Congenital Infections, Part 2:
Parvovirus, *Listeria*, Tuberculosis, Syphilis, and Varicella

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Drs Satti, Ali, and Weitkamp have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Abstract
The purpose of this two-part series on congenital infections is to provide the reader with an update on recent controversies and advances for a selected group of congenital infections. Part 1 covered cytomegalovirus, toxoplasmosis, rubella, and herpes simplex. This article focuses on parvovirus, *Listeria*, tuberculosis, syphilis, and varicella, offering a brief overview of rare and unusual causes for congenital infection.

Objectives
After completing this article, readers should be able to:

1. Describe the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of parvovirus infection.
2. Describe the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of *Listeria* infection.
3. Describe the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of tuberculosis.
4. Describe the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of syphilis.
5. Describe the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of congenital varicella syndrome.

Parvovirus
Epidemiology
Parvoviruses were discovered in 1975 by Cossart and associates during screening for hepatitis B surface antigen in blood donors. (1) B19 refers to the sample code in which this human parvovirus was isolated. In 1983, parvovirus B19 had been identified as the cause of erythema infectiosum (fifth disease), and in 1984, the first case reports of adverse outcomes of pregnancy in women who had parvovirus infection were documented. (2) In 1985, Anderson and colleagues showed that parvovirus causes human disease by intranasal inoculation in volunteers. (3)

Parvovirus infection occurs throughout the year, with the incidence peaking in temperate climates during spring and summer months. In the United States, the infection occurs mostly in late winter and early summer. It is transmitted from person to person via the respiratory route. The number of people who have parvovirus B19 immunoglobulin (Ig)G increases with age. By adulthood, 60% of the population is seropositive. The presence of IgG antibodies correlates with a lower risk of infection. This decreased risk was suggested from a study in which volunteers were inoculated with parvovirus B19 and four of five IgG-negative but only one of four IgG-positive volunteers developed serologic evidence of infection. (3) The susceptibility of pregnant women to parvovirus is the same as any other immunocompetent adult, although female sex has been suggested to be a risk factor in outbreaks. In an outbreak in Port Angeles, Washington, the attack rate in women was more than twice that seen with men. (4)

About 35% to 53% of pregnant women have been reported to have measurable concentrations of IgG to parvovirus, suggestive of prior immunity. (5)(6) The incidence of parvovirus B19 in pregnancy has been estimated to be 3.3% to 3.8%, with the incidence

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changing in various groups. (5)(6) Four percent of women of reproductive age have been documented to have serologic evidence of recent infection. (5) The incidence varies in different occupational groups. For example, one study showed that school teachers had the highest infection rate. (7) There are three possible routes of transmission. Respiratory transmission is the most common, and hematogenous spread and vertical transmission are also common. The placenta contains a parvovirus receptor, and transplacental transmission may occur at any time during pregnancy, with the risk of transmission being the highest in the first and second trimesters. The chance of vertical transmission has been estimated to be between 10% and 35%. The Public Health Laboratory Service (PHLS) Working Party on Fifth Disease conducted a survey of 193 women who had serologically confirmed parvovirus and showed a fetal infection rate of 33% based on fetal DNA hybridization studies, neonatal IgM concentrations, and persistence of IgG at 1 year of age. (8) No abnormalities were detected, and based on this study and other data, it has been suggested that parvovirus B19 is not a teratogen. (9)(10)

Clinical Manifestations

Fetal parvovirus infection is characterized by nonimmune hydrops fetalis, ascites, pleural effusion, hypertrophic cardiomyopathy, placentomegaly, and ventriculomegaly. Parvovirus B19 was recognized as a cause of intrauterine fetal death in 1984. The PHLS prospective study documented a significant risk of fetal loss, especially in the second trimester. (8) The fetal death rate in this study was estimated at 9%. In another study in which women who had positive IgM were followed through pregnancy, the fetal death rate was 17.2%. (11) Most pregnancy losses occurred between the 10th and 20th weeks of pregnancy, but not all fetal deaths were directly attributable to parvovirus B19 infection. Another ongoing study in the United States showed that fetal deaths are infrequent (unpublished Centers for Disease Control and Prevention [CDC] data), with two fetal deaths among 49 women followed to term. In a study of women who had stillbirths, 96 women who had spontaneous abortions were compared with an equal number of controls matched by age, duration of pregnancy, and location. The same rate of serologically confirmed parvovirus B19 infection (1%) in cases and controls suggested that parvovirus B19 was not responsible for a sizeable proportion of fetal deaths in the general population. (12) In a large study of 1,018 pregnant women, the fetal demise rate was 6.3%. (13) Fetal death was only observed when maternal parvovirus B19 infection occurred before completion of 20 weeks of gestation.

Parvovirus attacks not only the maternal red blood cells but also fetal erythrocyte precursors. Destruction of fetal red blood cells leads to nonimmune hydrops fetalis, which initially was believed to be a greater risk than the currently established risk of about 0% to 9%. (14) Hydrops can develop within 2 weeks and may resolve spontaneously or cause fetal death. In one study, spontaneous resolution occurred in 34% of 539 cases of parvovirus-associated hydrops. (15) Severe anemia can progress to congestive heart failure and circulatory compromise. Parvovirus B19 also is known to affect myocardial cells and can lead to myocardial injury. (16) Hydrops is seen more commonly when the infection occurs before 32 weeks of gestation.

Although some animal parvoviruses are teratogens, data supporting the concept that the risk of congenital anomalies in children born to mothers who are infected with parvovirus during pregnancy is greater than that in the general population is generally lacking. The first case of possible teratogenic effects of parvovirus B19 was reported in 1987. (17) Fetal demise with ocular anomalies occurred at 11 weeks. The mother had a history of rash and arthropathy at 6 weeks that was serologically confirmed. Ocular anomalies, cleft lip/palate, musculoskeletal anomalies, hepatocellular damage, myocarditis, congenital cardiomyopathy, and myositis have been described in newborns who have parvovirus infection. Disturbance of cerebral neuronal migration has been associated with congenital parvovirus B19 infection. (18) Figure 1 demonstrates a case of extensive right-sided polymicrogyria in a term infant who had DNA-confirmed congenital parvovirus B19 infection (Schulert GS et al, manuscript in preparation). In these rare instances, it is not clear if the virus causes a direct cytopathic effect or if the central nervous system injury is due to complications of the infection such as profound anemia, chronic hypoxia, or the inflammatory host response. In addition, persistence of viral antigen in healthy persons and concerns for false-positive polymerase chain reaction (PCR) assay results has led to skepticism about the existence of parvovirus B19-associated syndromes. (16)

Diagnosis

A maternal history of parvovirus infection with serologic confirmation is suggestive of congenital parvovirus infection in a neonate. Acute maternal infection should be suspected in any pregnant woman who has a rash and arthropathy. Testing maternal serum for antiparvo-

