**Pneumonia in the Pregnant Patient**

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**ABSTRACT** Pneumonia is an infrequent yet serious complication of pregnancy. It is the third most frequent cause of obstetric death. Disease in the pregnant host impacts both mother and fetus adding to morbidity and mortality in this population. The pregnant host is at greater risk of infection than her nonpregnant counterpart because of the accompanying immunosuppression of pregnancy.

Series to date have shown that the etiologic pathogens seen in the pregnant pneumonia patient are similar to those seen in the nonpregnant patient of comparable age. However, it is apparent that infection with any of these agents represents a greater hazard to the pregnant woman because of her physiologic defects in cell-mediated immunity. Careful management and vigilance to the vulnerability of the pregnant host will prevent some pneumonias, particularly influenza and aspiration pneumonia. As in any illness in the pregnant patient safety of antimicrobial therapy is paramount and leads to some differences in choice of therapy compared to the nonpregnant.

Key Words: pregnancy, pneumonia, viral pneumonia, bacterial pneumonia, fungal pneumonia, aspiration pneumonia

Pneumonia is an infrequent yet serious complication of pregnancy and is the most frequent cause of nonobstetric infection and the third most frequent cause of indirect obstetric death.1,2 The incidence of pneumonia in the pregnant patient may in fact be rising at the current time,3 as a result of both the declining health of certain segments of the child bearing population, and because of the growing trend in obstetrics for women with serious underlying illnesses to proceed with pregnancy in this era of sophisticated medical care.2

Particular types of pneumonia bear special significance for the pregnant patient, especially those of viral origin. Disease in the pregnant patient impacts both mother and fetus, adding morbidity and mortality when compared to the nonpregnant patient. In addition, pneumonia in the pregnant patient leads to an increased likelihood of complicated preterm delivery compared to pregnancies in which infection is absent. This article discusses the current epidemiology, bacteriology, clinical features, and management of pneumonia in pregnancy focusing on the spectrum of bacterial, viral, fungal, and aspiration pneumonias that are commonly encountered. Tuberculosis in pregnancy is discussed elsewhere but the role of HIV infection and its implications in the pregnant patient are given special attention. Throughout, we have emphasized the influence of the pregnant state on the course of pneumonia, highlighting its differences compared to the nongravid patient and demarcating its effect on maternal and fetal outcomes.

**PHYSIOLOGIC CHANGES IN PREGNANCY PREDISPOSING TO PNEUMONIA**

During pregnancy anatomic changes occur in the chest, which include the lower ribs flaring outwards, the subcostal angle increasing as the transverse diameter of the chest increases by about 2.1 cm and the circumference of the thoracic cage increasing by 5-7 cm. The diaphragm rises by 4 cm, but its excursions are not hampered by the enlarged uterus.2,4 These alterations decrease the ability of the pregnant patient to clear respiratory secretions and aggravate airway obstruction associated with pulmonary infections. The elevation of the di-
aphragm decreases functional residual capacity (FRC) and coupled with an increase in oxygen consumption during pregnancy, makes the pregnant patient less able to tolerate even brief periods of hypoxia particularly in the third trimester. Progesterone derived from the placenta stimulates the respiratory center in the brain to produce hyperventilation and a sensation of dyspnea, but the respiratory rate is normal and thus any evidence of tachypnea should be recognized as pathologic, and this finding can still be used to evaluate the severity of illness when pneumonia is present.

The major factor that predisposes pregnant women to severe pneumonic infections is the alteration in immune status. These alterations occur primarily in cell-mediated immunity making viral, fungal, and tuberculous infections particularly virulent in the pregnant patient. Multiple changes in the maternal immune system in pregnancy have been documented including a decreased lymphocyte proliferative response especially in the second and third trimesters, decreased natural killer cell activity, and decreased number of helper T4 cells. The trophoblast has been noted to produce substances that could block maternal recognition of fetal major histocompatibility antigens. Maternal serum may also block lymphokine secretion and lymphoproliferative responses to alloantigens and fetal lymphocytes may inhibit the maternal immune response by suppressing T-cell proliferation. These immune system adaptations are designed to protect the growing fetus from its antigenically different mother, but may make the mother more susceptible to infection.

The hormonal milieu in the pregnant state is also conducive to infection in several ways. Progesterone, human chorionicadotropin, alpha-fetoprotein and cortisol may inhibit cell-mediated immunity. Additionally, estrogens (the 17-estradiols) progesterone, and testosterone can enhance the in vitro growth of certain pathogens such as Coccidioides immitis. Additionally, the pregnancy confers a propensity to increased lung water making lung injury more likely.

**EPIDEMIOLOGY**

The incidence of pneumonia has varied widely in a number of published surveys, reflecting the different populations that have been studied. A study in 1939 reported that pneumonia complicated 1 in every 158 pregnancies. Hopwood studied 2790 pregnancies in 1965 reporting an increased incidence of 1 in 118 deliveries. More recently Benedetti et al examined 89,219 deliveries in a university and county hospital setting from 1972–1975 and they documented a decline in the incidence of pneumonia to 1 in 2288 deliveries.

Current series now reflect a rising incidence. Madinger et al studied 32,179 deliveries at a community hospital from 1983–1988 and found pneumonia to complicate 1 out of every 1287 deliveries. Finally, Berkowitz and LaSalsa examined 1120 case records at a large city hospital from 1988–1989 and found that antepartum pneumonia occurred in 1 of every 367 deliveries. This pattern of an increasing incidence of pneumonia complicating pregnancy in recent years may reflect the frequency of chronic illness among pregnant women as well as the rising prevalence of immune deficiencies including HIV infection and illicit drug use. Other factors that place the pregnant patient at increased risk for pneumonia are tobacco use and prior heart disease.

