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Pneumonia Complicating Pregnancy

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KEYWORDS
• Pregnancy • Pneumonia • Cesarean section • Aspiration

Community-acquired pneumonia (CAP) is a common illness that can be serious, particularly in pregnant patients. Pneumonia is the most common cause of fatal nonobstetric infection in pregnant patients.[1–3] Pneumonia is a cause of respiratory failure in pregnant patients, but newer data suggest that not all pneumonias are more common or more serious in pregnant women than in other populations in contrast to older studies. However, because pneumonia can affect both mother and fetus, it may lead to an increased likelihood of complicated preterm delivery compared with pregnancies in which infection is absent.

The reported incidence of pneumonia in pregnant women varies, probably because of the differences in the populations studied and the timing of the studies. A summary of studies that report the incidence of pneumonia in pregnancy is seen in **Table 1**.[4–8] Incidence of pneumonia of 6 in 1000 deliveries was reported before the seventies, declining in the seventies and eighties; more recent studies showed an increase, which may reflect women with chronic illnesses being able to become pregnant; prevalence of immune deficiencies (such as human immunodeficiency virus [HIV] infection), and rising illicit drug use in pregnant women. Although the incidence of pneumonia in pregnancy has declined, rates may be higher in large urban hospitals than in community settings, because of the pattern of the different populations at risk. Also, the available data generally come from those who are seen in a hospital and may not reflect milder forms of illness seen in a physician's office.

Pneumonia can also present in the postpartum period. Postpartum hospital admissions are generally related to infectious processes. Among the nonobstetric infections, gallbladder disease is the leading cause of postpartum admissions, followed by pneumonia. The odds of being admitted with pneumonia in the postpartum period are more than twice as high for patients who underwent cesarean deliveries compared with vaginal deliveries.[9] This higher prevalence may be due to more abdominal discomfort and splinting after cesarean deliveries. Other potential mechanisms may include comorbidities in patients necessitating cesarean deliveries, which may predispose patients to infections.

There are very few formally collected data sets about nosocomial pneumonia in the pregnant or postpartum patient, but in this category, one form is aspiration pneumonia complicating labor and delivery. Mendelson originally described gastric acid aspiration in obstetric patients undergoing labor and delivery,[10,11] and in the past, as many as 2% of all maternal deaths were due to aspiration.[11] The pregnant woman is physiologically predisposed to aspiration, because of the elevation of the intragastric pressure due to the gravid uterus, a relaxed gastroesophageal sphincter due to the circulating progesterone, and the delayed gastric emptying that accompanies pregnancy. These factors, the sedation and analgesia given during labor, and the vigorous

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Table 1
Reported incidence of pneumonia occurring in pregnancy

Study	Year of Publication	Setting	Results
Benedetti et al[4]	1982	89,219 deliveries in a university hospital	0.4 per 1000
Madinger et al[5]	1989	32,179 at a community hospital	0.78 per 1000
Berkowitz and LaSalsa[6]	1990	1120 case records at a large city hospital	2.72 per 1000
Munn et al[7]	1999	Comparison study to identify risk factors associated with antepartum pneumonia (59 cases vs 118 controls)	0.78–2.7 per 1000
Jin et al[8]	2003	Incidence of pneumonia in live births in the province of Alberta, Canada	1.47 per 1000

abdominal palpation during examinations all increase the threat of aspiration. Spinal anesthesia for cesarean section delivery could suppress cough reflex for at least 4 hours after delivery, possibly increasing the risk of aspiration during and after delivery.[12] The incidence of this complication has declined over time, with an increased awareness of the problem and with efforts directed toward prevention. In Mendelson's original series, the incidence was 1 in 667 deliveries,[11,13] but in the 1970s, the rate was as low as 1 in 6000 vaginal deliveries but 1 in 430 cesarean sections. More recent studies of cesarean section patients report a rate of 1 in 1431 to 1 in 1547.[11] Current strategies for raising gastric pH may be especially valuable for the cesarean section patient. Mortality from this complication has been very low in recent years, with 1 death in 9200 pregnancies.[11]

The impacts of pregnancy on pneumonia risk are listed (**Box 1**). Alterations in maternal cellular immunity have been described during pregnancy, especially in the second and third trimester, generally to protect the fetus from rejection by the mother. These include decreased lymphocyte proliferative response, especially in the second and third trimesters; decreased natural killer cell activity; changes in T-cell populations with a decrease in circulating helper T cells; reduced lymphocyte cytotoxic activity; and production of substances by the trophoblast that block maternal recognition of fetal major histocompatibility antigens.[2,14] Hormonal changes during pregnancy, including elevation of progesterone, human gonadotropin, α-fetoprotein, and cortisol, may also inhibit cell-mediated immune function.[14] These changes can predispose to infection with specific pathogens, such as viruses, fungi, and tuberculosis. Catanzaro[15] have shown that the hormonal changes lead to an increase in 17-estradiols, which can enhance the in vitro growth of *Coccidioides immitis*.[15]

Some of the physiologic changes of pregnancy may also predispose pregnant women to a severe pneumonia course, including elevation of the diaphragm by up to 4 cm, decrease in functional residual capacity, increase in oxygen consumption, and increase in lung water.[2,16,17] These alterations may decrease the ability of the pregnant woman to clear respiratory secretions and potentially aggravate airway obstruction associated with pulmonary infections. The elevation of the diaphragm, the associated decrease in functional residual capacity, and the increase in oxygen consumption during pregnancy make the pregnant woman less able to tolerate even brief periods of hypoxia, particularly in the third trimester.