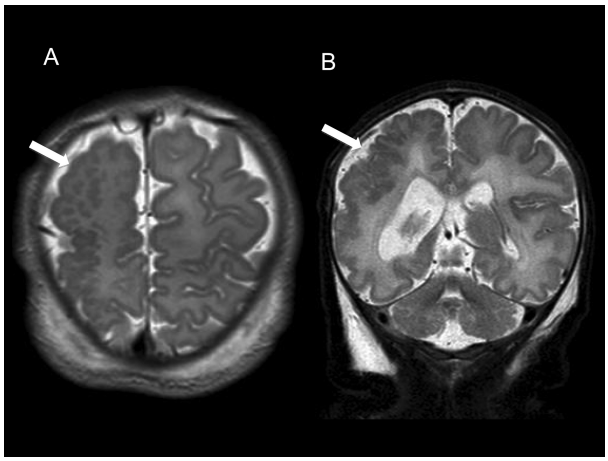


Figure 1. Axial (A) and coronal (B) T2-weighted magnetic resonance imaging of the brain of a term infant who had congenital parvovirus B19 infection demonstrating extensive polymicrogyria on the right.

virus B19 IgM and IgG is the first diagnostic step. Fetal hydrops and aplastic anemia are highly indicative of intrauterine fetal infection. Although maternal seroconversion does occur, maternal IgM values already may be negative at the onset of hydrops fetalis. (16) In these cases, amniotic fluid PCR assay can be performed and has a sensitivity greater than 97% and a specificity of 79% to 99%. (19) Fetal cord blood sampling is associated with a fetal loss rate of approximately 1%, and IgM antibodies frequently do not appear in the fetal circulation until after 22 weeks of gestation. (19) Postpartum testing of the infant can be performed by PCR assay of blood, bone marrow, liver, or other tissues. Viral culture is not useful because parvovirus B19 cannot be isolated on routine cell cultures. Electron microscopy can be used, but its sensitivity has not been fully established.

Other nonspecific findings associated with congenital parvovirus infection are nuchal translucency in the first trimester, ascites, pleural or pericardial effusion, skin thickening, hypertrophic cardiomyopathy, hepatosplenomegaly, hydrocephalus, microcephaly, intracranial calcifications, placentomegaly, and amniotic fluid volume disorders. Increased middle cerebral artery systolic velocities on cranial Doppler ultrasonography may be an early indicator of fetal anemia.

The pregnant woman who has contact with a child who has fifth disease should have the presence of maternal parvovirus B19 IgG and IgM antibodies assessed as soon as possible after exposure. Negative serology is consistent with susceptibility and should be repeated in 3 to 4 weeks. The sensitivity and specificity of the IgM antibody test is variable. However, presence of parvovirus B19 IgM in maternal blood or clinical signs consistent with acute maternal parvovirus B19 infection indicates acute infection and warrants fetal monitoring. Parvovirus B19 DNA can be detected in serum for up to 9 months after the acute viremic phase and, therefore, is not necessarily an indicator of recent infection. Fetal evaluations typically include weekly Doppler ultrasonographic measurements of the middle cerebral artery peak systolic velocity as an early sign of fetal anemia as well as ultrasonographic examinations for fetal hydrops.

Treatment

If a fetus shows evidence of hydrops after 18 weeks' gestation, the primary treatment option is intrauterine fetal blood transfusion. Blood transfusion typically is performed if a fetal blood sample shows hemoglobin values of less than 10 g/dL (100 g/L). A second transfusion (10 to 12 days after the first) and subsequent transfusions at intervals of 3 to 4 weeks often are undertaken until the fetus has reached at least 33 weeks of gestation. The procedure is less well tolerated if hydrops is very severe. The amount of blood required to correct fetal anemia is calculated using the formula proposed by Rodeck and associates: (20)

$$V\,(Hct3 - Hct1)/Hct2$$

where V=estimated fetoplacental volume, Hct1=pretransfusion hematocrit, Hct2=hematocrit of the transfused blood, and Hct3=the desired hematocrit.

In one retrospective study of 38 hydropic fetuses, an apparently normal infant was delivered in 9 of 12 (75%) cases treated with fetal blood transfusion versus 13 of 26 (50%) untreated patients. (21)

If severe anemia occurs after 28 weeks' gestation, early delivery may be considered. Hydropic infants need immediate resuscitation in the delivery rooms; most require mechanical ventilation and respiratory assistance. Abdominal paracentesis and thoracocentesis may be necessary for ascites and pleural effusion.

Prevention

Interventions to prevent the disease are of unproven value and, therefore, guidelines for prevention and control are limited. The CDC recommends that in school and child care settings, parents and employees be informed of outbreaks so the population at risk for serious complications can be identified and referred to physicians. Handwashing after contact with potentially infectious secretions and separating eating utensils decreases the risk of transmission. Some have recommended that

women not immune to parvovirus B19 be restricted from working in schools in which there are ongoing outbreaks. Routine screening of pregnant women is not recommended because adverse outcomes in pregnancy are rare. (9)

Listeria

Epidemiology

Listeriosis is a foodborne disease caused by *Listeria monocytogenes*, a gram-positive bacillus (Fig. 2) first described in 1926 to cause disease in laboratory animals. Following isolation of the pathogen in 1926, Burn established *L monocytogenes* as a cause of perinatal infection in humans in 1936. (22) *L monocytogenes* has been isolated from cattle, pigs, turkeys, chickens, ducks, and many other species. Although an uncommon cause of illness in the general population, *Listeria* can cause severe disease in immunocompromised patients and during pregnancy. The annual incidence of sporadic cases in the United States in 2009 was 0.34 per 100,000. (23) Based on this report, rates of listerial infection decreased by 26% in 2009 compared with the period of 1996 to 1998.

The largest epidemic of listeriosis in North America occurred in 1985 and involved mostly pregnant women and their newborns. The case fatality rate was 63% for early neonatal/fetal infections and 37% for late-onset neonatal infections. Most of the mothers were of Hispanic origin and had eaten a Mexican-style soft cheese before contracting the disease. (24) Other outbreaks were reported after consumption of raw vegetables, (25) coleslaw, or a specific brand of pasteurized milk. (26) Various other food items have been recognized as sources of infection.

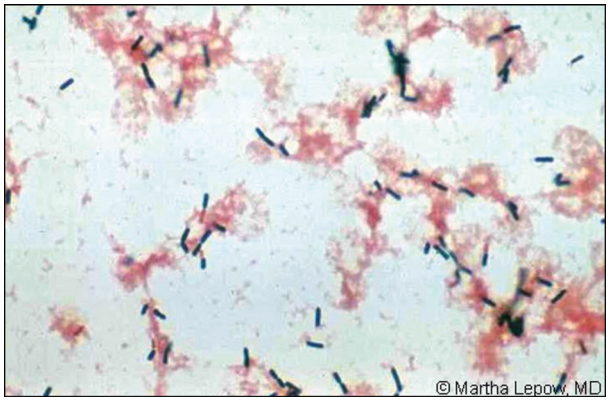


Figure 2. Cerebrospinal fluid in *Listeria monocytogenes* infection (listeriosis) shows characteristic gram-positive rods on Gram stain. Reprinted with permission from the *Red Book Online*. Image courtesy of Martha Lepow, MD.