**EFFECT OF PNEUMONIA ON OBSTETRIC OUTCOME**

Although pneumonia can occur at any time during gestation, Hopwood’s study found the mean time was 32 weeks and that preterm labor is more likely to occur if the pneumonia was present between the week 20 and 36 of gestation. Hopwood’s 1965 study found 17 of 23 patients to develop pneumonia between weeks 25 and 36 of gestation and 7 delivered during the course of their acute illness, with 2 mortalities among this group. In Benedetti’s more recent series of 39 cases of pneumonia in pregnancy, 16 presented before 24 weeks gestation, 15 from weeks 25 and 36 of gestation and 8 later than 37 weeks gestation.

Significant fetal complications are observed in all of the large studies of pneumonia in pregnancy. The majority of poor fetal outcomes occurred in mothers with underlying comorbid illnesses such as chronic respiratory disease, Madinger’s study found preterm delivery to occur in 5 of 6 women who presented with underlying maternal disease while Berkowitz noted a 12% rate of babies that were small for gestational age and women had infants who weighed 400 gm less than randomly selected patients without pneumonia.

Benedetti reported a 2.6% rate for intrauterine fetal death and Madinger noted a 12% neonatal death rate. Although most pregnant patients with pneumonia do well, it is critical to identify the high-risk mother with comorbid illness, and to monitor and to treat aggressively in an effort to avoid morbidity and mortality.

Berkowitz reported the outcomes of 25 patients, with pneumonia in pregnancy. Full-term delivery occurred in 14, 1 had preterm delivery, 3 un-
derwent voluntary termination of pregnancy, 3 had term babies that were small for gestational age and 4 were lost to follow-up. In this series most cases were diagnosed in the second and third trimesters.

Pneumonia was present at the time of delivery in 11 patients in Madinger’s study, being common in those who had bacteremia, need for mechanical ventilation, and serious underlying maternal disease. In addition to the complication of preterm labor, there were three perinatal deaths; although it is important to note that in this series as in the others, there was no evidence of congenital abnormalities as a direct result of pneumonia in the pregnancy. While no congenital syndrome has been attributed to antepartum pneumonia, fever, tachypnea, and hypoxemia may be harmful to the developing fetus. Preterm labor as a complication of infection may be the result of the uterine response to certain mediators of infection and inflammation. McGregor has hypothesized that certain bacteria induce the production of phospholipases, proteases and prostaglandins that can induce labor, though these speculations evolved with cervicovaginal infection in mind. Lung infection is known to induce similar compartmentalized inflammatory response, which has now been well documented in the nonpregnant pneumonia patient. It is quite possible that the cascade of mediators released by the active host inflammatory response to infection could exert distant effects on the uterus, leading to a high rate of labor during the course of pneumonia.

**EFFECT OF PNEUMONIA ON MATERNAL OUTCOMES IN PREGNANCY**

Pneumonia during pregnancy carries an increased risk of adverse outcome when compared to pneumonia in nonpregnant women. In data from the US Department of Health and Human Services, 2475 maternal deaths were examined from the years 1954–1957, to 0.6 per 100,000 births in the years of 1974–1978 and approximately 1% of these (24 deaths) were a result of pneumonia, which served as the most common nonobstetric infectious cause of mortality.

Mortality data from the state of Massachusetts show that infection-related deaths in pregnancy have declined from 8.8 per 100,000 live births in the years of 1954–1957, to 0.6 per 100,000 births in 1982–1985. Although pneumonia is an uncommon cause of death among all pregnant women, the mortality rate can still be quite high among those who do develop pneumonia in pregnancy. In the preantibiotic era, the maternal death rate was observed to be as high as 32% of all such cases. In Hopwood’s series, the mortality attributable to pneumonia in pregnancy declined to 8.6%, while Benedetti et al noted no maternal mortality, possibly because all the patients in this series were treated within 7 days of symptom onset and none were bacteremic. The severity of illness in this series was low, as estimated by blood gas measurement, since only 3 of 25 had a PaO₂ less than 60 mmHg on room air. The findings from Madinger’s series are contrary to this: of the 25 patients studied, 40% suffered multiple complications including 5 requiring intubation, 2 developing empyema, 1 with pneumothorax, 1 with pericardial tamponade and 1 with atrial fibrillation. There was, however, only one maternal death, occurring in a patient with cystic fibrosis who had been advised to avoid pregnancy. Importantly, the relatively low mortality in this severely ill population reflects the efficacy of current therapeutic modalities and the general good health of women of child bearing age. This conclusion is also borne out in other series, although viral lung infection and opportunistic lung infection still carry a substantial maternal mortality and morbidity.

**BACTERIOLOGY**

Virtually any infectious agent that causes pneumonia in the nonpregnant patient has been reported to complicate pregnancy. The relative frequencies of causative organisms remains difficult to determine because of incomplete methodologies in the documentation of the etiologic agent, with many etiologic agents remaining unidentified. The true incidences of viral, Mycoplasma, and Legionella pneumonias are difficult to estimate with-out comprehensive serological testing. Hopwood identified a responsible pathogen in only 9 of 23 cases, with no predominant pathogen, a mixture of gram-positive and gram-negative bacteria and Influenza A virus being implicated. Only 6 cases were lobar pneumonia, 13 were bronchopneumonia, and 4 involved atypical pathogens. Benedetti et al relied on sputum cultures and found a bacterial pathogen in 21 of 39 patients with Pneumococcus as the predominant pathogen, accounting for 13 cases. H influenza was the second most common pathogen.

