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Cytomegalovirus, Parvovirus B19, Varicella Zoster, and Toxoplasmosis in Pregnancy

Among the many physiologic changes that occur during pregnancy, the maternal immune system is altered to dampen the maternal inflammatory response and allow for fetal antigen tolerance (1, 2). Although such immunologic changes diminish the chance of fetal rejection, they potentially increase maternal and fetal vulnerability to certain infectious diseases. Common infections that cause mild-to-moderate disease in healthy adults and children can cause serious maternal and fetal complications if acquired during pregnancy. A unique concern with maternal infection is the potential for mother-to-child transmission or congenital infection. Cytomegalovirus (CMV), parvovirus B19, varicella zoster virus (VZV), and toxoplasmosis are common infections associated with moderate-to-severe fetal and infant complications when acquired congenitally. The purpose of this document is to update the current understanding of these infections, including their clinical presentations; their modes and risks of perinatal transmission; and their maternal, fetal, and infant effects, and to offer guidelines for preventing and managing these infections during pregnancy.

Background

Cytomegalovirus

Cytomegalovirus is a ubiquitous double-stranded DNA herpesvirus that is transmitted by sexual contact or direct contact with infected blood, urine, or saliva. After an incubation period of 28–60 days (mean, 40 days), CMV infection induces immunoglobulin M (IgM) antibody production followed by an immunoglobulin G (IgG) antibody response. Viremia can be detected for 2–3 weeks after primary infection (infection in a previously seronegative individual). Although adults with primary CMV infection are usually asymptomatic, individuals may experience a mononucleosis-like syndrome, with fever, chills, myalgias, malaise, leukocytosis, lymphocytosis, abnormal liver function, and lymphadenopathy (3). After the primary infection, CMV remains latent in host cells and recurrent, or secondary, infection can occur. Secondary infection (intermittent viral excretion in the presence of host immunity) can occur after reactivation of the latent endogenous CMV strain or by reinfection with a different exogenous viral strain (4).

Prevalence of CMV immunity, in primary or secondary infection, varies significantly by geographic region, socioeconomic status, and ethnicity (5–7). The incidence of primary CMV infection among previously seronegative pregnant women in the United States ranges from 0.7% to 4%, with estimates of secondary infection ranging up to 13.5% (7–11). Vertical transmission of CMV may occur as a result of transplacental infection after primary

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or secondary infection, exposure to contaminated genital tract secretions at delivery, or breastfeeding (12). Most infants with congenital CMV are asymptomatic at birth. Clinical findings of symptomatic congenital CMV infection include jaundice, petechiae, thrombocytopenia, hepatosplenomegaly, growth restriction, myocarditis, and nonimmune hydrops (10, 13, 14).

Cytomegalovirus is the most common congenital infection, occurring in 0.2–2.2% of all neonates (9, 15, 16). The annual cost of treating the permanent disabilities and complications caused by CMV infections in the United States is estimated to be more than $1.86 billion (17). Transplacental CMV transmission represents the most significant risk of developing clinical sequelae. Cytomegalovirus infection resulting from exposure to infected cervical secretions or breast milk is typically asymptomatic and is not associated with severe neonatal sequelae (18, 19). With primary maternal CMV infection, the overall risk of transmission to the fetus is approximately 30–40% (20–23). Although vertical transmission may occur at any stage of pregnancy, the risk of transmission is greatest in the third trimester (24, 25). Transmission rates for primary infection are 30% in the first trimester, 34–38% in the second trimester, and 40–72% in the third trimester. However, more serious fetal sequelae occur after maternal CMV infection during the first trimester. Of those fetuses infected in utero after a primary infection, 12–18% will have signs and symptoms of CMV infection at birth and up to 25% will develop sequelae (15, 26). Approximately 30% of severely infected infants die, and 65–80% of survivors have severe neurologic morbidity (8, 27, 28). The incidence of severe fetal infection is much lower after recurrent maternal infection than after primary infection. Vertical transmission after a recurrent infection is 0.15–2% (8, 26). Infants infected after maternal CMV reactivation generally are asymptomatic at birth. Congenital hearing loss is typically the most severe sequela of secondary infection, and congenital infection after recurrent infection is unlikely to produce multiple sequelae (26, 29).