Because cell-mediated immunity is weakened in pregnancy, pregnant women are at a higher risk of developing listeriosis, especially in the third trimester, which can lead to vertical transmission. In addition, local suppression of immunity in the placenta to prevent maternal rejection may contribute to fetal acquisition of maternal infection. In a review of 1,378 cases of listeriosis, 34% represented perinatal infections, and the case fatality rate was 45%. (27) Infections in the first two trimesters of pregnancy frequently result in intrauterine death. Acquisition of the organism through the birth canal and environmental sources, including cross-infection in nurseries, often leads to late-onset neonatal infection.

Clinical Manifestations

A pregnant woman who develops listeriosis may present with influenza-like symptoms, including fever, malaise, headache, gastrointestinal complaints, and back pain. Approximately 65% of mothers of children born with listeriosis develop these signs. (28) Infection contracted by the mother in early pregnancy often leads to abortion soon after symptoms develop. Later in pregnancy, listeriosis may cause stillbirth or preterm labor associated with meconium-stained or green-tainted amniotic fluid and an infected neonate. Congenital or early-onset illness presents in the first 2 to 3 days after birth with sepsis syndrome, congenital pneumonia, or disseminated granulomatous lesions called granulomatosis infantiseptic-um. Microabscesses and granulomas containing the organism are found throughout the body, particularly the lungs, liver, and spleen. In a Los Angeles epidemic, 70% of infants who had listeriosis were preterm, and 56% had respiratory distress and evidence of congenital pneumonia at birth. Four out of the five deaths observed were in children who had respiratory distress, suggesting that respiratory distress complicated by congenital pneumonia is a significant cause of mortality in neonatal listeriosis. (29)

Less commonly, late-onset neonatal listeriosis can occur from infection acquired during vaginal birth, although infections after cesarean sections have been reported. Meningitis is the most frequent presentation of late-onset listeriosis and is the third most common cause of neonatal meningitis in the United States. Importantly, third-generation cephalosporins, commonly prescribed for late-onset neonatal meningitis, are not effective against *L monocytogenes.*

Diagnosis

Listeriosis is diagnosed when a clinically compatible case is confirmed by laboratory studies. Laboratory diagnosis is made by isolation of *L monocytogenes* from a normally sterile site such as blood or cerebrospinal, joint, pleural, and pericardial fluid on a blood agar. A Gram stain of gastric aspirate material or biopsy specimens of the rash also may be helpful. Typically, *Listeria* appear as short, sometimes coccoid, gram-positive rods (Fig. 2) and can be confused with diphtheroids or streptococci. *L monocytogenes* may also appear as gram-negative and can be mistaken for *Haemophilus influenzae*. In the setting of fetal loss, diagnosis is confirmed by isolation of *L monocytogenes* from the placenta or fetal tissue. PCR-based methods are used predominantly to detect the pathogens in food products, but their use for clinical diagnosis may be established in the near future.

Treatment

A child who has neonatal listeriosis should be monitored for temperature regulation, respiratory and cardiovascular status, and dehydration. Patients should be isolated because of the risk of cross-infection in the nursery. Ampicillin plus an aminoglycoside is the regimen of choice. This combination is more effective than ampicillin alone in vitro. Cephalosporins are not effective against *Listeria*. For infections without meningitis, treatment for 10 to 14 days is considered sufficient, but a minimum of 14 to 21 days of treatment is recommended for meningitis.

Prevention

To prevent *L monocytogenes* infection, pregnant women should avoid unpasteurized milk products, soft cheeses, hot dogs, and deli or luncheon meats unless served steaming hot. Refrigerated meat spreads and smoked seafood should be avoided. Raw vegetables should be washed or cooked thoroughly. Hands, knives, and cutting boards should be washed after exposure to uncooked food. Food industry regulatory and educational efforts should be incorporated into the prevention of listeriosis. Prompt antimicrobial therapy for infections diagnosed in pregnancy may prevent vertical transmission to the fetus.

Tuberculosis

Epidemiology

Tuberculosis is caused by *Mycobacterium tuberculosis* and is transmitted from person to person via respiratory aerosol, with the lungs being the initial site of infection. Humans are the natural reservoirs; there are no animal reservoirs. In 2008, the World Health Organization (WHO) estimated that the incident cases had increased from 9.3 million in 2007 to 9.4 million globally. (30) Of the estimated 1.3 million deaths, 0.5 million were in women. (30) Tuberculosis among pregnant women is not uncommon, but because the prevalence is highest among the immigrant population, exact national data are not available. The prevalence of tuberculosis in pregnancy is estimated by using the prevalence of tuberculosis in women of childbearing age. The incidence of tuberculosis in pregnant women could be as high as in the general population, but congenital tuberculosis is a rarity. Until 1989, only 300 cases were reported in the literature, followed by a review of 29 cases in 1994. (31) From 2001 to 2005, more than 19 cases of congenital tuberculosis were reported. (32)(33) In 1969, Blackall reported that 3 out of 100 infants of mothers affected by active tuberculosis had congenital disease. (34) However, in one other study, no infected infants were diagnosed among 260 affected pregnancies. (35)

The criteria for distinguishing congenital tuberculosis from postnatally acquired disease were established initially by Beitzke in 1935 and later revised by Cantwell and associates in 1994. (31) Congenital tuberculosis was defined as a proven tuberculous lesion in an infant plus at least one of the following: 1) lesion occurring in the first week after birth, 2) primary hepatic complex or caseating granuloma, 3) maternal genital tract or placenta tuberculosis, or 4) exclusion of postnatal tuberculosis through contact investigation. Congenital infection is communicated via two possible routes: hematogenous spread through the umbilical vein, in which case the primary lesion is in the lung or liver; or ingestion or aspiration of infected amniotic fluid leading to pulmonary or gastrointestinal tuberculosis. Aspiration and hematogenous spread account for approximately 50% of the cases of congenital tuberculosis.