Madinger et al also found that *Streptococcus pneumoniae* was the most common pathogen, accounting for 4 of 25 cases, 2 of which were bacteremic. Again H influenzae was the second most common pathogen being complicated by bacteremia in one patient. The most common etiologic finding was however ‘unknown,’ a finding paralleled by many series of community acquired pneu-
monia in nonpregnant patients.\textsuperscript{21} Additionally serologic studies were rarely done to evaluate for atypical agents even though 3 cases were presumed to be due to Mycoplasma Pneumoniae. Berkowitz's series was also confounded by similar deficiencies, although \textit{Pneumococcus} and \textit{H influenzae} were the most common bacterial isolates and one patient did have a Legionella species isolated.\textsuperscript{3}

In total these four series give the best picture of the relative incidence of individual pathogens amongst the gravid pneumonia patient (Table 1). The findings are not radically different from the nonpregnant host of comparable age. The methodologic limitations are multiple due to incomplete and nonprospective diagnostic testing. In addition, numerous case reports and selected limited series have shown a role for other etiologic agents including mumps, infectious mononucleosis, swine influenza, influenza A, Legionella, Varicella, Chlamydia Pneumoniae, \textit{coccidioidomycosis} and other fungal pneumonias.\textsuperscript{5,18,22-36}

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 the physiologic defects in cell-mediated immunity.\textsuperscript{5} The overall incidence of Varicella in pregnancy has been reported as 1-5 per 10,000 births and the complications, both fetal and maternal present several management problems for clinicians, as will be discussed later. In the case of Varicella, pneumonia usually complicates primary infection in 0.3-1.8\% of all cases, but as many as 9\% of primary cases during pregnancy can be complicated by pneumonia.\textsuperscript{17} Influenza A is a common infection in pregnant women during epidemics and carries a higher mortality than in the nonpregnant patient,\textsuperscript{30} with the maternal mortality rates being as high as 30-50\% in the 1918 epidemic.\textsuperscript{2,20,30} In the Asian flu epidemic of 1957-1958, 10\% of all deaths occurred in pregnant women and almost 50\% of women of childbearing age who died were pregnant.\textsuperscript{30} This increased mortality was especially noted in the third trimester.

Another category of pneumonia is that of aspiration, a common obstetrical complication that can lead to chemical pneumonitis, or bacterial infection with pathogens found in the oropharynx and gastric juice, primarily anaerobes and gram-negative organisms.

**CLINICAL FEATURES AND MANAGEMENT OF SPECIFIC RESPIRATORY INFECTIONS**

**BACTERIAL PNEUMONIA**

As mentioned earlier, the incidence of pneumonia may be particularly high among women with comorbidities such as a prior history of respiratory disease or smoking.\textsuperscript{9} In one study, women who developed antepartum pneumonia were anemic 49\% of the time defined as a hemoglobin below 10 g/dl and this finding along with underlying medical illnesses was found to be a major risk factor for lung infection, with nearly a third of the patients also having serious coexisting medical illnesses.\textsuperscript{10} Berkowitz and LaSala's series confirmed these observations\textsuperscript{3} and also found illicit drug use to be another common finding among patients with pneumonia in pregnancy.

The clinical features of acute bacterial pneumonia are no different than in the nonpregnant state. Hopwood reported that among 25 patients, all had a preceding upper respiratory tract infection and 20 had cough. Fever above 101°F was seen in 18 while only 3 reported dyspnea and 5 had chills.\textsuperscript{9} This low incidence of reported dyspnea could be the result of the pregnant patient viewing dyspnea as a normal symptom and not one as pathologic. Benedetti examined the radiographic features of pneumonia in pregnancy and found 28 out of 39 patients to have a single lobar infiltrate while the remainder had multilobar pneumonia.\textsuperscript{10} Only one patient in the series had a pleural effusion.

When complications of pneumonia develop in the pregnant patient, they may be a consequence of a delay in recognition, leading Hopwood to recommend that all women with persistent upper respiratory distress have a chest radiograph.\textsuperscript{9} Madinger reported that although all 25 patients who had pneumonia did have signs and symptoms of lung infection, the diagnosis was initially overlooked in 5 patients.\textsuperscript{11} This may explain why respiratory failure, empyema, and other serious complications, adding to morbidity complicated half of those diagnosed with pneumonia (Table 2).

### Table 1. Etiologic Agents in the Pregnant Patient with Pneumonia

| Author     | Year | Number | S. pneumo | H. influenza | Unknown |
|------------|------|--------|-----------|--------------|---------|
| Hopwood    | 1965 | 23     | 13 (33.3\%) | 4 (10.2\%)   | 12 (52\%) |
| Benedetti  | 1982 | 39     | 4 (10.2\%)  | 2 (8\%)      | 18 (46\%) |
| Madinger   | 1989 | 25     | 4 (16\%)   | 2 (8\%)      | 11 (44\%) |
| Berkowitz  | 1990 | 25     | 6 (24\%)   | 2 (8\%)      | 14 (55\%) |
Postpartum pneumonia is also well described particularly since acid aspiration (Mendelson's syndrome) was first described as an important complication of obstetric anesthesia and can have a catastrophic outcome.\textsuperscript{37,38} Aspiration during labor and delivery is the most common cause of pneumonia in the postpartum period. Good and Waite have reported a case of postpartum lung abscess due to septic pulmonary embolus from a suppurative pelvic thrombophlebitis.\textsuperscript{39} This syndrome required heparin in addition to antibiotics and the patient recovered uneventfully.