Parvovirus B19

Parvovirus B19 is a single-stranded DNA virus that causes the childhood exanthema erythema infectiosum, also known as fifth disease. Children typically demonstrate a facial rash, sometimes similar in appearance to a slapped cheek, in addition to possible fever, body rash, and joint pain. In immunocompetent adults, the most common symptoms of parvovirus B19 infection are a reticular rash on the trunk and peripheral arthropathy, although approximately 20% of infected individuals are asymptomatic (30). Another manifestation of parvovirus B19 infection is transient aplastic crisis, which is more common in those with an underlying hemoglobinopathy. Most infections are mild; most individuals recover completely from parvovirus B19 infection and require only supportive care during the acute phase.

Transmission of parvovirus B19 most commonly occurs through respiratory secretions and hand-to-mouth contact. The infected person generally is infectious 5–10 days after exposure, before the onset of the rash or other symptoms, and is no longer infectious by the time of onset of the rash (31). In response to infection, IgM and IgG antibodies are produced. The IgM response, which persists for 1 month to several months, is indicative of a recent infection. IgG antibodies persist indefinitely and, in the absence of IgM, indicate prior infection and lifelong immunity. Prevalence of seropositivity to parvovirus B19 increases with age, and 50–65% of reproductive-aged women are seropositive (32–34). The risk of maternal parvovirus B19 infection varies with level of exposure to the infected individual. Exposure to a household member infected with parvovirus B19 is associated with a 50% risk of seroconversion (32, 34, 35). The risk of transmission in a child care setting or classroom is lower, approximately 20–50% (34, 36, 37).

After acute parvovirus B19 infection during pregnancy, rates of maternal-to-fetal transmission range from 17% to 33% (32, 38). Although most cases of fetal infection resolve spontaneously with no adverse outcomes, fetal parvovirus B19 has been associated with spontaneous abortion, hydrops fetalis, and stillbirth (30, 31). The rate of fetal loss among women with serologically proven parvovirus B19 infection ranges from 8–17% before 20 weeks of gestation to 2–6% after 20 weeks of gestation (39–43). In utero, parvovirus B19 infection can lead to nonimmune hydrops fetalis. An estimated 8–10% (potentially up to 18–27%) of cases of nonimmune hydrops fetalis are associated with parvovirus B19 infection (30, 31). Because the virus is cytotoxic to erythroid precursors, hydrops fetalis most often results from aplastic anemia, although hydrops also can be related to myocarditis or chronic fetal hepatitis (44). Severe effects are seen most frequently among fetuses when maternal parvovirus B19 infection occurs before 20 weeks of gestation (40).

The fetus is particularly vulnerable to disease transmission and severe complications in the second trimester because of the mechanisms of viral placental transport and rapid changes in fetal hematopoiesis that occur during this period (44). Stillbirth that results from maternal infection has occurred from 1 week up to 11 weeks after maternal infection. However, hydrops is unlikely to develop if it has not occurred by 8 weeks after maternal infection (45).

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Long-term neurodevelopmental outcomes are uncertain in fetuses with congenital parvovirus B19 infection that do not succumb to the disease. Earlier studies suggested no long-term adverse effects in fetuses with hydrops that have been transfused after maternal infection, whereas a more recent study suggested an increase in neurodevelopmental impairment among fetuses with hydrops that underwent transfusion (42, 43, 46).

Varicella Zoster Virus

Varicella zoster virus is a highly contagious DNA herpesvirus that is transmitted by respiratory droplets or close contact. The infection rate among susceptible (seronegative) contacts is 60–90% after exposure (47). The incubation period after infection is 10–20 days, with a mean of 14 days (47). The period of infectivity begins 48 hours before the rash appears and lasts until the vesicles crust over. The primary infection causes chickenpox, which is characterized by fever, malaise, and a maculopapular pruritic rash that becomes vesicular. After the primary infection, VZV remains dormant in sensory ganglia and can be reactivated to cause a vesicular erythematous skin rash known as herpes zoster, or shingles. The antibody to VZV develops within a few days after the onset of infection, and prior infection with VZV confers lifelong immunity to primary infection.

Before 1995, when a varicella vaccine became available in the United States, VZV infection was common, with about 4 million people becoming infected each year. Of those individuals who were infected, up to 13,000 required hospitalization and up to 150 died. After childhood varicella vaccination became routine, disease incidence decreased 82% from 2000 to 2010 and annual varicella-related deaths dropped from approximately 150 each year to 14 in 2007 (48, 49). Of the 14 deaths, 11 were adults 50 years or older, two were adults aged 20–49 years, and one was a young child (48).