Clinical Manifestations

Signs of congenital tuberculosis are usually seen in the second and third weeks after birth and may simulate bacterial/viral sepsis or other congenital infections such as syphilis and human cytomegalovirus infection. A review by Hageman and associates (36) in 1980 of 26 cases of congenital tuberculosis noted that the most common clinical manifestations were respiratory distress, fever, hepatomegaly or splenomegaly, poor feeding, lethargy or irritability, lymphadenopathy, and low birthweight. Cantwell and colleagues (31) reported the presenting signs in 29 additional cases as hepatosplenomegaly (76%), respiratory distress (72%), fever (48%), lymphadenopathy (38%), abdominal distension (24%), lethargy or irritability (21%), ear

discharge (17%), and papular skin lesions (14%). Fewer than 10% of patients exhibited vomiting, apnea, cyanosis, jaundice, seizures, and petechiae. The median age at presentation was 24 days (range, 1 to 84 days). Chest radiographs were abnormal in 23 infants, although 18 had nonspecific infiltrates, and overall mortality was 38% (22% among those who received chemotherapy). Meningitis is uncommon but has been reported. Congenital tuberculosis also may present with progressively worsening liver function and no respiratory symptoms.

Transmission of tuberculosis in the neonatal intensive care unit is possible, and the diagnosis requires a high index of suspicion, especially in cases of human immunodeficiency virus-infected mothers or mothers from endemic areas. (37)(38)

Diagnosis

The diagnosis of congenital tuberculosis is complicated by the fact that more than 50% of mothers may be asymptomatic and are diagnosed with tuberculosis only after the disease is diagnosed in their infants. (31) Congenital tuberculosis should be suspected and investigated in: 1) a newborn who has pneumonia that is not responding to antibiotic therapy, 2) a child who has nonspecific symptoms and whose mother was diagnosed with tuberculosis, 3) an infant who has a high cerebrospinal fluid lymphocyte count in the absence of any identifiable bacterial pathogen on culture, and 4) the presence of fever and hepatosplenomegaly.

For diagnostic purposes, tuberculin skin testing, chest radiographs, lumbar puncture, and cultures are recommended. Histologic inspection of the placenta for granulomata and acid-fast bacteria as well as evaluation of the mother for tuberculosis should be performed. Tuberculin skin tests are typically negative in newborns who have congenital or perinatally acquired infection. Fluorescent staining of early morning gastric aspirates is relatively sensitive, but the overall diagnostic yield of gastric aspirates is less than 50%. Even with the best culture techniques, *M tuberculosis* is isolated in fewer than 75% of infants diagnosed with pulmonary tuberculosis by other clinical criteria. (39) Even liquid media require a minimum of 1 to 6 weeks to yield results, and nucleic acid amplification tests continue to have limitations. Chest radiographs may show scattered infiltrates, bronchopneumonia, consolidation, and periportal hypodensities. However, these findings are usually not apparent initially.

Treatment

Treatment should be started as soon as the diagnosis is suspected without waiting for laboratory confirmation. Typically, treatment is initiated with a combination of isoniazid, rifampin, pyrazinamide, and an aminoglycoside such as amikacin. (39) Isoniazid is bactericidal, rapidly absorbed, and well tolerated. Neurotoxicity can be avoided by supplementing pyridoxine (vitamin B6) in exclusively breastfed infants. Rifampin is a bactericidal agent that is easily absorbed and readily penetrates the blood-brain barrier. It is hepatotoxic and upregulates hepatic cytochrome P450 enzymes, thereby increasing liver metabolism of many other drugs. Pyrazinamide is well absorbed orally, metabolized by the liver, and crosses the inflamed meninges.

Corticosteroids are indicated for patients who have meningitis and pericardial or pleural effusions with the expectation of decreasing mortality and improving neurologic outcome.

Asymptomatic infants of mothers who have active infection receive isoniazid prophylaxis in most cases for at least 2 to 3 months, at which time a tuberculin skin test determines the course of infection and need for further evaluation or treatment.

Prevention

Prevention begins with screening of high-risk obstetric patients in the prenatal period. It remains the only effective strategy in prevention of congenital tuberculosis. Some experts believe that a tuberculin skin test should be placed on all pregnant women, although it is typically recommended in the high-risk population only. Chest radiographs are not considered a valuable screening tool unless the tuberculin skin test result is positive. Extrapulmonary tuberculosis, including uterine disease, should be excluded. (33) Pyridoxine supplementation is indicated for all pregnant and breastfeeding women receiving isoniazid.

Syphilis

Syphilis has been the focus of debate by scientists for more than a millennium due to the controversies involved in its ambiguous origin, screening, and diagnosis. Sir William Osler went so far as to say that "one who knows syphilis knows medicine." The disease is caused by the spirochete *Treponema pallidum*, which has not yet been cultivated in vitro. The first major work on syphilis was performed in 1498 by the Spanish physician Francisco Lopez de Villalobos. Thereafter, immense progress was made in the knowledge, understanding, and management of the disease. Congenital syphilis occurs after infection of the placenta in pregnant women who have secondary syphilis that subsequently spreads hematogenously to the fetus. Transmission can occur at any stage of pregnancy.

Epidemiology

Due to its remarkable sensitivity to penicillin, congenital syphilis should have been eliminated around the time of World War II but was not. Today, the WHO estimates that about 1 million pregnancies are affected by syphilis worldwide. Forty percent of these pregnancies result in fetal or perinatal death, and 50% of surviving neonates suffer significant physical, developmental, and sensory impairments. (40) The number of cases is likely grossly underestimated because reporting has been hampered by the lack of definitive diagnostic techniques and inadequate access to prenatal care in many countries. (41) The congenital syphilis rate declined in the United States from 1991 to 2005 but increased 23% from 2005 to 2008. (42) This increase has been linked with the 38% rise in the primary and secondary syphilis rate among women from 2004 to 2007, especially in the southern United States.

Epidemiologic risk factors associated with syphilis are teenage mothers, poor prenatal care, illegal drug use, sexual promiscuity, contact with anyone with sexually transmitted infections (STIs) or a history of STIs, and living in underprivileged areas.

Clinical Manifestations

To prevent congenital syphilis, clinical signs in both the pregnant mother and the newborn must be recognized and the disease treated. Clinical manifestations in pregnant women do not differ from those of acquired syphilis. A chancre may be asymptomatic or overlooked due to its location inside the vagina, on the cervix, or on the labia. Disseminated disease presents 4 to 10 weeks after the appearance of the initial chancre. Dermatologic signs could include macular, papular, follicular, or pustular lesions and are accompanied by constitutional symptoms such as fever, weight loss, anorexia, fatigue, and arthralgias. Alopecia, hepatitis, glomerulonephritis, osteitis, iritis, and meningitis are some of the less common features.

Congenital syphilis is divided classically into early and late disease. Early congenital syphilis manifests in the first 2 postnatal years. Clinical signs that appear beyond this time are classified as late syphilis. Approximately 30% to 40% of fetuses that have congenital syphilis are stillborn, and approximately 75% of liveborn infants are asymptomatic at birth. (43) Most affected children develop symptoms between the third and fourteenth weeks after birth, and the wide spectrum of symptoms often makes the diagnosis difficult.