ETIOLOGY OF PNEUMONIA IN PREGNANCY

The available data on infectious agents causing pneumonia in pregnancy show similar results to the pathogens that can cause lung infection in nonpregnant adults. These data are derived mainly from observational, and often retrospective, studies in which only routine microbiological investigations have been used. Sputum and blood cultures were the main methods of diagnosis (**Box 2**).[2,17] Hopwood[18] identified a cause in only 9 of 23 cases, with a mixture of gram-positive bacteria, gram-negative bacteria, and influenza A virus. Benedetti and colleagues[4] found a bacterial pathogen in 21 of 39 patients, with pneumococcus being the predominant pathogen accounting for 13 cases and *Hemophilus influenzae*, the next most common pathogen. Madinger and colleagues[5] also found *Streptococcus pneumoniae* (pneumococcus) to be the most common and *H influenzae*, the second-most common pathogen isolated. In these studies, serologic testing was rarely performed to search for atypical pathogens, such as *Mycoplasma* or *Chlamydophila*. Berkowitz and

Box 1
Alterations in pregnancy leading to an increased incidence and risk of complications from pneumonia

- Immunologic changes
  - Reduced lymphocyte proliferative response
  - Diminished cell-mediated cytotoxicity
  - Reduced number of helper T cells
  - Reduced lymphokine response to alloantigens
- Maternal physiologic changes
  - Increase in oxygen consumption
  - Increase in lung water
  - Elevation of diaphragm
  - Aspiration more likely in labor and delivery
- Coexisting illnesses/habits
  - Smoking
  - Anemia
  - Asthma
  - Cystic fibrosis
  - Illicit drug use
  - HIV infection
  - Recent viral respiratory infection of influenza
  - Immunosuppressive illness and therapy
  - Placental abruption
- Labor and delivery
  - Increases risk of aspiration pneumonia (can be modified)

Data from Khan S, Niederman MS. Pneumonia in the pregnant patient. In: Rosene-Montela K, Bourjeily G, editors. Pulmonary problems in pregnancy. New York (NY): Humana Press; 2009. p. 177–96.

Box 2
Bacteriology of pneumonia in pregnancy (in decreasing order of frequency)

- *Streptococcus pneumoniae* (including drug-resistant streptococcus pneumonia)
- *Hemophilus influenzae*
- No pathogens identified
- Atypical pneumonia agents:
  - *Legionella* species (more common in severe pneumonia)
  - *Mycoplasma pneumoniae*
  - *Chlamydophila pneumoniae*
- Viral agents
  - Influenza A
  - Varicella
- *Staphylococcus aureus* (including methicillin-resistant strains)
- *Pseudomonas aeruginosa* (with bronchiectasis, cystic fibrosis)
- Aspiration
- Fungi
  - Coccidioidomycosis
- *Pneumocystis jiroveci* (with HIV infection)

Data from Khan S, Niederman MS. Pneumonia in the pregnant patient. In: Rosene-Montela K, Bourjeily G, editors. Pulmonary problems in pregnancy. New York (NY): Humana Press; 2009. p. 177–96.

LaSala[6] also found pneumococcus and *H influenzae* to be the most common pathogens.

These studies are limited by a lack of comprehensive diagnostic testing, but even today, routine diagnostic testing is not recommended,[19] and even when performed, the yield is affected by type of material analyzed (sputum, bronchial washing, blood cultures), whether the patient was receiving antibiotics at the time of study, and whether serologies and antigen detection are performed. Atypical pathogens are not identified by routine cultures of sputum, yet are common causes of pneumonia in the nonpregnant patient. As described in numerous case reports and selected limited series, CAP in pregnancy may be caused by mumps, infectious mononucleosis, swine influenza, influenza A, including the novel H1N1 virus, *Staphylococcus aureus* (including methicillin-resistant forms), legionella, varicella, *Chlamydophila pneumoniae*, coccidioidomycosis, and other fungal pneumonias.[3,15,20–26] Whether infection with any of these agents is more common in pregnancy than in the nonpregnant state is unknown, but certain pathogens represent a greater hazard to the pregnant woman, because of her physiologic defects in cell-mediated immunity.

During pregnancy, varicella has been reported in 1 to 5 per 10,000 births, and the complications present a challenge for clinicians, mother, and fetus. With varicella, pneumonia usually complicates primary infection in 0.3% to 1.8% of all cases, but as many as 9% of primary cases during pregnancy can be complicated by pneumonia.[27] Influenza A is a common infection in pregnant women during epidemics and carries a higher mortality than in the nonpregnant patient,[25] with the maternal mortality rates being as high as 30% to 50% in the 1918 epidemic.[2,3,17,28] In the

Asian flu epidemic of 1957 to 1958, 10% of all deaths occurred in pregnant women, and almost 50% of women of childbearing age who died were pregnant.[25,29] This increased mortality was especially noted in the third trimester. During the 2009 to 2010 H1N1 influenza epidemic, severe illness caused by influenza was seen in pregnant women, increasing their morbidity and mortality and impacting the health of mother and fetus. Pregnant patients with H1N1 who were hospitalized showed an increased risk of obstetric complications, including premature and emergency cesarean delivery, and an increased risk of fetal complications, such as fetal distress and fetal death. Antivirals given early in the presentation of the disease seemed to improve outcomes in these patients.[30]

Another viral infection documented in pregnancy was severe acute respiratory syndrome (SARS) infection caused by a coronavirus. One series[31] described 12 patients with SARS during pregnancy, with 7 in the first trimester, and 5 in the second and third. Overall mortality was 25%, with half being admitted to the intensive care unit (ICU) and one-third requiring mechanical ventilation. Fetal complications were common, with 4 of the 7 infections that occurred in the first trimester leading to spontaneous abortion and most of the others leading to preterm labor and babies that were small for gestational age.

Other current microbiologic considerations should be recognized in patients with CAP. Up to 40% of *S pneumoniae* may be antibiotic-resistant (drug-resistant streptococcus pneumonia [DRSP]). In vitro resistance of *S pneumoniae* is fairly low level in many cases; however, the impact of such resistance on outcomes when usual therapies are administered is difficult to document.[19] If the patient has received any antibiotic in the 3 months preceding CAP and the pneumonia is due to pneumococcus, the organism is more likely to be resistant to an agent that was recently used.[32] In addition to recent antibiotic therapy, another risk of DRSP is exposure to a child in day care, a potentially common risk for women who are pregnant.[19] Community-acquired strains of methicillin–resistant *S aureus* (CA-MRSA) are not being reported commonly but may cause serious forms of CAP after influenza infection.[33] The organism can lead to a severe, bilateral necrotizing infection, because of the production of various toxins, including the Panton-Valentine leukocidin. Although this organism most commonly leads to skin and soft tissue infection, there is a case report of a severe necrotizing pneumonia due to CA-MRSA, which seeded the lung 9 days postpartum from septic pelvic thrombophlebitis because of an infected episiotomy site.[34] Two other recent case reports[35,36] of CA-MRSA in the fourteenth week of pregnancy in a 21-year-old woman and in a woman in her thirty-second week of pregnancy described successful treatment with a combination of linezolid and rifampin. In the second case, clindamycin, an agent that can reduce bacterial toxin production and serve as an antibacterial agent, was also added. Aspiration is a form of pneumonia that can be a postpartum or obstetric complication, causing a chemical pneumonitis or a bacterial infection involving the pathogens found in the oropharynx and gastric contents, primarily anaerobes and gram-negative enteric organisms.