Even before routine vaccination, varicella infection was uncommon in women during pregnancy (estimated to occur in 0.4–0.7 per 1,000 pregnant women) because of the high prevalence of natural immunity (50). Maternal varicella infection is likely to be even lower now, with the introduction of routine vaccination and the overall reduction in disease. Pregnancy complicated by maternal varicella infection is associated with maternal, fetal, and neonatal effects. The disease is usually benign and self-limited in children, with adults suffering more serious morbidity, such as encephalitis and pneumonia. Approximately 10–20% of pregnant women with varicella infection will develop pneumonia, which is a significant risk factor for maternal mortality, estimated to be as high as 40% (51, 52).

In pregnancy, varicella may be transmitted across the placenta, which results in congenital or neonatal chickenpox. The risk of congenital varicella syndrome is low (0.4–2%); limited to exposure during early pregnancy (first trimester 0.4%, second trimester 2%, third trimester 0%); and characterized by skin scarring, limb hypoplasia, chorioretinitis, and microcephaly (53–57). Neonatal VZV infection is associated with a high neonatal death rate when maternal disease develops from 5 days before delivery to 48 hours postpartum as a result of the relative immaturity of the neonatal immune system and the lack of protective maternal antibodies (58, 59). Susceptible (seronegative) pregnant women theoretically can acquire varicella infection from exposure to individuals with herpes zoster infection (shingles). However, transmission is extremely rare because contact with an open cutaneous lesion is required and viral shedding is lower with recurrent varicella infection compared with primary chickenpox (51, 54, 60).

Toxoplasmosis

Toxoplasmosis is caused by the intracellular parasite *Toxoplasma gondii*. *T gondii* exists in several forms: a trophozoite, which is the invasive form, and a cyst or an oocyst, which are latent forms (61). Human infection is acquired by consumption of cysts in undercooked meat from infected animals, consumption of insect-contaminated food, contact with oocysts from the feces of infected cats (the only definitive hosts), or contact with infected materials or insects in soil (62). Infection with *T gondii* usually is asymptomatic, although after an incubation period of 5–18 days, some nonspecific symptoms may occur. In the immunocompetent adult, the clinical course is benign and self-limited. Most often, toxoplasmosis presents as asymptomatic cervical lymphadenopathy, with symptoms occurring in only 10–20% of infected adults. Other symptoms include fever, malaise, night sweats, myalgias, and hepatosplenomegaly. Parasitemia can occur after infection, which in pregnant women can seed the placenta and cause subsequent fetal infection. Congenital transmission of *T gondii* from an infected woman results in an overall risk of congenital toxoplasmosis ranging from 20% to 50% without treatment (63–65). The later in gestation that the infection occurs, the more likely transmission is to occur. The rate of vertical transmission increases from 10% to 15% in the first trimester, to 25% in the second trimester, and to more than 60% in the third trimester (65–67). The severity of fetal infection depends on gestational age at the time of transmission. The earlier the fetus is infected, the more severe the disease (65, 67). Most infected infants do not have clinical signs of infection at birth, but as many as 90% will develop sequelae, including

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chorioretinitis and subsequent severe visual impairment, hearing loss, or severe neurodevelopmental delay (63, 68, 69). Other clinical manifestations of congenital toxoplasmosis include rash, hepatosplenomegaly, ascites, fever, periventricular calcifications, ventriculomegaly, and seizures (70–72).

Immunoglobulin M antibodies appear soon after acute infection and reach maximum levels in 1 month (63, 73). Immunoglobulin G antibodies appear after IgM antibodies, are detectable within a few weeks after infection, and confer immunity. High titers of IgG and IgM may persist for years.