In addition to stillbirth (which may be preceded by nonimmune hydrops fetalis), signs of early syphilis may include intrauterine growth restriction, hepatosplenomegaly, rash, condyloma lata, snuffles (syphilitic rhinitis), jaundice (syphilitic hepatitis), pseudoparalysis, or edema (nephrotic syndrome). Hepatomegaly is the most consistent feature of congenital syphilis and is present in almost all cases, even in the absence of splenomegaly. Liver enzymes may be elevated. Nasal fluid is highly infectious, and snuffles are followed by a maculopapular rash. The most common skin lesion starts as pink and oval macules, which subsequently become coppery brown and desquamate (Fig. 3). Pemphigus syphiliticus is characterized by vesiculobullous eruptions involving the palms and soles. In the immediate newborn period, Coombs-negative hemolytic anemia can be found. Other findings include leukocytosis, thrombocytopenia, or leukopenia. Nephrotic syndrome can occur at 2 to 3 months of age and is characterized by pretibial, scrotal, or periorbital edema and ascites. Central nervous system manifestations include meningitis, choroiditis, hydrocephalus, and seizures. Osteochondritis, especially of the long bones and ribs, ensues at about 8 months of age. Wimberger sign consists of bilateral destruction of the upper medial tibial metaphyses (Fig. 4).

Although less common, diaphyseal periostitis in long bones is most characteristic of congenital syphilis. (43) Late congenital syphilis is not infectious and involves stigmata that represent scars from early disease. These include Hutchinson teeth (peg-shaped and notched incisors with marked thinning), mulberry molars, and saddle nose deformity. Eye findings are interstitial keratitis, healed chorioretinitis, secondary glaucoma, and corneal scarring. Central nervous system involvement often results in intellectual disability, hydrocephalus, epilepsy, optic nerve atrophy, or cranial nerve palsies with eighth

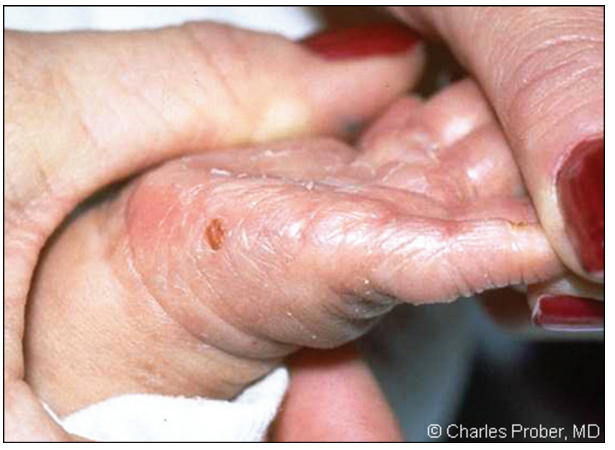


Figure 3. Congenital syphilis with desquamation over the hand. Reprinted with permission from the *Red Book Online*. Image courtesy of Charles Prober, MD.

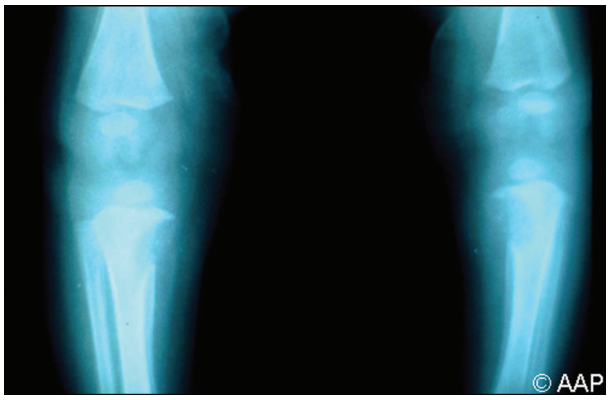


Figure 4. Congenital syphilis with proximal tibial metaphysitis (Wimberger sign). Reprinted with permission from the *Red Book Online*.

nerve deafness. Neurosyphilis is typically asymptomatic, but tabes and juvenile paresis may occur. Saber shins, Higoumenakia sign (unilateral enlargement of the sternoclavicular portion of the clavicle), and Clutton joints (bilateral knee effusions) are some of the scars from earlier skeletal involvement.

Diagnosis

Placental histologic evaluation is a valuable diagnostic tool for congenital syphilis, which is characterized by a triad of enlarged hypercellular villi, necrotizing funisitis, and acute or chronic villitis. (44) Confirmatory diagnosis requires identification of *T pallidum* in fetal/neonatal tissues or in the placenta via dark field microscopy. Because *T pallidum* cannot be cultured, serologic tests are critical, despite the lack of sensitivity and specificity. The tests can be categorized as treponemal and nontreponemal. Treponemal tests include the fluorescent treponemal antibody absorption (FTA-ABS) and the particle agglutination (TP-PA) tests. Nontreponemal tests are the Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma reagin (RPR) test. (45) Any positive nontreponemal test result must be confirmed with a treponemal test.

Maternal antibodies are transferred passively via the placenta, making distinction between mother's and infant's antibodies difficult. However, if the neonatal antibody titers are more than four times those of the mother, it is unlikely that they were transferred passively. Infection acquired by the mother later in pregnancy results in transfer of infection to the fetus before antibodies can be made and low antibody titers in the neonate.

Any infant who has: 1) fourfold or greater maternal nontreponemal antibody titer, 2) clinical signs, 3) missing or undocumented maternal treatment, 4) maternal treatment less than 4 weeks before delivery, 5) maternal treatment with anything but penicillin, or 6) maternal evidence of reinfection or relapse (fourfold or greater increase in maternal titers) should be evaluated with complete blood and platelet counts, cerebrospinal fluid examination, quantitative VDRL testing, and long-bone radiographs (Fig. 4). Ophthalmologic examination, neuroimaging, auditory brainstem response, and liver function testing are added if infection is strongly suspected. Human immunodeficiency virus testing should be considered. An algorithm for evaluation and treatment of infants born to mothers who have positive syphilis serology can be found in the Report of the American Academy of Pediatrics Committee on Infectious Diseases (Fig. 5). (45)

Treatment

Treatment of infants of mothers who have documented syphilis almost always is indicated, unless the mother has been appropriately and successfully treated before pregnancy and the infant is asymptomatic. In all other cases, either a one-time intramuscular (IM) dose of 50,000 units/kg benzathine penicillin G or a 10-day course of intravenous (IV) or IM penicillin G is recommended. (45) Adequate follow-up evaluation of untreated and treated infants is critical. (43)