The debate about whether the classification of atypical vs. typical has any practical use regarding the choice of antibiotic therapy is ongoing in the pregnant population. The typical pneumonia syndrome with fever, purulent sputum, chills and a lobular infiltrate is classically considered suggestive of pneumococcal or \textit{Haemophilus Influenzae} pneumonia. In contrast the atypical pneumonia syndrome with low-grade fever, gradual onset, mucoid sputum and patchy or interstitial infiltrates, is suggestive of infection with the atypical pneumonia pathogens.\textsuperscript{40} Maccato has suggested that empiric antibiotic therapy of pneumonia in pregnancy be based on determination of these clinical patterns,\textsuperscript{40} but recent studies in nonpregnant patients indicate that Legionella infection can present with an overlap of clinical features common to both syndromes.\textsuperscript{41} Additionally, when serious pneumonia is present, Legionella is frequently a common pathogen.\textsuperscript{41} These observations lead to the recommendation that regardless of the clinical features in the pregnant patient, patients with serious pneumonia in pregnancy should be treated for Pneumococcus, Haemophilus influenzae and Legionella infection. For those with uncomplicated community acquired pneumonia, therapy should be targeted at Pneumococcus, H influenzae and possibly atypical agents, depending on a variety of clinical assessments. When bacterial pneumonia complicates influenza, the most common superinfection in addition to Pneumococcus and H influenzae are \textit{Staphylococcus Aureus} and gram-negative bacteria. Nosocomial pneumonia is most commonly a gram-negative infection and aspiration pneumonia involves anaerobes as well as gram-negative pneumonia.

### Therapy of Bacterial Pneumonia

Paramount in the choice of antibiotic therapy in the pregnant patient is safety of the agent. Penicillins, cephalosporins, and macrolides (excluding erythromycin estolate) are safe. Clindamycin is also probably a safe agent although clinical experience is limited.\textsuperscript{40,42}

The penicillins are only 50% protein bound and can cross the placenta to achieve fetal concentrations that are 50% of maternal levels.\textsuperscript{43} The cephalosporins cross the placenta less effectively but also appear to have no adverse effect on the fetus. Tetracyclines are well known to lead to risk of fulminating maternal hepatitis when given in the third trimester of pregnancy and also stain and deform the fetal teeth when given at any time during the pregnancy.\textsuperscript{43} The neonate exposed to tetracyclines \textit{in utero} can also go on to develop bony deformities. Sulfonamides administered shortly before delivery can cause fetal kernicterus and the safety of trimethoprim is unknown. Chloramphenicol in the fetus, as in the adult, can lead to bone marrow suppression and even aplastic anemia. Near term chloramphenicol produces ‘gray baby syndrome’ of gray facies, flaccidity, and cardiovascular collapse.\textsuperscript{43}

Most patients with community acquired pneumonia can be adequately treated with ampicillin or a cephalosporin, which will have activity against pneumococcus, Haemophilus influenzae and some nonpseudomonal gram-negative bacteria. If atypical infection is strongly suspected a macrolide is the drug of choice. Aminoglycosides should be used only if there is a strong clinical indication of serious gram-negative infection, as there is significant risk of otoxicity to the fetus. Vancomycin poses serious risk to the fetus causing fetal nephrotoxicity and otoxicity and similarly should only be used if absolutely necessary. Therapy with these agents can be monitored following drug serum levels. Drugs to be distinctly avoided in pregnancy include the tetracyclines, chloramphenicol and all sulfa compounds.
Supportive therapy of the pregnant patient with pneumonia is no different than in the non-gravid state; hydration, antipyretic therapy, and supplemental oxygen remain key. The goal of oxygen therapy is to maintain the arterial oxygen tension greater than 70 mmHg as hypoxemia is less well tolerated in the pregnant female.

Importantly 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 is mandatory. Respiratory failure requiring mechanical ventilation has occurred in pregnancy and requires close monitoring of both the mother and the fetus. Preterm labor is a well described complication of pneumonia and may also need to be treated using tocolytics if the patient can tolerate them.

**VIRAL PNEUMONIAS**

**Influenza Virus**

The influenza viruses are myxoviruses of three antigenically different types, A, B, C that can cause disease in humans. Most epidemics in humans are due to type A. In the swine influenza virus is one type of influenza A that can cause human infection and at least one case of fatal pneumonia in pregnancy has been ascribed to this pathogen. Pregnancy leads to an increased risk of complications and mortality from this infection noted during the 1918 worldwide pandemic and the Asian flu epidemic of 1957–1958. In the 1918 epidemic, influenza during pregnancy had a 30% maternal mortality, increasing to 50% in the presence of pneumonia. Mortality rose in tandem with duration of pregnancy to a maximum of 61% when influenza was contracted in the ninth month of pregnancy. 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.