Clinical Considerations and Recommendations

Cytomegalovirus

▶ *Which methods are used to diagnose maternal cytomegalovirus infection and what are the diagnostic criteria?*

Most adult CMV infections are asymptomatic, which makes recognition of primary infection difficult. Cytomegalovirus may be detected by viral culture or polymerase chain reaction (PCR) of infected blood, urine, saliva, cervical secretions, or breast milk, although diagnosis of CMV infection in adults usually is established by serologic testing. Serum samples collected 3–4 weeks apart, tested in parallel for anti-CMV IgG, are essential for the diagnosis of primary infection. Seroconversion from negative to positive or a significant increase (greater than fourfold [eg, from 1:4 to 1:16]) in anti-CMV IgG titers is evidence of infection. In addition, the use of IgG avidity assays, which measure the maturity of the IgG antibody, combined with IgM titers allows for improved identification of primary infection (sensitivity of 92%) when compared with standard serial serologic assays (74). For the first 2–4 months after initial CMV infection, immature, or low-avidity, IgG antibodies are produced, followed by high-avidity IgG production. The ability to ascertain the timing of CMV infection varies by assay, but the presence of IgM and low-avidity IgG is consistent with primary infection occurring within the past 2–4 months (75, 76). The presence of CMV-specific IgM is a useful but not completely reliable indication of a primary infection because only 10–30% of women with detectable CMV-specific IgM will have a primary infection (75, 77). Further, CMV-specific IgM titers may not be positive during an acute infection, may persist for many months after the primary infection, may be present during reactivation or reinfection, or may be present in the absence of infection (7, 8). The reported sensitivity of CMV IgM serologic assays is 50–90% (8, 75).

▶ *Which methods are used to diagnose fetal cytomegalovirus infection and what are the diagnostic criteria?*

Congenital CMV may be suspected prenatally after a documented maternal primary infection or, more commonly because universal screening is not recommended, after ultrasound findings suggestive of infection. These findings include abdominal and liver calcifications, hepatosplenomegaly, echogenic bowel or kidneys, ascites, cerebral ventriculomegaly, intracranial calcifications, microcephaly, hydrops fetalis, and growth restriction (78–81). Nevertheless, such findings are more likely to be associated with other abnormalities, such as aneuploidy, and the positive predictive value of each of these markers for CMV infection is quite weak (82). The presence of echogenic bowel, for instance, is only predictive of CMV infection approximately 3% of the time (79).

After detection of maternal infection or suspected fetal infection based on ultrasound findings, congenital CMV can be detected in the amniotic fluid of infected fetuses by either culture or PCR. Fetal blood sampling, which is less sensitive than amniotic fluid testing and carries additional risks for the fetus, is not warranted (75, 83). The sensitivity of CMV amniotic fluid culture ranges from 70% to 80% compared with a sensitivity of 78% to 98% for PCR (specificity of 92% to 98%) (84–91). The sensitivity of amniotic fluid testing for prenatal diagnosis of congenital CMV infection is markedly lower if performed before approximately 21 weeks of gestation (91, 92). Although a positive culture or PCR is highly predictive of congenital infection, the detection of CMV in amniotic fluid does not predict the severity of congenital CMV infection.

▶ *How should maternal and fetal cytomegalovirus infections be managed?*

Currently, no therapies are available for the treatment of maternal or fetal CMV infection. Antiviral medications such as ganciclovir, valganciclovir, and foscarnet are approved by the U.S. Food and Drug Administration (FDA) only for treatment of patients with acquired immunodeficiency syndrome (AIDS) or organ transplants. Although ganciclovir has been shown to cross the placenta by simple diffusion and reportedly has been used for treatment of congenital CMV, its use is not recommended outside of a research protocol because of risks that have been documented in animal studies (93). In one recent study of the prevention of congenital CMV infection, valganciclovir appeared to

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improve hearing and neurodevelopmental measures at age 6 months among congenitally infected neonates (94). However, the effectiveness of valganciclovir treatment in the reduction of long-term neurologic sequelae remains unknown, and its use in routine clinical care is not recommended.

Passive immunization with CMV-specific hyperimmune globulin also is under investigation as a potential means of preventing congenital CMV infection among women with known primary infection. A prospective cohort study conducted in Italy suggested that the use of CMV-specific hyperimmune globulin was associated with a lower chance of congenital infection (22). A subsequent randomized, placebo-controlled, double-blind trial, also conducted in Italy, failed to confirm these findings (23). Based on the cumulative findings thus far, CMV-specific hyperimmune globulin is not recommended for the prevention of congenital CMV infection outside of a research protocol.

In cases of known maternal CMV infection, referral to a maternal–fetal medicine or infectious disease specialist with expertise in pregnancy management may be warranted. Typically, serial ultrasonographic surveillance that includes assessment of fetal anatomy (eg, the cerebral ventricles) and growth is performed.