Prevention

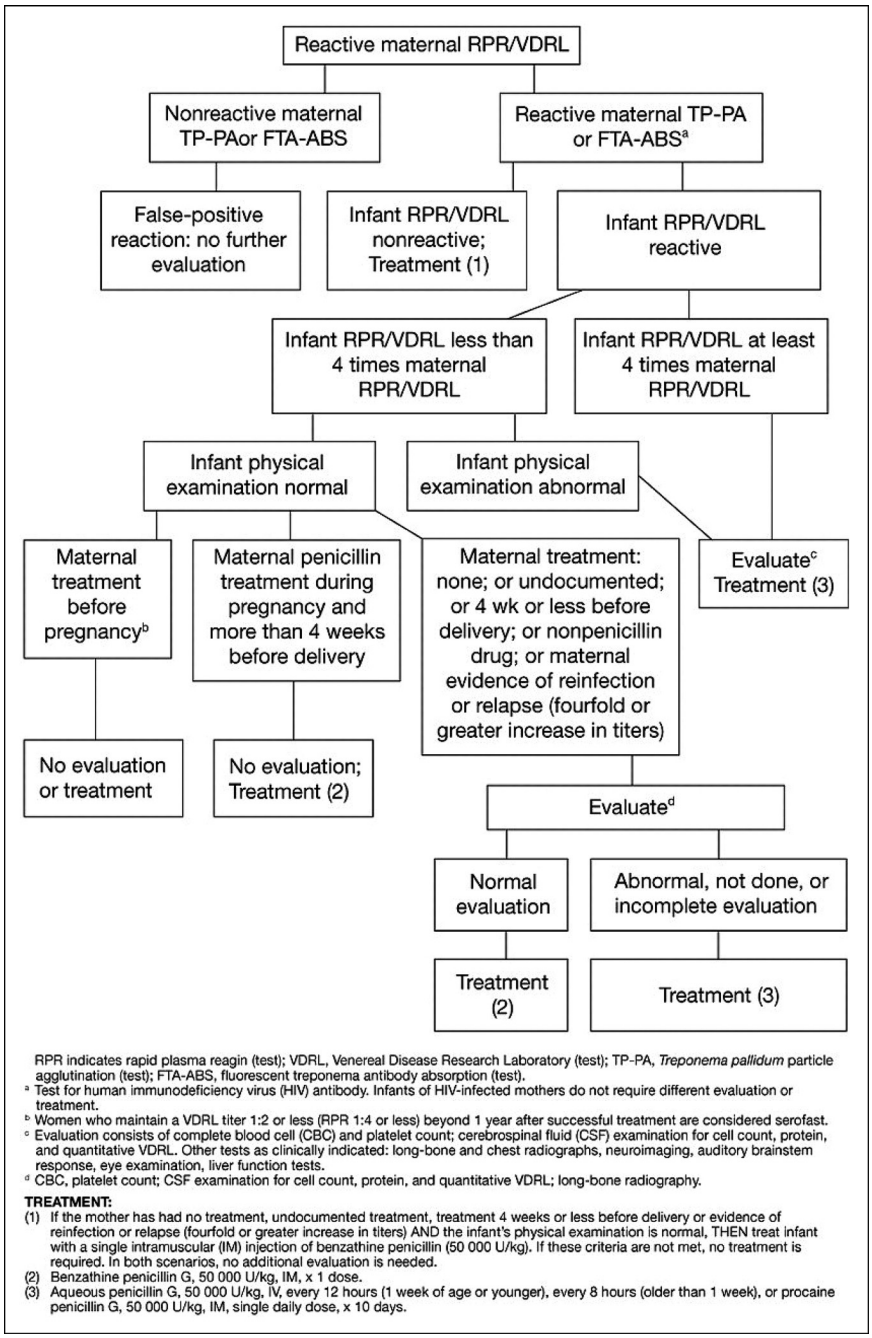
Congenital syphilis can be prevented by early detection of maternal infection and treatment at least 30 days before delivery. The CDC recommends serologic syphilis testing for all pregnant women at the initial perinatal visit. In communities and populations that have a high risk for congenital syphilis, serologic testing and a sexual history should be obtained at 28 weeks' gestation and at delivery. (46) Both syphilis and congenital syphilis are reportable diseases in the United States, and prenatal testing is required by law in almost all states. Education about STIs and prenatal care are important in reducing the incidence of congenital syphilis.

Varicella-Zoster Virus (VZV)

VZV belongs to the Herpesviridae family and causes varicella (chickenpox) with a primary infection and herpes zoster (shingles) with reactivation later in life.

Epidemiology

The incidence of varicella has declined significantly since universal immunization programs. However, in temperate climates, approximately 5% of women of childbearing



RPR indicates rapid plasma reagin (test); VDRL, Venereal Disease Research Laboratory (test); TP-PA, *Treponema pallidum* particle agglutination (test); FTA-ABS, fluorescent treponema antibody absorption (test).

[a] Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment.

[b] Women who maintain a VDRL titer 1:2 or less (RPR 1:4 or less) beyond 1 year after successful treatment are considered serofast.

[c] Evaluation consists of complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL. Other tests as clinically indicated: long-bone and chest radiographs, neuroimaging, auditory brainstem response, eye examination, liver function tests.

[d] CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long-bone radiography.

TREATMENT:

(1) If the mother has had no treatment, undocumented treatment, treatment 4 weeks or less before delivery or evidence of reinfection or relapse (fourfold or greater increase in titers) AND the infant's physical examination is normal, THEN treat infant with a single intramuscular (IM) injection of benzathine penicillin (50 000 U/kg). If these criteria are not met, no treatment is required. In both scenarios, no additional evaluation is needed.

(2) Benzathine penicillin G, 50 000 U/kg, IM, x 1 dose.

(3) Aqueous penicillin G, 50 000 U/kg, IV, every 12 hours (1 week of age or younger), every 8 hours (older than 1 week), or procaine penicillin G, 50 000 U/kg, IM, single daily dose, x 10 days.

Figure 5. Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis. Reprinted with permission from the *Red Book Online*.

age remain susceptible to VZV. (47) The true incidence of VZV infection in pregnancy is unknown, but the annual infection rate in the United States has been estimated to be between 1.6 and 4.6 per 1,000 pregnancies. Assuming a VZV infection rate during pregnancy of 2 in 1,000, a fetal risk of 1% during the first 20 weeks of gestation, and a birth rate of 4.1 million per year, 41 cases of congenital varicella syndrome (CVS) per year would be expected. (48)

VZV can be transferred transplacentally from the mother to the fetus, leading to adverse outcomes in the infant. Fetal infection in the first 20 weeks of gestation can result in a constellation of anomalies known as varicella embryopathy or CVS, first recognized in 1947 by Laforet and Lynch. (49) Few congenital infections have been reported, possibly because most women of childbearing age are immune. The overall risk of CVS after maternal infection during pregnancy has been estimated to be 1% or less. (47)(48)(50)(51) Between 1947 and 2000, 112 cases of CVS were reported in the literature, with more than half since 1991. (52)

In a prospective study conducted from 1980 to 1993, 1,373 pregnant mothers who had varicella were studied. (50) The risk of CVS was highest (2%) if infection occurred between 13 and 20 weeks of gestation. No cases of CVS were observed with infections beyond 20 weeks of gestation or among 366 mothers who were diagnosed with herpes zoster during pregnancy. In 2002, Harger and associates (51) conducted a cohort study of 362 women who had clinical varicella infection. Only one case (0.4%) of definite CVS was found after maternal varicella at 24 weeks' gestation. Fetal death at 20 weeks occurred in two cases, and fetal hydrops was noted at 17 weeks in one case after maternal varicella in the first trimester.

