pneumonia have been found to be significantly less than controls [37,40].

With the increasing number of pregnant women infected with human immunodeficiency virus, *Pneumocystis carinii* pneumonia (PCP) deserves specific mention. Among pregnant women, this is the leading cause of AIDS-related death in the United States [47]. Symptoms include dry cough, dyspnea, and tachypnea. A diffuse infiltrate is seen on chest radiograph. Ahmad and coworkers [48] reported 22 cases of PCP in pregnancy. The mortality rate was extremely high at 50%. Fifty-nine percent required mechanical ventilation. These numbers may be inflated because none of the patients were on antiretroviral therapy, because all were diagnosed with HIV when diagnosed with PCP. Treatment is with trimethoprim-sulfamethoxazole or pentamidine. HIV-infected patients who have a CD4+ T-lymphocyte count less than 200/µL, a history of oropharyngeal candidiasis, or an AIDS-defining illness should receive prophylaxis [49]. The preferred regimen is trimethoprim-sulfamethoxazole, one double-strength tablet per day. Prophylaxis is 90% to 95% effective [50].

Viral pneumonia

Viral pneumonia is most commonly caused by influenza and varicella-zoster virus (VZV). Influenza in pregnancy has been described in great detail earlier in this article. VZV is a DNA virus that affects 0.7 per 1000 pregnancies [51]. Pneumonia is the most common complication in adults, occurring in 10% of cases [52]. Before the availability of antiviral therapy, mortality rates in pregnant women who had VZV pneumonia were quoted as high as 35% to 40% [53,54]. The mortality rate in the era of antiviral therapy is approximately 14% [54,55]. Risk factors for varicella pneumonia include smoking and the presence of 100 or more skin lesions [52]. 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.

Congenital varicella syndrome occurs in 1% to 2% of cases of maternal varicella, depending on gestational age [56–58]. In a study conducted by the Maternal Fetal Medicine Unit Network of 347 pregnant women who had varicella [59], the rate of congenital varicella was 0.4%. Congenital varicella is characterized by limb hypoplasia, chorioretinitis, cutaneous scars, and cortical atrophy [60,61].

Varicella pneumonia has been associated with preterm labor [60], although this was not substantiated in a later study of 18 women who had varicella pneumonia [52]. Varicella-zoster immunoglobulin given within 96 hours of exposure to varicella can attenuate or prevent infection in susceptible individuals. It is not contraindicated in pregnancy. The varicella vaccine, however, is contraindicated in pregnancy because it is a live-attenuated vaccine [62].

Severe acute respiratory syndrome (SARS) is caused by a novel coronavirus. Since 2002, this atypical pneumonia has affected over 8000 people and resulted in more than 800 deaths worldwide [63]. 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 women as in nonpregnant women, and include fever, chills, rigors, malaise, and myalgias [64]. Patients are most infectious during the second week of illness. Chest radiograph findings are most often generalized, patchy, interstitial infiltrates [63]. Patients have been noted to have lymphopenia [64] as well as thrombocytopenia [63].

Diagnosis can be made by culture, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and indirect fluorescent antibody (IFA). Guidelines and protocols for diagnostic tests are available on the World Health Organization Web site at http://www.who.int/csr/sars/en/.

Complications of SARS pneumonia include respiratory failure, superimposed bacterial infections, and disseminated intravascular coagulation (DIC). The largest case series of pregnant women who had SARS comes from Wong and coworkers in China [65]. 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; however, there have been no cases of vertical transmission reported. Treatment includes broad-spectrum antibiotics to cover superimposed bacterial infections, high dose steroids, and possibly ribavirin. Ribavirin has been shown to have teratogenic effects in animals [66,67], and its use in pregnancy has not been established.

Fungal pneumonia

Fungal pneumonia in pregnancy is most often seen in those women who are immunocompromised; however, with the physiologic suppression of cell-mediated immunity in pregnancy, fungal pneumonia can be seen in otherwise healthy women. There have only been a handful of cases of pneumonia secondary to histoplasmosis reported [68]. Although still extremely limited, there are more case reports of blastomycosis. Lemos and colleagues [69] reviewed 19 cases of blastomycosis in pregnancy. Seventy-eight percent had pulmonary involvement, and all recovered or were at least reported as having a "good response." In two cases, the newborn died and was found to have blastomycosis at autopsy. Treatment is with amphotericin B or ketoconazole. Ely and coworkers [70] reported four cases of cryptococcal pneumonia. All were otherwise healthy women. Cryptococcal pneumonia is difficult to diagnosis. In this case series, all women eventually underwent a lung biopsy to make the diagnosis. Symptoms include cough, chest pain, and dyspnea. Chest radiograph findings can vary greatly and include infiltrates, mass lesions, and adenopathy. Treatment is with amphotericin B. Coccidioidomycosis results from the inhalation of *Coccidioides immitis*. One third of infected persons will develop a symptomatic illness.

Complications of coccidioidomycosis include pneumonia and disseminated disease [71]. Symptoms include cough, fever, and erythema nodosum [72]. Erythema nodosum has been reported to be a marker of good outcome in pregnant women [73]. Dissemination of disease in pregnancy is a controversial topic. Historically, dissemination was reported to be 40 to 100 times more frequent in pregnancy [74]. Caldwell and colleagues [72] found the incidence of dissemination in pregnancy to be 9%, three times the rate of the nonpregnant population. In their series, 23/32 recovered without treatment, and there were no deaths. Risk factors include living in an endemic area, smoking, older age, diabetes, and low socioeconomic status [71]. Treatment is with amphotericin B.

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 the majority of pregnant women are young and healthy, intense, early treatment is likely to result in a good outcome.

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