▶ *How should women be counseled about prevention of cytomegalovirus?*

Some groups of women are at higher risk of CMV infection. In one study, 11% of seronegative child care workers demonstrated seroconversion within 10 months of hire (95). Other studies have shown that 53% of families with young children have one or more seronegative family members who seroconvert within a year (96, 97). In two studies, increasing parity was associated with increasing CMV seroprevalence (98, 99). This demonstrates the possibility of child-to-mother transmission (98). Some have suggested that pregnant women should be instructed on the importance of personal hygiene and safe-handling techniques (eg, the use of latex or nonlatex gloves and rigorous hand washing after exposure to potentially infected articles, such as diapers, or respiratory secretions), as well as avoidance of sharing utensils with or kissing young children if saliva is present. Such guidelines may be difficult to implement because they often are considered impractical or burdensome. At present, such patient instruction remains unproven as a method to reduce the risk of congenital CMV infection.

Although a vaccine is not yet available, development of a CMV vaccine for primary prevention has been the focus of several studies. A recombinant glycoprotein, adjuvant vaccine was tested in a phase II trial of seronegative women of reproductive age and demonstrated 50% efficacy in preventing CMV infection at 1 year (100). However, efficacy was not sustained in the long term and the number of women with CMV infection was not sufficient to determine whether the vaccine prevented congenital infection. Phase III studies are needed to demonstrate efficacy and safety (101).

▶ *Should women be screened for cytomegalovirus before or during pregnancy?*

Routine serologic screening of pregnant women for CMV is not recommended (102, 103). The limitations of maternal IgM antibody screening in differentiating primary from recurrent infection makes the results difficult to use in counseling patients about fetal risk. In addition, maternal immunity does not eliminate the possibility of fetal infection given that up to 75% of congenital CMV infections worldwide may be due to reactivation of latent virus or reinfection with a new viral strain (104). The lack of a proven treatment to prevent congenital transmission further diminishes the potential benefit of universal screening (23).

Parvovirus B19

▶ *Which methods are used to diagnose maternal parvovirus B19 infection and what are the diagnostic criteria?*

Pregnant women exposed to parvovirus B19 should have serologic screening performed as soon as possible after exposure to determine if they should be monitored for seroconversion (105).

Women who are IgM negative and IgG positive have evidence of previous exposure and immunity and, thus, are not at risk of transplacental transmission. Women who are IgM positive, regardless of IgG status, should be monitored for potential fetal infection. Women who are IgM and IgG negative are susceptible to parvovirus B19 infection and serologic testing should be repeated in 4 weeks. If repeat testing demonstrates positive IgM or IgG, these women should be monitored for potential fetal infection.

▶ *Which methods are used to diagnose fetal parvovirus B19 infection and what are the diagnostic criteria?*

Fetal infection can be diagnosed using PCR to detect parvovirus B19 DNA in amniotic fluid (106–108). Although tests that measure quantitative serum and tissue DNA viral load exist, they are not widely available, and qualitative PCR (with a sensitivity that has been reported to be as high as 100%) is used to diagnose fetal infection during pregnancy (44). Testing for fetal parvovirus B19

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infection should be considered when ultrasonography reveals hydrops fetalis.

▶ *How should maternal and fetal parvovirus B19 infections be managed?*

Pregnant women with acute parvovirus B19 infection based on serologies should be monitored for the development of fetal anemia using serial ultrasonography. Standard monitoring should include assessment for ascites, placentomegaly, cardiomegaly, hydrops fetalis, and impaired fetal growth. In addition, Doppler assessment of the peak systolic velocity of the fetal middle cerebral artery should be performed because this measure has been identified as an accurate predictor of fetal anemia (109–113). However, fetal death can occur without evidence of hydrops fetalis (107, 114). Serial ultrasonographies should be performed every 1–2 weeks for 8–12 weeks after exposure. In the absence of ultrasound evidence of fetal sequelae by 8–12 weeks after exposure, adverse outcomes related to parvovirus B19 infection are highly unlikely (105, 115).

If hydrops fetalis is present or severe fetal anemia is suspected in the setting of parvovirus B19, fetal blood sampling should be performed to determine the fetal hematocrit in preparation for fetal transfusion. Although there is procedure-related risk, intrauterine transfusion should be considered if severe fetal anemia is present (116–119).