CLINICAL FEATURES AND MANAGEMENT OF BACTERIAL/ATYPICAL PATHOGEN PNEUMONIA

Clinical Findings

The clinical presentations of pneumonia during pregnancy has not been found to differ substantially from the findings in nonpregnant adults and include fever, cough, pleuritic chest pain, rigors, chills, sputum production, and dyspnea.[37–39] A report by Ramsey and Ramin[39] found that 9.3% of pregnant pneumonia patients reported a productive cough; 32.2%, shortness of breath; and 27.1%, pleuritic chest pain.

Disease Severity

Although most women do not have multilobar illness,[4] in one series, the presence of this finding was correlated with a greater risk of a complicated course of illness, a finding also seen in nonpregnant patients.[40] Many different methods are used to define severity of illness in patients with CAP, but the Pneumonia Severity Index (PSI), which incorporates historical data, laboratory information, and physical findings, developed in the United States can help to define the need for inpatient and ICU care.[41] The PSI uses a complex scoring system assessment of patient age, comorbidity, and laboratory and clinical data to define a patient's risk of death. The calculated score is used to place the patient into one of 5 groups, each with increasing mortality risk. In its original derivation, pregnant patients were omitted, but Shariatzadeh and Marrie[38] have observed that all pregnant patients evaluated by them fell into the low-risk classes I and II, similar to age-matched controls. However, twice as many pregnant patients were hospitalized as age-matched controls with similar PSI scores, yet with a shorter length of stay. Thus, the PSI may underestimate the need for inpatient care in pregnancy, or physicians were being more cautious with admitting pregnant women even if

there was a fairly low predicted mortality risk. Similarly, Yost and colleagues[40] found that a PSI-based recommendation would have meant that two–thirds of admitted pregnant CAP patients could have been sent home, but if this had been done, 10 of 79 would probably have required readmission because of a complicated course.

Although guidelines suggest criteria for ICU admission in the CAP patient, these recommendations should probably be liberalized for the pregnant patient, because of a reduced physiologic ability to tolerate hypoxemia. Also, if certain infections are present, such as varicella-zoster or other viruses, the potential for rapid progression in pregnancy is high enough that expectant ICU observation may be justified. In the H1N1 epidemic, the hospitalization rate in pregnant women was 4 times higher than in the general population and was associated with a high risk of death and ICU admission.[42] Also, death from H1N1 in pregnant women was more common than for seasonal influenza.[43] Criteria for severe CAP used in the new American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines but not specific to pregnant women include the presence of at least one major criterion, such as the need for mechanical ventilation or septic shock requiring vasopressors, or the presence of 3 minor criteria.[19] The minor criteria include respiratory rate of at least 30 breaths per minute, PaO_2/FiO_2 ratio less than or equal to 250 mm Hg, multilobar infiltrates, confusion or disorientation, blood urea nitrogen greater than or equal to 20 mg/dL, white blood cell count less than 400 per mm^3, platelet count less than 100,000 per mm^3, hypotension requiring aggressive fluid resuscitation, and hypothermia. The guideline also suggested that criteria such as hypoglycemia, hyponatremia, asplenia (as in sickle cell disease), and unexplained acidosis be considered in deciding the need for ICU admission.[19]

Diagnostic Testing

Hopwood[18] recommended that all women with persistent upper respiratory distress have a chest radiograph to avoid delays in recognizing the presence of CAP. In one series, 98% of patients with antepartum pneumonia had positive findings on their chest radiographs at admission or on repeat examination, including infiltrates, atelectasis, pleural effusion, pneumonitis, or pulmonary edema.[7] In another series[4] of pneumonia in pregnancy, 28 of 39 patients had an infiltrate confined to a single lobe, whereas the remainder had multilobar pneumonia, and only 1 had a pleural effusion. Madinger and colleagues[5] reported that although all 25 pregnant patients who had pneumonia did have signs and symptoms of lung infection, the diagnosis was initially overlooked in 5 patients. This may explain why respiratory failure, empyema, and other serious complications adding to morbidity complicated diagnosis in half of those with pneumonia.

The ATS/IDSA guidelines for the management of adults with CAP also recommended that all patients with suspected CAP should have a chest radiograph (with an abdominal shield during pregnancy).[19] All admitted patients should also have an assessment of gas exchange (oximetry or arterial blood gas), routine blood chemistry, and blood counts. Blood cultures can give false-positive results and are only recommended in patients with severe illness, especially if there has been no prior therapy with antibiotics; for these patients, 2 sets of blood cultures are recommended. Sputum culture and Gram stain should be obtained if a drug-resistant pathogen or an organism not covered by usual empiric antibiotic therapy is suspected. Routine serologic testing is not recommended for any population with CAP. However, for patients with severe CAP, Legionella urinary antigen and pneumococcal urinary antigen tests are recommended, and aggressive efforts at establishing an etiologic diagnosis should be made, including consideration of bronchoscopy.

Antimicrobial Therapy

Initial therapy is empiric, based on the expected organisms, and should be directed in all patients at *S pneumoniae* (including DRSP in patients with recent antibiotic therapy or underlying chronic heart or lung disease and those with exposure to a child in daycare); *H influenzae* (especially in cigarette smokers); and *atypical* pathogens, such as *C pneumoniae, Mycoplasma pneumoniae*, and, in the setting of severe CAP, *Legionella pneumophila*. In choosing an antibiotic for bacterial pneumonia, the agent's safety in pregnancy and efficacy must be considered. Penicillins, cephalosporins, and erythromycin are all safe and potentially effective antimicrobials for CAP.[44] The penicillins are only 50% protein-bound and can cross the placenta to achieve fetal concentrations that are 50% of maternal levels. Clindamycin is probably also safe, but there is limited clinical experience with this agent.[45] The fluoroquinolones are commonly used to treat CAP in nonpregnant patients but are usually avoided during pregnancy, because of the risk of fetal arthropathy and malformations in animal studies and because they can be mutagens and carcinogens. However, sporadic reports of safe use in pregnancy have appeared, suggesting that they can be used if absolutely necessary.[46] Other drugs to be avoided in pregnancy include tetracyclines (the mother is at risk of fulminant

hepatitis, and these agents can stain and deform fetal teeth and cause bony deformities); chloramphenicol (which can cause bone marrow suppression in fetus, and if given near term, can cause "gray baby syndrome" with gray facies, flaccidity, and cardiovascular collapse); and sulfa compounds (can cause fetal kernicterus).[47] Aminoglycosides should be used only if there is a clinical indication of serious gram-negative infection, because there is significant risk of ototoxicity to the fetus. Vancomycin poses serious risk to the fetus, causing fetal nephrotoxicity and ototoxicity, and similarly, should only be used if absolutely necessary. Linezolid is a protein synthesis inhibitor. Linezolid has no safety data available in human pregnancies. A few case reports describe use of this drug in MRSA pneumonia.[35,36]