Influenza has an acute onset after an incubation period of 1–4 days and presents as a high fever, coryza, headache, malaise, and cough. If uncomplicated, the chest examination is normal as is the chest radiograph and the entire symptom complex resolves within approximately 3 days. If symptoms continue for 5 or more days, then complications are suspected, especially in the pregnant patient. Pneumonia may be one of the complications of influenza infection, and this may be a secondary bacterial pneumonia or a viral infection of the lung parenchyma. The autopsy findings from the 1957 epidemic found that pregnant patients died as a result of fulminant viral pneumonia in most cases. In contrast, nonpregnant patients died of secondary bacterial pneumonia, caused by *S. aureus*, pneumococcus, *H. influenzae*, and certain enteric gram-negative bacteria.

Primary influenza pneumonia in the pregnant patient may evolve into fulminant respiratory failure requiring mechanical ventilation and positive end expiratory pressure (PEEP) for prolonged periods. Chest radiology demonstrates rapid progression from a unilateral infiltrate to diffuse bilateral disease. Survivors of influenza have been found to have shorter duration of symptoms before hospitalization and a shorter mean time in hospital before mechanical ventilation was instituted. Those who go on to survive this infection begin to improve radiographically after 5–7 days, with 50% clearing seen at 3–5 weeks and maximal improvement in 3–5 months.

Antibiotic therapy should be instituted as soon as pneumonia complicates the influenza patient, directed at pathogens likely to result in a secondary bacterial infection. Ampicillin/sulbactam and some cephalosporins are acceptable choices. If viral pneumonia seems likely, antiviral agents should be started. Influenza pneumonia in pregnancy has been managed with oral amantadine and inhaled ribavirin. Amantadine is effective against Influenza A and acts by blocking the release of viral nucleic acids and can be used for prophylaxis in high-risk pregnant patients or for therapy in complicated cases. It has been found to be nonembryotoxic in mice at 25 times the dose used in humans, however it is excreted in breast milk and therefore should only be used in the highest risk patient. Ribavirin has *in vitro* activity against both influenza A and B but clinical data are limited. Aerosolized ribavirin has inconsistent antiviral or clinical effects in uncomplicated influenza pneumonia. We are aware of no data evaluating ribavirin in pregnant patients. Induction of labor is unnecessary if the pneumonia is appropriately managed unless indicated from the obstetrician’s standpoint. Influenza virus can pass the placenta along with maternal IgG antibodies and investigators believe that it is unlikely that influenza virus leads to any congenital syndrome.

Routine vaccination is not recommended for influenza in pregnancy unless the mother has high-risk medical conditions comprising pulmonary, cardiac, or immune systems. If vaccination is to be administered it should be given after the first trimester of pregnancy unless the influenza season begins at that time.

**Varicella pneumonia**

Several major issues deserve attention in cases of Varicella in pregnancy: the effects of chickenpox
on the course of pregnancy; the incidence and severity of Varicella pneumonia itself; the treatment and prevention of Varicella infection in pregnancy, particularly with acyclovir; and the effect of the infection on the fetus.

Pneumonia is the most serious complication of Varicella to the mother, being fatal in as many as 40% of cases. Varicella in the nonpregnant individual leads to a mortality of 11–17% but this rate rises to as much as 35–40% in pregnant patients.17,45 Haake et al reviewed 34 cases of Varicella pneumonia in pregnancy and found a 35% mortality.17 The overall incidence of Varicella in pregnancy has been estimated from 1–5 per 10,000. Harris and Rhoades compiled 43 published cases of Varicella pneumonia during gestation18 with 12 deaths. Smego and Asperilla carried out a review of 21 cases published before 1991 of Varicella pneumonia during gestation, which were treated with acyclovir, 3 of whom died.45

Varicella-Zoster (VZ) is a DNA virus that usually carries a benign, self-limited illness in children, but may infect up to 1.8% of all adults.36 Studies show that the susceptibility of pregnant patients in our environment is of 4–6.8%.46 Pregnancy may increase the rate of Varicella pneumonia complicating primary infection and smoking may also be a risk factor for the development of Varicella pneumonia, with infected smokers having a higher rate of pneumonia as a complication than infected nonsmokers may.17–49 An increased intensity of skin eruption is also cited as a risk factor for pneumonia.36

Pregnancy enhances the virulence of the VZ virus as the host has a physiologic T-cell defect, as explained earlier. The mortality in pregnant women has been related to the higher levels of circulating steroids in the blood, circulatory overload and the modified respiratory parameters. Most reports are in agreement that Varicella pneumonia is most likely to complicate pregnancy in the third trimester and the infection occurring at this time is more severe and complicated if it occurs at this time.18,26,45

This leads to more complicated and mortal infections than in comparison to the non-pregnant state. The incubation period of Varicella lasts between 14–18 days,50 but can vary between 10 days to 3 weeks. The incubation in exposed fetus is of about 11 days after the mother’s outbreak.51,52 In the mother the appearance of the virus in blood is produced from 24 to 48 hours before the exanthem. It is during this period that 24% of fetuses develop transplacental infection.51 Malformations are produced in 1.2% of the exposed fetus.53

Clinically Varicella pneumonia presents 2–5 days after the onset of fever rash and malaise and is heralded by the onset of pulmonary symptoms,17,18,42 including cough, dyspnea, pleuritic chest pain, and even hemoptysis. In one series all patients with VZ pneumonia had oral mucosal ulcerations.18 Severity of illness may range from asymptomatic radiographic infiltrates to fulminant respiratory failure and ARDS.17,18 Typically chest radiography reveals diffuse miliary or nodular infiltrates that resolve by 14 days unless complicated by ARDS.24 Late sequelae of Varicella pneumonia are diffuse pulmonary calcification.26 The severity of infiltrates has been described to peak with the height of the skin eruption in one case report.54