▶ *How should women be counseled about prevention of parvovirus B19?*

When outbreaks of parvovirus B19 infection occur in situations in which prolonged, close-contact exposure occurs, such as in schools, homes, or child care centers, options for prevention of transmission are limited. Exposure cannot be eliminated by identifying and excluding individuals with acute parvovirus B19 infection; up to 20% are asymptomatic, and those with infection are infectious before they develop symptoms. Exclusion of pregnant women from the workplace during endemic periods is not recommended. If pregnant women are exposed to individuals who are suspected or known to be infected with parvovirus B19, they should report this exposure to their obstetrician–gynecologists or other obstetric providers.

▶ *Should all women be screened for parvovirus B19 before or during pregnancy?*

Routine serologic screening of pregnant women for parvovirus B19 is not recommended. Given the low incidence of seroconversion during pregnancy combined with the variable risk of fetal transmission and subsequent sequelae, targeted screening for parvovirus B19 during pregnancy currently is not recommended either (120). Testing should be performed for patients with symptoms consistent with parvovirus B19 infection or for those with exposure to suspected or confirmed acute infections.

Varicella Zoster Virus

▶ *Which methods are used to diagnose maternal varicella zoster virus infection and what are the diagnostic criteria?*

Varicella, or chickenpox, usually is diagnosed based on the clinical findings of a classic pruritic, vesicular rash, so laboratory testing is not needed. If laboratory diagnosis is required, a sample taken from an unroofed skin lesion or vesicular fluid can be tested using a qualitative varicella PCR assay. Pregnant women should have varicella immunity status documented in early pregnancy by a history of previous infection or varicella vaccination. If a pregnant woman denies a history of either varicella vaccination or prior infection, documentation can be accomplished with the use of varicella IgG serology.

▶ *Which methods are used to diagnose fetal varicella zoster virus infection and what are the diagnostic criteria?*

Although two small studies estimated the rate of congenital varicella syndrome after maternal infection with VZV to be 1–2%, these studies were subject to bias, and these rates may be overestimated (54, 56). Fetal varicella can be indicated by the presence of ultrasonographic abnormalities after documented acute maternal infection. Ultrasound findings suggestive of congenital varicella include hydrops, hyperechogenic foci in the liver and bowel, cardiac malformations, limb deformities, microcephaly, and fetal growth restriction (121). In one series, five fetuses with congenital VZV demonstrated ultrasound findings consistent with fetal infection, and all the infants died by 4 months of age (122). However, not all fetuses with congenital VZV and ultrasound abnormalities fare poorly (123). Furthermore, a recent evaluation of congenitally infected children demonstrated that those who did not have anatomic abnormalities due to VZV infection had normal neurodevelopment (124).

▶ *How should maternal and fetal infections with varicella zoster virus be managed?*

Oral acyclovir, if started within 24 hours of developing the rash, has been shown to reduce the duration of new lesion formation and the total number of new lesions

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and to improve constitutional symptoms (125–127). Oral acyclovir appears to be safe and, given the potential for severe maternal illness from VZV infection, should be considered for use in pregnant women if lesions develop (128). Although the efficacy of intravenous acyclovir has not been established in randomized controlled trials, it may reduce maternal morbidity and mortality associated with varicella pneumonia (52, 129).

Maternal treatment with acyclovir has not been shown to ameliorate or prevent the fetal effects of congenital varicella syndrome (130). Varicella-zoster immune globulin (VZIG) should be given to infants born to women who develop varicella between 5 days before and 2 days after delivery, although this treatment does not universally prevent neonatal varicella (131). Infants who develop varicella within the first 2 weeks of life should be treated with intravenous acyclovir (128, 132).

▶ *How should women be counseled about prevention of varicella zoster virus?*

Nonpregnant women of reproductive age should be questioned about previous infection with varicella before conception and offered vaccination if no history of chickenpox or prior vaccination is elicited and if nonimmune serologies have been documented (133). Vaccination should be emphasized for those who have close contact with individuals at high risk of severe disease (eg, health care personnel, family contacts of individuals with immunocompromising conditions) or are at high risk of exposure or transmission (eg, teachers; child care employees; residents and staff members in institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; international travelers) (133). Pregnant women who do not have a history of varicella infection or of immunization and show no serologic evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of the pregnancy. The second dose should be administered 4–8 weeks after the first dose (133).