Current guidelines for CAP recommend that patients should not receive empiric therapy with a β-lactam (penicillin or cephalosporin) alone and that all patients be treated for atypical pathogens and pneumococcus. For an outpatient with mild CAP and no risks of DRSP, therapy should be with an oral macrolide such as azithromycin, which is better tolerated than erythromycin. Clarithromycin is not recommended for use in pregnancy, because of adverse embryonic and fetal outcomes in animal studies. If an outpatient with mild illness is at risk of DRSP, therapy should be given with a macrolide combined with high-dose amoxicillin (3 g/d), cefpodoxime, or cefuroxime (500 mg twice daily).

If the patient is admitted to hospital, therapy should be initially given intravenously with azithromycin or erythromycin if the patient has no risks of DRSP and intravenous macrolide and ceftriaxone or cefotaxime rather than cefuroxime[19] in patients at risk of DRSP. Yost and colleagues[40] studied 119 women with CAP who were hospitalized, and 83% received erythromycin monotherapy, with only one having a poor clinical response but with 5 requiring discontinuation because of intestinal symptoms. Azithromycin may be better tolerated as an intravenous macrolide than erythromycin.

In the ICU-admitted patient with severe CAP, no patient should get monotherapy, and combination therapy should be with cefotaxime or ceftriaxone plus a macrolide (azithromycin or erythromycin) if pseudomonal risks are not present. Pseudomonal risks include bronchiectasis, prolonged corticosteroid therapy, and cystic fibrosis, and if present, should be treated with an antipseudomonal β-lactam (imipenem, meropenem, cefepime, or piperacillin-tazobactam), an aminoglycoside (amikacin, gentamicin, tobramycin), and a macrolide. CA-MRSA should be considered in patients with severe CAP after influenza. However, although the safety of vancomycin and linezolid in pregnancy is not established, benefits of these drugs in patients with severe pneumonia probably outweigh the risks of the drugs, and patients should be counseled accordingly.

Supportive Care

Supportive therapy of the pregnant patient with pneumonia is similar to the nongravid state; hydration, antipyretic therapy, and supplemental oxygen remain key. The goal of oxygen therapy is to maintain the arterial oxygen tension at greater than 70 mm Hg, because hypoxemia is less well tolerated in pregnant women. Respiratory alkalosis leads to reduction in uterine blood flow, and thus, work of breathing should be decreased whenever possible in the pregnant pneumonia patient; adequate oxygenation may require the use of noninvasive ventilation. Respiratory failure mandating mechanical ventilation has occurred in pregnancy and requires close monitoring of mother and fetus. Preterm labor is a known complication of systemic infections, which should be suspected and addressed based on gestational age, fetal maturity, and maternal and fetal wellbeing.

Prevention of Aspiration

Pregnancy can increase the risk of aspiration, particularly in the peripartum period.[10] Patients can aspirate bacteria from the oropharynx (enteric gram-negatives or anaerobes), solid particulate matter from the stomach, or liquid stomach contents, including gastric acid. The aspiration of bacteria leads to a pneumonia that usually begins at least 24 hours after the event. When particulate matter is aspirated, it can lead to immediate bronchospasm, cough, and possibly cyanosis. Aspiration of gastric contents leads to symptoms that begin 6 to 8 hours after the event, at which time the patient usually presents with tachypnea, bronchospasm, pulmonary edema, or hypotention.[10] The risk of pneumonitis is substantially increased if the aspirated fluid has a pH of less than 2.4.[48]

The major thrust of management is prevention. Regional anesthesia is preferred over general anesthesia. In the latter scenario, airway protection with cricoid pressure and rapid sequence induction at the time of endotracheal intubation can reduce the risk of aspiration.[11] Raising gastric acid pH pharmacologically may also help avoid some of the complications of aspiration, but no data document a clear benefit or preference for antacids over histamine type-2 blockers and proton pump inhibitors.[49]

VIRAL PNEUMONIA EVALUATION AND MANAGEMENT

Influenza Virus

The influenza viruses are myxoviruses of 3 antigenically different types, A, B, and C, that can cause disease in humans, but most epidemics in humans are due to type A, as was the case with the novel H1N1 virus. First identified in 1933, influenza remains a significant cause of morbidity and mortality from febrile respiratory illness worldwide.[28,50] Pregnant women are at increased risk of acquiring influenza and developing complications of infection. In one study by Neuzil and colleagues,[28] pregnant women were affected more often than nonpregnant women. Influenza also led to hospitalization for acute cardiopulmonary illness more often in older women during the third trimester and in those with underlying medical conditions, such as asthma.[28,51] Historically, influenza in pregnancy has been associated with a high rate of morbidity and mortality, and epidemic infection may lead to more complications than sporadic infection.[52] The course of influenza was first reported during the epidemic of 1918 when 1350 cases in pregnant women who had an influenza-like illness were evaluated, and pneumonia was a complication in 585(43%) of these. In 52% of these patients, pregnancy was interrupted, and there were 308 (23%) maternal deaths. The mortality was highest in the last 3 months of pregnancy, especially when complicated by pneumonia.[50] Overall, in the 1918 epidemic, influenza during pregnancy had a 30% maternal mortality, increasing to 50% in the presence of pneumonia.[53] Mortality rose in parallel with gestational age to a maximum of 61% when influenza was contracted after 36 weeks of gestation. In the 1957 epidemic, 50% of women of childbearing age who died were pregnant and 10% of all the influenza deaths were among pregnant women.