All patients with VZ pneumonia warrant aggressive therapy with antiviral therapy and early hospitalization. Multiple investigators have used acyclovir, a DNA polymerase inhibitor in the pregnant patient. Experience with safety of acyclovir is well documented in pregnancy by a number of investigators16,24,25,45,50,56–58 and it does not appear to be teratogenic.48,55 In a study of 312 pregnancies in which acyclovir was used, no increase in the number or pattern of birth defects was seen.50 There is, however, no distinct proof regarding the efficacy of acyclovir in terms of improving outcome. Haake et al reviewed the early initiation, namely within 36 hours of admission acyclovir therapy compared to none in pregnant patients with Varicella pneumonia.17 Those receiving early therapy were found to have an improved hospital course after the fifth hospital day, lower mean temperature, less tachypnea and improved oxygenation.17 The recommended dose is 7.5 mg/kg every 8 hours intravenously although doses of 3–18 mg/kg have been used. Treatment is recommended for seven days. Fetal extraction normally produces an improvement of respiratory parameters.

The effects of Varicella on the fetus are of concern. In addition to maternal complications, Varicella can lead to intrauterine infection in 10–20% of mothers born carrying this infection in pregnancy.45 Traditionally, fetal involvement has been divided into three areas: ‘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 confinement.28 Varicella embryopathy was first described in 1947 by Laforet and Lynch and has since been redefined by a number of authors.28,59–63 The embryopathy includes limb hypoplasia, skin scarring, central nervous system involvement, and other skeletal lesions.39,60,62,63 This embryopathy has been reported as late as infection at 26 weeks.28

The largest series of congenital Varicella was recently published in Europe in which 1373 pregnancies complicated by VZ from 1980–1993 were evaluated. Fetal abnormalities occurred commonly in the children of women infected between 13 and
20 weeks of gestation. Fetal anomalies varied from skin lesions to lethal multiorgan system involvement. Importantly, the use of VZ Varicella immune globulin in a pregnant patient may not eliminate the incidence of embryopathy, but if given before maternal infection develops, it may decrease or attenuate fetal disease. Immune prophylaxis with IgG, VZ should be applied during the first 92 hours, after close exposure of a seronegative pregnant patient in a dosage of 5 vials of 125 intramuscular units with the aim to prevent disease in the mother but not in the fetus.

**Other Viruses**

Maternal infection with rubeola has been well reported and may adversely affect pregnancy outcome leading to spontaneous abortion and preterm delivery. Three to five percent of measles cases in adults may be complicated by pneumonia and bacterial superinfection is not uncommon.

Infectious mononucleosis has also been reported to complicate pregnancy in an otherwise healthy 17-year-old patient. This patient developed necrotizing epiglottitis.

**Fungal Pneumonias**

Fungal pneumonia is rare and is not different in the pregnant patient. Scant reports exist in the literature, although several fungi, notably coccidioidomycosis, can complicate pregnancy. This is not surprising as pregnancy can have a reversible T-cell defect associated with it, and this may lead to increased risk for dissemination and higher mortality. An increased rate of dissemination of the infection has been reported, particularly when the infection is acquired in the third trimester. Several older studies did report a higher maternal mortality for disseminated infection with coccidioidomycosis; one recent study has reported no mortality in pregnancy. Cantanzaro examined the published experience with coccidioidomycosis in pregnancy and looked at both maternal and fetal complications as a function of when the infection was acquired. In one 1951 series, among 5 patients who had infection before pregnancy, the disease remained stable and did not disseminate. There were 12 patients who acquired infection in the first trimester leading to one fatal disseminated disease with associated fetal loss. The other 11 had pulmonary infection only and recovered without dissemination and 10 of the pregnancies were completed successfully. Among 5 women who were infected in the second trimester, one developed meningitis, and one died of disseminated infection. The course was much different for the 11 women who acquired infection in the final trimester. Disseminated infection developed in 7, all of whom died. Other investigators also reported high rates of dissemination and maternal mortality, especially for infection acquired in the third trimester.

Wack et al reviewed the experience in Tucson Arizona looking at 47,120 pregnancies. The discharge diagnoses of all women who delivered between 1979 and 1985 were examined and only 10 cases of coccidioidomycosis were found. In 7 patients the infection was found before the third trimester and all recovered uneventfully, only two were treated with ketoconazole. Three other women had their infection diagnosed immediately post partum and presumably had become infected in the third trimester. Two of the three patients developed fulminant disseminated infection with meningitis needing long-term therapy for chronic infection. The third patient with a post partum diagnosis recovered uneventfully. No patient had any fetal loss attributable to infection. Current experience therefore with coccidioidomycosis infection only partly confirms earlier experience. Development of the infection can occur during pregnancy but is relatively rare. Dissemination can certainly develop, especially if the infection occurs late in the pregnancy, but maternal mortality and fetal loss are preventable with appropriate treatment.

Both amphotericin and ketoconazole had been used for treatment of fungal pneumonia but the optimal therapy is yet to be determined. Although few patients have received these drugs, no teratogenicity has been reported. Maternal toxicity remains a concern with amphotericin as in the non-gravid host particularly with regard to exacerbation of anemia.