In contrast to varicella, herpes zoster during pregnancy is not considered a risk to the fetus. (53) Only one case of possible CVS has been reported in an infant born to a mother who had disseminated zoster at 12 weeks' gestation. (54)

Perinatally acquired varicella in the newborn classi-

cally occurs in the first 10 days after birth if the mother is infected from 5 days before to 2 days after delivery. It may occur in 17% to 30% of newborns, and the fatality rate prior to advanced neonatal intensive care unit care and availability of varicella-zoster immune globulin was 31%. (49) This severity has been attributed to the lack of maternal antibody transfer before perinatal infection.

Clinical Manifestations

The spectrum of clinical features of CVS is wide. (47)(54) It includes skin lesions with dermatomal distribution (72%), neurologic defects (62%), eye diseases (52%), and skeletal anomalies (44%). (55) About 30% of symptomatic infants die in the first postnatal months. (55) The most characteristic findings of CVS are limb hypoplasia with cicatricial skin scarring (Fig. 6), chorioretinitis, cataracts, and brain abnormalities. These include cortical atrophy, intellectual disability, and seizures. Bulbar palsies resulting in dysphagia and aspiration pneumonia have been described. Reported intestinal defects consist of duodenal stenosis, colon atresia, microcolon, and sphincter dysfunction.

The dermatomal distribution of skin lesions and segmental involvement of the musculoskeletal and nervous systems led some to hypothesize that CVS is not caused by direct VZV effects. (54) However, the sequelae may be the consequence of herpes zoster development in utero in combination with an immature cellular immune response. (48) Serious complications of perinatally acquired varicella are pneumonia and bacterial superinfections, sometimes leading to toxic shock syndrome and necrotizing fasciitis. Cerebellar ataxia, encephalitis, and meningitis are other severe complications of neonatal varicella.

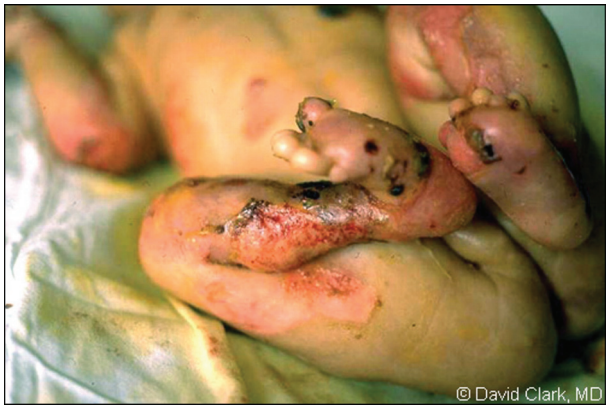


Figure 6. Congenital varicella with short-limb syndrome and scarring of the skin. The mother had varicella during the first trimester of pregnancy. Reprinted with permission from the *Red Book Online*. Image courtesy of David Clark, MD.

Diagnosis

Diagnosing congenital varicella starts with recognizing the disease in the pregnant mother. Varicella lesions in pregnancy begin as papules, progressing to pustules and followed by crusts. The lesions tend to appear first on the face and scalp and then spread centripetally. Associated constitutional symptoms are fatigue, malaise, and fever. The diagnosis is clinical, although serology can be used to confirm the diagnosis.

Acute recent infection is demonstrated by positive IgM and negative IgG antibodies. Persistence of VZV antibodies in the infant beyond 8 months of age is highly suggestive of intrauterine acquisition of varicella. VZV can be identified by PCR or by immunofluorescence techniques in skin scrapings or from vesicle fluid.

Findings of CVS on fetal ultrasonography include intrauterine growth restriction, microcephaly, ventriculomegaly, echogenic foci in the liver, and limb deformities. Fetal infection can be confirmed by detection of VZV DNA in fetal blood and amniotic fluid via PCR assay. Diagnostic criteria and algorithms have been published. (53)

Treatment

Data on the use of acyclovir for neonatal varicella are limited, but the drug has been extensively used for neonatal herpes simplex virus infection. Infants who have clinical signs of active varicella infection typically are treated with IV acyclovir until no new lesions develop. Antibiotics should be administered for bacterial superinfections, and complications should be treated appropriately.

Prevention

The continued occurrence of CVS cases (55) supports the need for expert medical counseling for women who contract varicella during pregnancy. It also highlights the value of universal immunization in early childhood. Women of reproductive age should be offered varicella vaccine at the time of their annual examination if they are susceptible to infection. Testing for varicella immunity is recommended at prenatal visits, and nonimmune mothers should be offered vaccination before discharge after delivery. A second dose should be administered 4 to 8 weeks after delivery, and pregnancy should be avoided for 1 month after each dose of vaccination.

A passive vaccine, varicella-zoster immune globulin, is prepared from blood donors who have high titers of varicella antibody. It is effective up to 96 hours after exposure. Its role is primarily attenuation rather than prevention of disease. The agent can be administered to pregnant women who are susceptible to infection to reduce the chances of transmission to the fetus. The

Table. Rare and Unusual Origins of Congenital Infection

Organism	Category	Comment
Brucella melitensis (59)(60)	Bacteria	*Brucella* usually is transmitted through direct contact with infected animals and humans or by eating contaminated food. Transplacental transmission has been reported and may be associated with neonatal morbidity.
Chlamydophila abortus (61)(62)	Bacteria	Pregnant women should avoid contact with laboring and/or aborting sheep and goats. *Chlamydia* and newly identified *Chlamydia*-like organisms play an emerging role in miscarriage, stillbirths, and preterm labor in both animals and humans.
Babesia microti (63)(64)	Protozoa	In two case reports of congenital babesiosis, infants presented at 4 to 5 weeks of age after maternal tick bite before delivery in an epidemic area.
Trypanosoma cruzi (65)(66)	Protozoa	Chagas disease is one of the most important endemic parasitic infections in Latin America. Maternofetal transmission occurs in 5% to 6% of cases. Outside endemic areas, Chagas disease often is unrecognized because pregnant women may be asymptomatic. Associated symptoms in the infant include prematurity/low birthweight, respiratory distress syndrome, hepato- and splenomegaly, and neurologic signs.
Coccidioides immitis (67)(68)	Fungi	Disseminated maternal coccidiomycosis can cause placentitis and neonatal disease after aspiration of infectious vaginal secretions. Although the placenta has been considered impermeable to the coccidioidin spherule, rare case reports suggest the possibility of in utero infection.
Histoplasma capsulatum (69)(70)	Fungi	Rare cases have been reported of transplacentally infected infants of mothers who have disseminated histoplasmosis in association with human immunodeficiency virus disease.
Lymphocytic choriomeningitis virus (LCMV) (71)(72)(73)	Viruses	LCMV continues to be an underrecognized cause of congenital anomalies. Maternal infection arises after contact with laboratory, wild, or pet rodents and their excretions. Sequelae include chorioretinopathy, intracranial calcifications, microcephaly, and hydrocephalus.
Human herpesvirus 6 (HHV6) (74)(75)	Viruses	Based on molecular detection methods, congenital asymptomatic HHV6 infections are relatively common (1%). The clinical importance is unclear, and long-term follow-up may be advisable because at least one case of poor neurologic outcome has been described.