However, since 1958, pregnancy has not been associated with an enhanced morbidity and mortality from influenza until the H1N1 infections in 2009 to 2010. Influenza pneumonia occurred in 12% of 102 pregnant patients with influenza in the 2003-to-2004 season and led to complications, such as respiratory failure, meningitis, and myocarditis.[3] In April of 2009, the first cases of influenza A H1N1 were registered in Mexico and were associated with an unexpected number of deaths. Data from the surveillance system of the Mexican health authorities[54] showed a death rate of about 1% of all confirmed 6945 cases, and the highest risk group was in the 10- to 39-year-old age group. Out of the 63 deaths in the period from April to July, 2009 in Mexico, 4 were in pregnant women. All pregnant workers were taken out of work during the period of the pandemic in Mexico. Surveillance data from the US Centers for Disease Control (CDC)[30] collected between August 21 and December 31, 2009 showed that 5% of 509 hospitalized pregnant women died, and those with delayed antiviral therapy (more than 4 days after onset of symptoms) were more likely to be admitted to an ICU (relative risk 6.0) and have worse outcomes, such as death. The most common comorbid conditions found in these patients were asthma and obesity. In that subset, it seemed that patients with advanced pregnancy (second and third trimester) were at a higher risk of death, with four of the 56 deaths having occurred in the first trimester (7.1%), 15 in the second (26.8%), and 36 in the third (64.5%). Previous reports from the US CDC database collected in the first 2 months of the pandemic[55] showed a high mortality in pregnant women. Six deaths occurred in pregnant women in the initial months of the epidemic, all in women who had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation. A case-series from the state of Victoria in Australia[56] identified 43 pregnant patients admitted to the hospital with H1N1, 8 of whom were in the ICU. Again, asthma, obesity, and diabetes were conditions commonly present in these patients, but about half had no comorbidities and the only identified risk factor of influenza was pregnancy. Pneumonia was a common complication found in 11 of the 43 pregnant patients. Only one patient died and there were 2 fetal deaths and one neonatal death, pointing to the importance of worse outcomes for mother and fetus. Influenza was associated with preterm delivery, and 36% of patients delivered while admitted to the hospital for influenza.

The clinical symptoms of influenza do not seem to be altered by pregnancy, even if it is a more severe illness than in the nonpregnant patient. The incubation period is 1 to 4 days, and symptoms include cough, fever, malaise, coryza, headache, and myalgias.[57] In an uncomplicated case, influenza may resolve in 3 days or less. If symptoms persist for more than 5 days, especially in a pregnant patient, complications, such as pneumonia, should be considered. Pneumonia, either a viral or a secondary bacterial infection, is a well-recognized complication of influenza.

When pneumonia complicates influenza in pregnancy, antibiotics should be started and should be directed at the likely pathogens that can cause secondary infection, including pneumococcus, *H influenzae,* and *S aureus* including MRSA. Therapy for these organisms has been discussed

earlier, but antiviral agents should be started if a viral pneumonia is likely, especially early in the course of illness.[2] Antiviral agents, such as amantadine and rimantadine, can prevent illness in exposed patients and reduce the duration of symptoms if given within 48 hours of its onset. Amantadine is effective against Influenza A, whereas oseltamivir and zanamivir are active against influenza A and B; all can be used for prophylaxis in high-risk pregnant women or for therapy in complicated cases.[2] Animal reports of teratogenicity with the use of Amantadine seem to be species-specific. Although many reports describe various congenital malformations associated with the use of amantadine and oseltamivir, none provide sufficient information for a conclusion on the developmental toxicity of these drugs to be reached. Despite these concerns, pregnancy is certainly not a contraindication for the use of antivirals, because during the 2009 H1N1 epidemics, the use of antiviral therapy with oseltamivir, zanamivir, and amantadine, alone or in combination, was associated with better outcomes if initiated earlier at onset of the symptoms (before day 2).[30] The CDC recommends that for pregnant patients, antiviral drugs should be started as soon as possible after the onset of influenza symptoms. Oseltamivir and zanamivir are found in breast milk; however, the concentrations of oseltamivir in breast milk is about 1% of serum levels, and no adverse effects of lactation exposure to zanamivir was found in rats.

Although antivirals can be prophylactic after exposure, the primary method of influenza prevention is vaccination. The recommendation of the Advisory Committee on Immunization Practices is that all women who will be pregnant during the influenza season receive the vaccine. The same principle applies to the novel H1N1 virus vaccine. Vaccination can also be performed safely in any trimester of pregnancy but should be avoided in the first trimester, if possible, unless the timing of the influenza season necessitates immunization at that time.[58,59] The inactivated form of the vaccine (not the nasal vaccine) is used for pregnant women and other high-risk groups. Breast-feeding is not a contraindication to vaccination.[59]

Varicella Pneumonia

Varicella is a particular problem that can complicate pregnancy, having a higher incidence and severity than in nonpregnant patients and with the potential to complicate the course of pregnancy and lead to congenital defects. Pneumonia is the most serious complication of varicella, but when varicella is present in the pregnant patient, it carries a high mortality, between 35% and 40%.[3,27] Haake and colleagues[27] reviewed 34 cases of varicella pneumonia in pregnancy and found a 35% mortality. Although only 5% to 10% of cases occur in adults, this population accounts for 25% to 55% of fatal cases. A recent series from Spain indicated that among the 46 patients studied with varicella pneumonia, 24% were treated in the ICU but none of them died, including 2 females who were pregnant.[60] Varicella-zoster (VZ) is a DNA virus that usually causes a benign, self-limited illness in children (chickenpox), but up to 10% of the adult population is susceptible to primary infection.[17] Studies show that the infection rate in pregnant women is as high as 4% to 6.8%, but after a close exposure, the risk of infection may be as high as 70%.[61] Pregnancy may also increase the rate of pneumonia as a complication of primary infection, and smoking may also be a risk factor of developing this complication, with infected smokers having a higher rate of pneumonia than infected nonsmokers.[62]

Pregnancy also enhances the virulence of the VZ virus as a consequence of functional T-cell abnormalities and of the higher levels of circulating corticosteroids, along with circulatory overload and altered respiratory reserve. Most reports have shown that when varicella pneumonia complicates pregnancy, it is usually in the third trimester and that infection occurring at this time is more severe and complicated than if it occurs earlier.[20,63] The incidence of pulmonary involvement in primary varicella infection is approximately 16%.[3]