The varicella vaccine is given to anyone 12 months of age or older as a two-dose regimen. Conception should be delayed for 3 months after the last dose because there is a small chance of mild varicella infection after vaccination with the live, attenuated vaccine. However, standard vaccine surveillance systems have not detected any cases of congenital varicella after inadvertent administration of the varicella vaccine during early pregnancy (134). Thus, varicella vaccine exposure during early pregnancy does not warrant pregnancy termination (133).

Pregnant women who have no history of chickenpox or who lack immunity documented by serology should avoid VZV-infected individuals until their rash lesions have crusted over and they are no longer infectious (133). Pregnant women who are not immune to VZV and are exposed to someone with active primary infection with chickenpox should receive VZIG as soon as possible, ideally within 96 hours of exposure, to prevent or attenuate the disease manifestations of VZV infection (135). According to the Centers for Disease Control and Prevention, in circumstances when VZIG cannot be given within the ideal window, it still may be given up to 10 days after exposure (136). Although prevention of maternal VZV infection through VZIG administration should eliminate the possibility of congenital transmission, evidence to support this theory is insufficient. At present, VZIG can only be obtained directly from the manufacturer because of regulations related to sole-source production and FDA approval under the orphan drug program (136).

▶ *Should women be screened for varicella zoster virus before or during pregnancy?*

A history of chickenpox infection is 97–99% predictive of the presence of serology consistent with past infection and life-long immunity (133). Women of reproductive age should be asked before conception about their VZV immune status (evidence of immunity conferred either by prior infection or two-dose vaccination) and vaccinated before pregnancy if indicated. Proof of immunity, when not suggested by history, is obtained by testing for the varicella IgG antibody. If nonimmunity is ascertained after a woman becomes pregnant, postpartum vaccination is recommended (133).

Toxoplasmosis

▶ *Which methods are used to diagnose maternal toxoplasmosis infection and what are the diagnostic criteria?*

Although isolation of *T gondii* from blood or body fluids establishes the presence of acute infection, serologic testing for the detection of the specific antibody to *T gondii* is the primary method of diagnosis in the clinical setting. Serologic assays for toxoplasmosis are not well standardized and have high rates of false-positive and false-negative test results (73, 137). Immunoglobulin M titers may persist for many months or years after acute infection (63, 73). Immunoglobulin G and IgM testing should be used for the initial evaluation of a pregnant woman suspected to have

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toxoplasmosis. A negative IgM test result and a positive IgG test result are indicative of remote infection and pose no concern for fetal transmission in an immunocompetent woman (73, 137). Negative IgM and IgG test results indicate either the absence of infection or a recent acute infection without enough time for seroconversion. If IgM and IgG test results are positive, the patient has had either a recent infection or a false-positive result. If acute infection is a possibility, serologic testing should be repeated in 2–3 weeks to look for an increase in IgG antibodies consistent with recent infection (73, 137). Consideration should be given to performing initial and repeat serologies in an experienced toxoplasmosis reference laboratory in which specific confirmatory tests, such as the Sabin–Feldman dye test or indirect fluorescent antibody test, are performed (63, 73, 137).

If maternal toxoplasmosis infection has been serologically confirmed, reference laboratories can perform IgG avidity testing to determine when the infection may have occurred. Low avidity is indicative of primary infection within the past 5 months, which may be helpful information in prenatal diagnosis and counseling (137, 138).

▶ *Which methods are used to diagnose fetal toxoplasmosis infection and what are the diagnostic criteria?*

Ultrasonography can demonstrate severe congenital toxoplasmosis; suggestive findings include ventriculomegaly, intracranial calcifications, microcephaly, ascites, hepatosplenomegaly, and intrauterine growth restriction. Amniocentesis should be offered to pregnant women when fetal toxoplasmosis is suspected. Polymerase chain reaction of amniotic fluid is the preferred diagnostic test, given its relatively high sensitivity and specificity and its lower risk to the fetus than cordocentesis (66, 67, 137, 139–143). Amniocentesis should be performed after 18 weeks of gestation to lessen the chance of a false-negative test result (142).