primary indication in pregnant women is to prevent complications of varicella in the mother rather than to protect the fetus because the exact effectiveness in protecting the fetus is not well determined. Varicella-zoster immune globulin is recommended for neonates whose mothers developed varicella rash between 5 days before and 2 days after delivery. It also should be considered in exposed newborns whose mothers are varicella-nonimmune and in preterm infants born before 28 weeks' gestation (or birthweight ≤1,000 g), regardless of maternal history. In these cases, acquired maternal antibodies may be lacking. (56) If varicella-zoster immune globulin is not available, immune globulin intravenous can be used. There is no well-controlled study for prophylactic use of acyclovir to prevent neonatal varicella. However, several anecdotal reports have documented the benefit from such therapy, usually in combination with immune globulin. (48) Neonates born to

mothers who have varicella either should be discharged or placed under airborne and contact isolation until day 21 of age unless they received varicella-zoster immune globulin or immune globulin intravenous, in which case isolation lasts 28 days. Infants who have CVS do not require isolation as long as they do not have active lesions. (56)

Two live attenuated vaccines are available in the United States that are based on the OKA strain of VZV. Because the effects of varicella vaccine on the fetus are unknown, active immunization is contraindicated during pregnancy. However, in 1995, vaccine manufacturers, in collaboration with the CDC, established a pregnancy registry to monitor outcomes in pregnant women who accidentally received varicella vaccine 3 months before or during pregnancy. During the first 10 years of the registry and more than 500 reported cases of exposure, no birth defects similar to CVS were noted, suggesting that the risk, if any, is low.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the epidemiology, pathogenesis, prevention, clinical manifestations, and diagnostic features of perinatal *Listeria monocytogenes* infection.
- Know the treatment and complications of perinatal *Listeria monocytogenes* infection.
- Know the epidemiology, prevention, and pathogenesis of perinatal infections with *Treponema pallidum*.
- Know the clinical manifestations and diagnostic features of perinatal infections with *Treponema pallidum*.
- Know the management and complications of perinatal infections with *Treponema pallidum*.
- Know the epidemiology, pathogenesis, and prevention of perinatal infections with *Mycobacterium tuberculosis*.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with *Mycobacterium tuberculosis*.
- Know the epidemiology, prevention, and pathogenesis of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.
- Know the epidemiology, pathogenesis, and prevention of perinatal parvovirus infections.
- Know the clinical manifestations, diagnostic features, treatment, and complications of perinatal parvovirus infections.
- Plan the management of an exposure to varicella in the newborn nursery or newborn intensive care unit.

Rare and Unusual Causes of Congenital Infections

The large inventory of pathogens that, under certain conditions, can cause harm to the developing pregnancy product is increasingly recognized, in part due to international migration and travel. These include bacteria, viruses, fungi, and protozoa (Table). A recent review by McClure and Goldenberg (57) provides a comprehensive list of microorganisms and viruses that have been associated with stillbirth. In addition to the growing list of pathogens, clinicians should be aware of genetic or noninfectious environmental causes for sequelae that mimic congenital infections. (58)

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NeoReviews Quiz

1. Human parvovirus was first isolated in 1975, and its adverse effects on the fetus were first documented by case reports in 1984. Of the following, the *most* accurate statement regarding parvovirus infection during pregnancy is that:
   A. Adverse effects of the virus on the fetus are largely teratogenic.
   B. Among occupational groups, health-care workers have the highest infection rate.
   C. Fetal infection rate based on DNA hybridization studies is 80%.
   D. Maternal immunoglobulin G antibodies correlate with lower fetal infection rate.
   E. Risk of transplacental transmission is highest in the third trimester of pregnancy.

2. Listeriosis is a food-borne disease caused by *Listeria monocytogenes*, a gram-positive bacillus. A large epidemic of listeriosis in North America occurred in 1995, affecting mostly pregnant women and their newborns. Of the following, the food item involved as the source of infection in this epidemic was:
   A. Coleslaw.
   B. Partially cooked meat.
   C. Pasteurized milk.
   D. Raw vegetables.
   E. Soft cheese.

3. Because cell-mediated immunity is weakened in pregnancy, pregnant women are at high risk for developing listeriosis, especially in the third trimester, which can lead to vertical transmission. The resultant neonatal infection is classified as early-onset when it manifests within 2 to 3 days after birth or late-onset when manifestations become apparent later after birth. Of the following, the *most* common clinical manifestation of late-onset listeriosis in the neonate is:
   A. Hepatitis.
   B. Meningitis.
   C. Myocarditis.
   D. Pneumonia.
   E. Retinitis.

4. Congenital tuberculosis is distinguished from postnatally acquired tuberculosis by a proven tuberculous lesion in the infant plus one of the criteria that include occurrence of the lesion in the first week after birth and evidence of maternal genital or placental tuberculosis. Of the following, the *most* common presenting feature of congenital tuberculosis in the infant is:
   A. Ear discharge.
   B. Hepatosplenomegaly.
   C. Lymphadenopathy.
   D. Meningitis.
   E. Skin lesions.

5. Congenital syphilis is classically divided into early and late disease manifestations. Early congenital syphilis manifests in the first 2 postnatal years, whereas late congenital syphilis represents residual stigmata from early disease. Of the following, the *most* consistent feature of early congenital syphilis is:
   A. Hepatomegaly.
   B. Peritibial edema.
   C. Pseudoparalysis.
   D. Skin rash.
   E. Snuffles.

6. Varicella-zoster virus (VZV) can be transferred transplacentally from the mother to the fetus and results in congenital varicella syndrome in the infant. Of the following, the risk of congenital varicella syndrome in the infant is highest when maternal VZV infection occurs at the gestational age of:
   A. 16 to 20 weeks.
   B. 21 to 24 weeks.
   C. 25 to 28 weeks.
   D. 29 to 32 weeks.
   E. 33 to 36 weeks.