The varicella virus can have a period of incubation of 10 days to 3 weeks.[3] In the mother, the virus is in the blood for 24 to 48 hours before the exanthem, and during this period, 24% of fetuses develop transplacental infection,[64] which can lead to congenital malformations in 1.2% of exposed fetuses. Clinically, varicella pneumonia presents 2 to 5 days after the onset of fever, vesicular rash (chickenpox), and malaise and is heralded by the onset of pulmonary symptoms,[2,20] including cough, dyspnea, pleuritic chest pain, and even hemoptysis. In one series, all patients with VZ pneumonia had oral mucosal ulcerations. Severity of illness may range from asymptomatic radiographic infiltrates to fulminant respiratory failure and acute lung injury.[20] Typically, chest radiographs reveal interstitial, diffuse miliary or nodular infiltrates that resolve by 14 days unless complicated by acute lung injury and respiratory failure.[64] The severity of infiltrates has been described to peak with the height of the skin eruption. One of the late radiographic sequelae of varicella pneumonia is diffuse pulmonary calcification.[65]

All patients with VZ pneumonia require antiviral agents (acyclovir) and early hospitalization. Mechanical ventilation may be needed in up to half of all pregnant women, and this group has a mortality rate of at least 25%. Registry and other data on acyclovir, a DNA polymerase inhibitor in the pregnant patient, have shown no increase in birth defects following in utero exposure to this drug.[66–68] In a study of 312 pregnancies in which acyclovir was used, no increase in the number or pattern of birth defects was seen.[67] However, there is no evidence of the efficacy of acyclovir for improving outcome, although some studies have suggested that this therapy can reduce the risk of developing respiratory failure and mortality for mother and fetus. Haake and colleagues[27] reviewed the early initiation of therapy within 36 hours of admission and found that those receiving early therapy had an improved hospital course after the fifth hospital day, lower mean temperature, less tachypnea, and improved oxygenation compared with those who were not treated. The recommended dose is 7.5 mg/kg every 8 hours intravenously, although doses of 3 to 18 mg/kg have been used. Treatment is recommended for 7 days. Some small series have suggested a benefit from adjunctive corticosteroid therapy.[3]

The effects of varicella on the fetus include intrauterine infection in 10% to 20%. Traditionally, fetal involvement has occurred in 3 patterns: "varicella embryopathy" stemming from maternal disease developing before 20 weeks' gestation, congenital varicella from 20 weeks' gestation until term but more commonly close to term, and neonatal disease occurring when the pregnant patient has active lesions at the time of delivery.[69] Varicella embryopathy was first described in 1947 and has since been redefined by several authors, but it includes limb hypoplasia, skin scarring, central nervous system involvement, and other skeletal lesions. This embryopathy has been reported with infection occurring as late as 26 weeks.[69]

The largest series of congenital varicella reported 1373 pregnancies complicated by VZ from 1980 to 1993. Fetal abnormalities occurred most commonly in the children of women infected between 13 and 20 weeks of gestation than at any other time in pregnancy.[70] Fetal anomalies varied from skin lesions to lethal multiorgan system involvement. Because of concern about fetal effects, the use of prophylactic immune globulin is recommended within 96 hours of exposure to prevent maternal illness in women without prior varicella infection (negative Ig G titers) or immunization. Although the use of VZ immune globulin in a pregnant woman may not eliminate the incidence of embryopathy, if given before maternal infection develops, it may decrease or attenuate fetal disease.[70] Immunoprophylaxis with zoster immune globulin should be given early after close exposure of a seronegative pregnant women, with the aim of preventing disease in the mother but not in the fetus. Although expensive, one analysis suggested that the use of this approach is likely to be cost-effective.[22] The varicella vaccine, however, is contraindicated in pregnancy because it is a live- attenuated vaccine.

Other Viruses

Pneumonia may complicate up to 50% of adult measles cases, and bacterial superinfection is common. In one report of 3 cases of rubeola during pregnancy, all patients had bacterial superinfection and 2 had preterm labor.[26]

SARS is caused by a coronavirus, which can affect pregnant women, leading to symptoms that are the same as in nonpregnant women and include fever, chills, rigors, malaise, and myalgias.[71] Patients are most infectious in the second week of illness. Laboratory findings include marked lymphopenia and thrombocytopenia, and chest radiographs show patchy to generalized interstitial infiltrates.[71] The case fatality was 25% in 12 cases that were reported in pregnancy, and other complications included first-trimester spontaneous abortions, preterm births, and intrauterine growth restriction. Treatment includes broad-spectrum antibiotics to cover superimposed bacterial infections, high-dose corticosteroids, and, possibly, ribavirin, which has been teratogenic in animals.[31]

FUNGAL PNEUMONIA

Fungal pathogens can cause pneumonia in pregnancy, including *Cryptococcus neoformans, Histoplasma capsulatum, Sporothrix schenkii, Blastomyces dermatitidis, and Coccidioides immitis*.[39] Fungal pneumonia in pregnancy is rare and usually resolves without treatment in healthy women. However, disseminated disease carries a more serious prognosis and can complicate pregnancy, particularly with infection in the third trimester and in those with HIV infection.[15,21]

Coccidioidomycosis generally occurs in the Southwestern United States and symptoms include fever, cough, headache, malaise, weight loss, and erythema nodosum. Although most patients have pulmonary involvement (including an infiltrate, pleural effusion, miliary infiltrates, or cavitation), disseminated disease involves the central nervous system, skin, and bones. Those with erythema nodosum have a lower rate of

disseminated disease and a higher rate of recovery.[21]

For disseminated disease or severe pneumonia, treatment with intravenous amphotericin B is recommended, followed by oral fluconazole postpartum.[21,72] Earlier series used ketoconazole and itraconazole, but fluconazole is preferred as a more effective, more bioavailable agent.[21] Fluconazole has been associated in case reports with congenital anomalies similar to Antley-Bixler syndrome, mainly with high-dose and prolonged use of the drug, such as doses used to treat systemic fungal infections. Although case reports do not establish teratogenicity, it is unlikely that occurrence of an unusual genetic abnormality with high-dose fluconazole would occur by chance alone. Animal reports on reproductive effects of amphotericin B are incomplete. Although the lack of birth defects in infants exposed in utero to the drug does not establish its safety, the use of amphotericin in severe fungal pneumonia should not be delayed. The severity of fungal infections and the potential for morbidity and mortality may justify the use of drugs such as fluconazole. Proper patient counseling should happen in those cases. Other fungal infections have been reported in pregnancy but are uncommon, and the impact of pregnancy on these infections and the bearing of these infections on the outcome of pregnancy is uncertain.[2]

PNEUMONIA COMPLICATING HIV INFECTION

Pregnancy can theoretically accelerate the progression of underlying HIV infection-related immune suppression, and respiratory infection can be the AIDS-defining illness for some pregnant patients, leading to an increased risk of maternal and fetal mortality.[73] Also, vertical transmission of HIV infection to the newborn is a serious concern. Antiretroviral therapy may improve CD4+ count and reduce the risk of respiratory infection, but if this therapy is stopped in pregnancy, the risk of respiratory infection rises.