▶ *How are maternal and fetal infections with toxoplasmosis managed?*

Suspected maternal infection should be confirmed in a reference laboratory, given the poor test performance of toxoplasmosis serologies in many commercial laboratories (144, 145). A Cochrane review of more than 3,000 publications suggests that maternal treatment does not reduce or prevent fetal infection but may reduce congenital disease severity (146–148). In the presence of acute maternal infection, consultation with an expert in maternal–fetal medicine or infectious disease should be obtained. Pregnant women who are acutely infected with toxoplasmosis should be treated with spiramycin to reduce transplacental parasitic transfer (149). Spiramycin is a macrolide antibiotic that concentrates in, but does not readily cross, the placenta (149). Use of spiramycin after confirmatory testing in a reference laboratory generally requires assistance from the FDA because the drug is not commercially available in the United States (145, 150). Fetal infection with toxoplasmosis should be treated with a combination of pyrimethamine, sulfadiazine, and folinic acid because this regimen more effectively eradicates parasites in the placenta and fetus than spiramycin alone and can lessen the severity of disease in the affected fetus (151, 152). Treatment of infants with symptomatic congenital toxoplasmosis consists of pyrimethamine, sulfadiazine, and folinic acid for 1 year (72, 153).

▶ *How should women be counseled about prevention of toxoplasmosis?*

Factors associated with acquisition of *T gondii* include handling materials contaminated by cat feces; consuming contaminated undercooked meat, dairy, produce, or water; and working in soil without gloves. Pregnant women should be counseled on proper hand washing techniques, pet care measures, and dietary recommendations to prevent toxoplasmosis, as well as many other infectious illnesses. Much attention has been given to educational programs to reduce maternal *T gondii* infection and, thus, congenital toxoplasmosis. Despite the successes demonstrated in some observational studies, several reviews (including a Cochrane review) suggest that weaknesses in study design prevent the conclusion that such strategies effectively reduce congenital toxoplasmosis (154–156).

▶ *Should women be screened for toxoplasmosis before or during pregnancy?*

Routine serologic screening of pregnant women for toxoplasmosis is not recommended. There are many challenges involved in routine screening, including a relatively low seroprevalence (approximately 38% of pregnant women have evidence of prior toxoplasmosis infection), which means that most women are susceptible to infection; relatively low incidence of acute infection; lack of standardized serologic assays outside of reference laboratories; and cost (147, 157). In the United States, prenatal screening for toxoplasmosis should be limited to women who are immunosuppressed or human immunodeficiency virus (HIV) positive.

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Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Pregnant women with acute parvovirus B19 infection based on serologies should be monitored for the development of fetal anemia using serial ultrasonography. In addition, Doppler assessment of the peak systolic velocity of the fetal middle cerebral artery should be performed, because this measure has been identified as an accurate predictor of fetal anemia.
- Oral acyclovir appears to be safe and, given the potential for severe maternal illness from VZV infection, should be considered for use in pregnant women if lesions develop. Although the efficacy of intravenous acyclovir has not been established in randomized controlled trials, it may reduce maternal morbidity and mortality associated with varicella pneumonia.
- Pregnant women who are not immune to VZV and are exposed to someone with active primary infection with chickenpox should receive VZIG as soon as possible, ideally within 96 hours of exposure, to prevent or attenuate the disease manifestations of VZV infection.
- Pregnant women who are acutely infected with toxoplasmosis should be treated with spiramycin to reduce transplacental parasitic transfer.
- Fetal infection with toxoplasmosis should be treated with a combination of pyrimethamine, sulfadiazine, and folinic acid because this regimen more effectively eradicates parasites in the placenta and fetus than spiramycin alone and can lessen the severity of disease in the affected fetus.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- Routine serologic screening of pregnant women for CMV is not recommended.
- Pregnant women exposed to parvovirus B19 should have serologic screening performed as soon as possible after exposure to determine if they should be monitored for seroconversion.
- If hydrops fetalis is present or severe fetal anemia is suspected in the setting of parvovirus B19, fetal blood sampling should be performed to determine the fetal hematocrit in preparation for fetal transfusion. Although there is procedure-related risk, intrauterine transfusion should be considered if severe fetal anemia is present.
- Routine serologic screening of pregnant women for parvovirus B19 is not recommended.
- Routine serologic screening of pregnant women for toxoplasmosis is not recommended.

The following recommendation is based primarily on consensus and expert opinion (Level C):

- Pregnant women should have varicella immunity status documented in early pregnancy by a history of previous infection or varicella vaccination. If a pregnant woman denies a history of either varicella vaccination or prior infection, documentation can be accomplished with the use of varicella IgG serology.

Proposed Performance Measure

Documentation of screening for varicella risk status

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990–March 2015. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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