Other fungal infections have been reported in the literature including cryptococcosis, blastomycosis, and spirotrichosis. No consensus exists regarding therapy or the effect of pregnancy on the course of these illnesses or the effect upon outcome.

**Aspiration Pneumonia**

Mendelson’s original description of gastric acid aspiration was made in obstetric patients undergoing labor and delivery. The entity of aspiration pneumonia in pregnant patients is a familiar one and in fact in the 1960s as many as 2% of all maternal deaths were due to aspiration. The pregnant patient is physiologically predisposed to aspiration. These factors include elevation of the intragastric pressure due to the gravid uterus, a relaxed gastroesophageal sphincter because of the circulating progesterone and delayed gastric emptying that accompanies pregnancy. These factors coupled
with sedation and analgesia given in the labor room and vigorous abdominal palpation during examinations all increase the threat of aspiration.

Acid aspiration is an important complication of obstetric anesthesia as already mentioned with a potentially catastrophic outcome. In an attempt to minimize this risk, some form of chemophylaxis is given preoperatively. Drug regimens include a combination of H2 type receptor antagonist, a promotility agent such as metoclopramide and sodium citrate. Omeprazole has also been studied though there is no agreement that any one regimen is superior reflected by wide variations in practice from hospital to hospital. Aspiration in the pregnant patient usually occurs in the labor room at the time of delivery or while undergoing endotracheal intubation. Aspiration may involve bacteria present in the oropharynx (S. Aureus, gram-negatives or anaerobes), liquid gastric contents or solid particulate matter from the stomach. A pneumonia infection will result from the aspiration of bacteria typically at least 24 hours after the event. Particulate matter when aspirated will lead to acute bronchospasm cough and cyanosis. Aspiration of gastric juice leads to somewhat different symptoms following 6 to 8 hours later when the patient develops tachypnea, bronchospasm pulmonary edema hypotension and hypoxemia. The pH of the gastric fluid is critical and minimal lung injury occurs when aspirated gastric juice has a pH above 2.5.

Respiratory failure in the postpartum period should raise a high index of clinical suspicion of aspiration. Supportive management is indicated primarily with the use of supplemental oxygen, bronchodilators, and ventilatory support if indicated. If signs of infection evolve, antibiotic therapy to cover gram-negatives, gram-positives, and anaerobes must be initiated, though not all aspirations lead to pneumonia. There is no established role for steroids.

The major thrust of management is, however, prevention. Regional anesthesia is preferred over general. If general anesthesia is mandated, then the patient must be nil per orum for a full 24 hours. Airway protection is paramount even with regional anesthesia and cricoid pressure and rapid sequence induction must accompany endotracheal intubation. The importance of raising gastric acid pH has already been mentioned earlier on.

**PNEUMONIA COMPLICATING HUMAN IMMUNODEFICIENCY VIRUS IN PREGNANCY**

Mid July 1996, the World Health Organization (WHO) estimated that 21.8 million adults and children were living with HIV and AIDS with 94% living in developing nations. Forty-two percent of the adults were women. Looking at the last decade, the total number of HIV infections in adults has more than doubled from 10,000,000 in 1990 to 25.5 million in 1996. Again 42% of these were women.

Vertical transmission of HIV has been reported in utero, at delivery and post partum. Transmission has been reported to correlate with virologic factors such as viral burden i.e. p24 antigenemia. Immunologic host factors such as low maternal CD4 count and high CD8 count, sociodemographic factors and antiretroviral intervention may also determine the risk of transmission.

The new protease inhibitors have been found to reduce viral burden close to undetectable levels. Logic would support use of these agents during gestation might reduce the rates of vertical transmission.

Management of pregnancy, labor and delivery in the HIV positive parturient may be complicated by the systemic effects of AIDS, opportunistic infections, abnormalities in the pregnancy, and concurrent illnesses. The number of women with HIV infection is increasing rapidly. In the US 11.5% of patients with AIDS are women. Between 1989 and 1990 there was a 34% increase in cases among women compared to an equivalent increase of 21% in men. In 1991, AIDS was the fourth most common disease in women aged 25–44. Black and Hispanic women are more likely to have the disease and although they represent only 19% of the population, they account for 72% of the cases of AIDS in the United States.

Vertical transmission has been reported as ranging from 7 to 39% with approximately half occurring during gestation. Reported rates may vary because of the difficulty in defining the rates of HIV infection in the newborn.

The effect of pregnancy on the progression of HIV is not clear. Pregnancy of itself leads to a decrease in T-cell helper activity. In normal pregnancy the T4 cell count drops to 700 to 800 cells/microlitre at 28 weeks and increases to 1000 at the time of delivery. The counts remain at this level into the post partum period. Asymptomatic patients with HIV show the same pattern, although counts are close to 20% lower than in the non HIV patient and fall in the post partum period.

Koonin’s 1989 series identified 20 women with HIV infection retrospectively who died within one year of termination of pregnancy between 1981 and 1988. The mean interval between diagnosis of AIDS and death was only 113 days and the primary cause of death was PCP. Koonin’s work suggests that the natural history of HIV infection may be accelerated by pregnancy although at this time there exist no well designed prospective studies to confirm this.