Bacterial respiratory infections are the most common respiratory complication of HIV infection, but a low CD4+ count (<200 cells per μL) predisposes to bacterial pneumonia and to pneumonia with *Pneumocystis jiroveci* (PCP), which can be a serious infection risk for both mother and fetus. In one review of 22 patients with PCP in pregnancy, 59% with respiratory failure necessitating mechanical ventilation, 50% mortality for the mothers, 5 intrauterine deaths, and 4 neonatal deaths were reported.[74] Women with PCP infection should receive therapy with trimethoprim-sulfa (TMP-SMX), along with corticosteroids if hypoxemia is present. These patients should be monitored for preterm labor and at the time of delivery, and women receiving TMP-SMX or dapsone should have their newborns monitored closely for hyperbilirubinemia and kernicterus. Immune reconstitution inflammatory syndrome may occur in the postpartum period. For HIV-infected women without active PCP, prophylaxis is best done when the CD4+ cell count falls to less than 200 cells per μL using TMP-SMX, but because of teratogenic risk with this medication in the first trimester, consideration should be given to the use of aerosolized pentamidine because of its lack of systemic absorption.

SUMMARY

Pneumonia in pregnancy is associated with a higher morbidity and mortality than in the nonpregnant population. Several physiologic and immunologic changes that occur in pregnancy may predispose to infection and impair the ability of pregnant patients to respond to respiratory pathogens. The early recognition and treatment of the diverse etiologic agents of pneumonia can improve outcomes for fetus and mother. Antibiotics should be selected with fetal safety in mind. Pneumonia can be prevented by avoidance of aspiration, use of influenza vaccination, and treatment with appropriate prophylaxis of known HIV-positive patients with a CD4 cell count of less than 200 cells per mL or those with a previous earlier history of pneumonia.

REFERENCES

1. Kaunitz AM, Hughes JM, Grimes DA, et al. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–12.
2. Rodrigues JM, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med 1992;13:679–91.
3. Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med 2005;33:S390–7.
4. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. Am J Obstet Gynecol 1982; 144:413–7.
5. Madinger NE, Greenspoon JS, Elrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161:657–62.
6. Berkowitz K, LaSala A. Risk factors associated with increasing prevalence of pneumonia during pregnancy. Am J Obstet Gynecol 1990;163:981–5.
7. Munn MB, Groome LJ, Atterbury JL, et al. Pneumonia as a complication of pregnancy. J Matern Fetal Med 1999;8:151–4.
8. Jin Y, Carriere KC, Marrie TJ, et al. The effects of community acquired pneumonia during pregnancy

ending in a live birth. Am J Obstet Gynecol 2003;18: 800–6.
9. Belfort MA, Clark SL, Saade GR, et al. Hospital readmission after delivery: evidence for an increased incidence of nonurogenital infection in the immediate postpartum period. Am J Obstet Gynecol 2010;35:e1–7.
10. Baggish MS, Hooper S. Aspiration as a cause of maternal death. Obstet Gynecol 1974;43:327–36.
11. Engelhardt T, Webster NR. Pulmonary aspiration of gastric contents in anaesthesia. Br J Anaesth 1999;83:453–60.
12. Gayat E, Lecarpentier E, Retout S, et al. Cough reflex sensitivity after elective caesarean section under spinal anaesthesia and after vaginal delivery. Br J Anaesth 2007;99:694–8.
13. Dines DE, Baker WG, Scantland WA. Aspiration pneumonitis—Mendelson's syndrome. JAMA 1961; 176:229–31.
14. Lederman MM. Cell-mediated immunity and pregnancy. Chest 1984;86:6S–9S.
15. Catanzaro A. Pulmonary mycosis in pregnant women. Chest 1984;86:14S–9S.
16. Rigby FB, Pastorek JG II. Pneumonia during pregnancy. Clin Obstet Gynecol 1996;39:107–19.
17. Khan S, Niederman MS. Pneumonia in the pregnant patient. In: Rosene-Montela K, Bourjeily G, editors. Pulmonary problems in pregnancy. New York (NY): Humana Press; 2009. p. 177–96.
18. Hopwood HG. Pneumonia in pregnancy. Obstet Gynecol 1965;25:875–9.
19. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
20. Harris RE, Rhoades ER. Varicella pneumonia complicating pregnancy: report of a case and review of the literature. Obstet Gynecol 1965;25:734–40.
21. Spinello I, Johnson R, Baqui S. Coccidioidomycosis and pregnancy. Ann N Y Acad Sci 2007;1111:358–64.
22. McKendrik MW, Lau J, Alston S, et al. VZV infection in pregnancy: a retrospective review over 5 years in Sheffield and discussion on the potential utilisation of varicella vaccine in prevention. J Infect 2007;55:64–7.
23. Biem J, Roy L, Halik J, et al. Infectious mononucleosis complicated by necrotizing epiglottitis, dysphagia, and pneumonia. Chest 1989;96:204–5.
24. Gherman RB, Leventis LL, Miller RC. Chlamydial psittacosis during pregnancy: a case report. Obstet Gynecol 1995;86:648–50.
25. McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. Arch Intern Med 1990;150:213–5.
26. Stein SJ, Greenspoon JS. Rubeola during pregnancy. Obstet Gynecol 1991;78:925–9.
27. Haake DA, Zakowski PC, Haake DL, et al. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. Rev Infect Dis 1990;12:788–98.
28. Neuzil KM, Reed GW, Mitchel EF, et al. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148: 1094–102.
29. Winterbauer RH, Ludwig WR, Hammar SP. Clinical course, management and long-term sequelae of respiratory failure due to influenza viral pneumonia. Johns Hopkins Med J 1977;141:148–55.
30. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010;303: 1517–25.
31. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with SARS. Am J Obstet Gynecol 2004;191:292–7.
32. Vanderkooi OG, Low DE, Green K, et al. Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis 2005;40:1288–97.
33. Micek ST, Dunne M, Kollef MH. Pleuropulmonary complications of Panton-Valentine leukocidin-positive community-acquired methicillin-resistant Staphylococcus aureus: importance of treatment with antimicrobials inhibiting exotoxin production. Chest 2005;128:2732–8.
34. Rotas M, McCalla S, Liu C, et al. Methicillin-resistant staphylococcus aureus necrotizing pneumonia arising from an infected episiotomy site. Obstet Gynecol 2007;109:533–6.
35. Mercieri M, Di Rosa R, Pantosti A, et al. Critical pneumonia complicating early -stage pregnancy. Anesth Analg 2010;110:852–4.
36. Broadfield E, Doshi N, Alexander PD, et al. Cunning and community-acquired pneumonia. Lancet 2009; 373:270.
37. Finland M, Dublin TD. Pneumococcal pneumonias complicating the pregnancy and puerperium. JAMA 1939;250:1027–32.
38. Shariatzadeh MR, Marrie TJ. Pneumonia during pregnancy. Am J Med 2006;119:872–6.
39. Ramsey PS, Ramin KD. Pneumonia in pregnancy: medical complications of pregnancy. Obstet Gynecol Clin North Am 2001;28:553–69.
40. Yost NP, Bloom SL, Richey SD, et al. An appraisal of treatment guidelines for antepartum community acquired pneumonia. Am J Obstet Gynecol 2000;183:131–5.
41. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community- acquired pneumonia. N Engl J Med 1997;336:243–50.
42. Louie JK, Acosta M, Jamieson DJ, et al. Severe 2009 H1N1 influenza in pregnant and postpartum women in california. N Engl J Med 2010;362:27–35.
43. Callaghan WM, Chu SY, Jamieson DJ. Deaths from seasonal influenza among pregnant women in the

United States, 1998–2005. Obstet Gynecol 2010; 115:919–23.
44. Hollingsworth H. Pneumonia in pregnancy. Obstet Gynecol 1985;65:605–12.
45. Maccato ML. Respiratory insufficiency due to pneumonia in pregnancy. Obstet Gynecol Clin North Am 1991;18:289–99.
46. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother 1998;42:1336–9.
47. Levin S, Jupa JE. Principles of antibiotic use in obstetrics and gynecology. Obstet Gynecol Annu 1976;5:293–313.
48. Hollingsworth HM, Pratter MR, Irwin RS. Acute respiratory failure in pregnancy. J Intensive Care Med 1989;4:11–34.
49. Paranjothy S, Griffiths JD, Broughton HK, et al. Interventions at caesarean section for reducing the risk of aspiration pneumonitis. Cochrane Database Syst Rev 2010;1:CD004943.
50. Harris JW. Influenza occurring in pregnant women. JAMA 1919;72:978–80.
51. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol 2003;2:145–55.
52. Laibl VR, Sheffield JS. Influenza and pneumonia in pregnancy. Clin Perinatol 2005;32:727–38.
53. Larsen JW. Influenza and pregnancy. Clin Obstet Gynecol 1982;25:599–603.
54. Echevarría-Zuno S, Mejía-Aranguré JM, Mar-Obeso AJ, et al. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. Lancet 2009;374:2072–9.
55. Jamieson DJ, Honein MA, Rasmussen SA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. Lancet 2009;374:451–8.
56. Hewagama S, Walker SP, Stuart RL, et al. 2009 H1N1 influenza A and pregnancy outcomes in Victoria, Australia. Clin Infect Dis 2010;50:686–90.
57. Cox NJ, Subbarao K. Influenza. Lancet 1999;354: 1277–82.
58. Deinard AS, Ogburn P. Influenza vaccination program effects on maternal health and pregnancy outcome. Am J Obstet Gynecol 1981;140:240–5.
59. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza. Recommendations of the advisory committee on immunization practices. MMWR Recomm Rep 2004;53:1–40.
60. Chiner E, Ballester I, Betlloch I, et al. Varicella-zoster virus pneumonia in an adult population: has mortality decreased? Scand J Infect Dis 2010;42: 215–21.
61. Sauerbrei A, Sonntag S, Wutzler P. [Prevalence of varicella zoster in pregnant patients]. Zentralbl Gynakol 1990;112:223–6 [in German].
62. Ellis M, Neal K, Webb A. Is smoking a risk factor for pneumonia in adults with chickenpox? BMJ 1986; 294:1002.
63. Zambrano MA, Martinez A, Minguez JA, et al. Varicella pneumonia complicating pregnancy. Acta Obstet Gynecol Scand 1995;74:318–20.
64. Cox SM, Cunningham FG, Luby J. Management of varicella pneumonia complicating pregnancy. Am J Perinatol 1990;7:300–1.
65. Eder SE, Apuzzio JJ, Weiss G. Varicella pneumonia during pregnancy: treatment of two cases with acyclovir. Am J Perinatol 1988;5:16–8.
66. Centers for Disease Control. Pregnancy outcomes following systemic prenatal acyclovir exposure-June 1, 1984–June 30, 1993. MMWR 1993;42: 806–9.
67. Andrews EB, Yankasas BC, Cordero JF, et al. Acyclovir in pregnancy registry: six years experience. Obstet Gynecol 1992;79:7–13.
68. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984–1999. Birth Defects Res A Clin Mol Teratol 2004;70: 201–7.
69. Katz VL, Kuller JA, McMahon MJ, et al. Varicella during pregnancy: maternal and fetal effects. West J Med 1995;163:446–50.
70. Enders G, Miller E, Cradock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet 1994;343:1548–51.
71. Peiris JS, Yuen KY, Osterhaus AS, et al. The severe acute respiratory syndrome. N Engl J Med 2003; 349:2431–41.
72. Ely EW, Peacock JE, Haponik EE, et al. Cryptococcus pneumonia complicating pregnancy. Medicine 1998;77:153–67.
73. Kumar RM, Uduman SA, Khurrana AK. Impact of pregnancy on maternal AIDS. J Reprod Med 1997; 42:429–34.
74. Ahmad H, Mehta NJ, Manikal VM, et al. Pneumocystis carinii pneumonia in pregnancy. Chest 2001;120: 666–71.