The expanding HIV epidemic encompasses more pregnant patients than ever before. This has
led to the recently published recommendations regarding routine HIV testing, with consent for all pregnant women in the US. During 1994, an estimated 7000 infants were born in the US to HIV seropositive women. Women account for 10% of all AIDS cases in the US, and from 1981–1988 80% of all women with AIDS were of reproductive age. Seroprevalence of HIV infection in pregnant women is 0.16% although some individual hospitals report seroprevalence rates as high as 6–8%. The epidemic of HIV infection can no longer be considered localized to major metropolitan areas and HIV infection is being identified in women from rural areas and smaller communities more often than in the past. A rural health care setting in Florida recently reported a 5% seroprevalence rate for pregnant women. The maternal to fetal transmission rate is approximately 20–30% with the majority of infants who were born to an infected mother being ultimately uninfected.

It is important to note that amongst intravenous drug abusers, who are pregnant, HIV seroprevalence has been reported to be as high as 9.4–29.6%. Transmission of the virus to the fetus, preterm labor, and the development of opportunistic infection in the mother may complicate pregnancy in these patients.

FETAL AND OBSTETRIC COMPLICATIONS OF HIV INFECTION

Maternal to fetal transmission rate of HIV is approximately 20–30% with the majority of patients who are born to an infected mother being ultimately uninfected. Recent research (AIDS Clinical Trials group Protocol 076 [ACTG-076]) has shown that for selected women zidovudine may lower the perinatal HIV transmission rate by two-thirds. Transmission may occur by one of three routes; in utero, at delivery, and in the neonatal period when the infant is breast-fed. Mothers with HIV infection can transmit the virus whether they are symptomatic or not, but transmission may be more likely in the offspring of symptomatic infected mothers. Bamji et al conducted a prospective study of 116 infected and 396 uninfected infants at 7 New York City hospitals for a mean of 26 month period from 1986 to 1995. They found two or more nonspecific HIV related symptoms, AIDS or death occurred in 83% of infected children by one year children. Estimated infant mortality was 160/1000 live births, and median survival after AIDS was 21 months. Fifty-five percent of children infected survived >12 months after the diagnosis of AIDS. Fetal AIDS syndrome is characterized by growth failure, microencephalopathy, a prominent box like forehead, prominent eyes, and a flattened nasal bridge. As in other maternal infections HIV predisposes to preterm labor. Interestingly, in studies that have controlled for complicating factors such as socioeconomic status and drug abuse history the presence of HIV infection alone has not been a risk factor for preterm labor.

MATERNAL COMPLICATIONS OF HIV INFECTION

Evidence exists that HIV infection progresses more aggressively in the pregnant patient and that the opportunistic infections are particularly virulent when they occur in the pregnant patient. PCP is the most common opportunistic infection in both pregnant and nonpregnant HIV infected patients, occurring in 85% of this population at some point during their illness, with a mortality ranging from 5–40% per episode. Koonin et al examined the clinical course of 20 women who died from AIDS during or within 1 year of completing a pregnancy and found that many of these patients died very shortly after termination of the pregnancy. The time between diagnosis of AIDS and death was found to be a mean of only 113 days. Of the 20 patients, 16 died of PCP, and in this group the mean time from diagnosis to death was only 59 days. In contrast the mean survival interval for nonpregnant women is 298 days after diagnosis of AIDS. Even among intravenous drug abusers who have AIDS and die of PCP, the survival of the nonpregnant women is a mean of 187 following diagnosis.

From the above we can draw several important conclusions. AIDS has an accelerated course in pregnancy; and the short survival of mothers following delivery exemplifies one of the many hardships that offsprings of HIV infected mothers face. Clearly the likelihood of shortened maternal survival and risk of perinatal transmission should encourage clinicians to counsel HIV seropositive women carefully about pregnancy.

However, current US Public Health Service recommendations state that neither aerosolized pentamidine nor oral TMP-SMX is safe in pregnancy although other modalities were not addressed. Instead prophylaxis is recommended in the postpartum period for high-risk women. Others do not agree and advise drug therapy, including prophylaxis to be available to HIV infected women throughout pregnancy if there is a possible benefit. If an HIV positive woman does become pregnant and develops PCP therapy should be started with trimethoprim sulfamethoxazole along with corticosteroids. In the postpartum period breast-feeding should be avoided because this adds an additional risk of perinatal transmission to the infant.
Oral TMP-SMX does appear to be the most effective agent for both primary and secondary PCP prophylaxis. Aerosolized pentamidine, oral dapsone either alone or combined with pyramethamine, pyramethamine with sulfadoxine, and clindamycin with primaquine are all also effective. The risk of any prophylactic agent given in pregnancy must be considered along with the risk of development of PCP in the doubly immunosuppressed pregnant HIV positive woman. Aerosolized pentamidine is felt to be the only currently recognized prophylaxis and this is merely a local and not systemic agent.

SUMMARY

Pneumonia is infrequently complicated by pneumonia though lung infection by bacteria, viruses, and fungi can lead to serious maternal and fetal hazards. Pneumonia may lead to preterm labor and certain infecting agents may cross the placenta and infect the fetus, most notably the HIV virus. Due to the host immunosuppression that accompanies pregnancy, viral infections normally controlled by cell-mediated immunity may be more severe and occasionally lethal. Additionally, the physiologic changes of pregnancy make any respiratory infectious insult difficult to control. Careful management and vigilance to the vulnerability of the pregnant patient will prevent some pneumonias, particularly influenza and aspiration pneumonia. When treating the pregnant pneumonia patient, the safety of the antimicrobial agents must be considered, and therapy may differ from that used in the nonpregnant patient.

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