

TORCH INFECTION

Toxoplasmosis

The obligate intracellular parasite *Toxoplasma gondii* has a life cycle with two distinct stages (Kim, 2015). The feline stage takes place in the cat—the definitive host—and its prey. Unsporulated oocysts are excreted in feces. In the nonfeline stage, tissue cysts containing bradyzoites or oocysts are ingested by the intermediate host, including humans. Gastric acid digests the cysts to release bradyzoites, which infect small-intestinal epithelium. Here, they are transformed into rapidly dividing tachyzoites, which can infect all cells within the host mammal. Humoral and cell-mediated immune defenses eliminate most of these, but tissue cysts develop. Their lifelong persistence is the chronic form of toxoplasmosis. Human infection is acquired by eating raw or undercooked meat infected with tissue cysts or by contact with oocysts from cat feces in contaminated litter, soil, or water. Prior infection is confirmed by serological testing, and its prevalence depends on geographic locale and parasite genotype. In the United States, seroprevalence in persons aged 10 to 19 years is 5 to 30 percent, and this can exceed 60 percent in those older than 50 (Kim, 2015). Thus, a significant segment of pregnant women in this country are susceptible to infection. The incidence of prenatal infection resulting in birth of a newborn with congenital toxoplasmosis varies from 0.8 per 10,000 live births in the United States to 10 per 10,000 in France (Cook, 2000). Between 400 and 4000 cases of congenital toxoplasmosis are diagnosed annually in the United States (Jones, 2014).

Maternal and Fetal Infection

Most acute maternal infections are subclinical and are detected only by prenatal or newborn serological screening. In some cases, maternal symptoms may include fatigue, fever, headache, muscle pain, and sometimes a maculopapular rash and posterior cervical lymphadenopathy. In immunocompetent adults, initial infection confers immunity, and prepregnancy infection nearly eliminates any risk of vertical transmission. Infection in immunocompromised women, however, may be severe, and reactivation may cause encephalitis, retinochoroiditis, or mass lesions. Maternal infection is associated with a fourfold increased preterm delivery rate before 37 weeks (Freeman, 2005).

The incidence and severity of fetal toxoplasmosis depend on gestational age at the time of maternal infection. Risks for fetal infection rise with gestational age. A metaanalysis estimated the risk to be 15 percent at 13 weeks, 44 percent at 26 weeks, and 71 percent at 36 weeks (SYROCOT Study Group, 2007). Conversely, the severity of fetal infection is much greater in early pregnancy, and these fetuses are much more likely to have clinical findings of infection (American College of Obstetricians and Gynecologists, 2017). Importantly, most infected fetuses are born without obvious stigmata of toxoplasmosis. Clinically affected neonates usually have generalized disease expressed as low birth weight, hepatosplenomegaly, jaundice, and anemia. Some primarily have neurological disease with intracranial calcifications and with hydrocephaly or microcephaly (Dhombres, 2017). Many eventually develop chorioretinitis and exhibit learning disabilities. This classic triad—chorioretinitis, intracranial calcifications, and hydrocephalus—is often accompanied by convulsions. Infected neonates with clinical signs are at risk for long-term complications (Abdoli, 2014; Wallon, 2014).

Screening and Diagnosis

With IgG antibody confirmed before pregnancy, there is no risk for a congenitally infected fetus. The American College of Obstetricians and Gynecologists (2017) does not recommend prenatal screening for toxoplasmosis in areas of low prevalence, including the United States. Screening should be performed in immunocompromised pregnant women, including those with HIV infection. In areas of high toxoplasmosis prevalence—for example, France and Austria— routine screening has resulted in diminished congenital disease (Kim, 2015; Wallon, 2013).

Pregnant women with suspected toxoplasmosis should be tested. The parasite is rarely detected in tissue or body fluids. Antitoxoplasma IgG develops within 2 to 3 weeks after infection, peaks at 1 to 2 months, and usually persists for life— sometimes in high titers. Although IgM antibodies appear by 10 days after infection and usually become negative within 3 to 4 months, they may remain detectable for years. Thus, IgM antibodies are not used alone to diagnose acute toxoplasmosis (Dhakal, 2015). Best results are obtained with the Toxoplasma Serologic Profile performed at the Palo Alto Medical Foundation Research Institute (www.toxolab@pamf.org). Toxoplasma IgG avidity increases with time.

Thus, if a high-avidity IgG result is found, infection in the preceding 3 to 5 months is excluded. Multiple tests are available that allow high avidity results to confirm latent infection with a 100-percent positive-predictive value (Villard, 2013).

Congenital toxoplasmosis is suspected when sonography reveals findings such as hydrocephaly, intracranial or hepatic calcifications, ascites, placental thickening, hyperechoic bowel, and growth restriction. Prenatal diagnosis of congenital toxoplasmosis is performed using PCR amplification of toxoplasma DNA in amniotic fluid (Filisetti, 2015; Montoya, 2008). The sensitivity of PCR varies with gestational age and is lowest before 18 weeks (Romand, 2001).

Management

No randomized clinical trials have assessed the benefit and efficacy of treatment to decrease the risk for congenital infection. A systematic review of data from 1438 treated pregnancies found weak evidence for early treatment to reduce congenital toxoplasmosis risks (SYROCOT Study Group, 2007). Treatment has been associated with a reduction in rates of serious neurological sequelae and neonatal demise (Cortina-Borja, 2010).

Prenatal treatment is based on two regimens—spiramycin alone or a pyrimethamine–sulfonamide combination given with folinic acid (American College of Obstetricians and Gynecologists, 2017). These two regimens have also been used consecutively (Hotop, 2012). Little evidence supports the use of a specific regimen (Montazeri, 2017; Valentini, 2015). That said, most experts will use spiramycin in women with acute infection early in pregnancy to reduce vertical transmission. Because it does not cross the placenta, spiramycin may not be used to treat fetal infection. Pyrimethamine–sulfadiazine with folinic acid is selected for maternal infection after 18 weeks' gestation or if fetal infection is suspected.

Prevention

There is no vaccine for toxoplasmosis, so avoidance of infection is necessary if congenital infection is to be prevented. Efforts include: (1) cooking meat to safe temperatures; (2) peeling or thoroughly washing fruits and vegetables; (3) cleaning all food preparation surfaces and utensils that have contacted raw meat, poultry, seafood, or unwashed fruits and vegetables; (4) wearing gloves when changing cat litter, or else delegating this duty; and (5) avoiding feeding cats raw or undercooked meat and keeping cats indoors. Although these preventive steps are recommended, no data support their effectiveness (American College of Obstetricians and Gynecologists, 2017; Di Mario, 2015).

SYPHILIS

Despite the availability of adequate therapy for decades, syphilis remains a major issue for both mother and fetus. From 2001 through 2015, the primary and secondary syphilis rates have risen almost yearly (Centers for Disease Control and Prevention, 2016c). In the United States in 2015, the combined rate for both of these among women was 1.8 cases per 100,000 persons (de Voux, 2017). For congenital syphilis, after a nadir in 2012, rates have also risen yearly to reach 12.4 cases per 100,000 live births in 2015. Of risks, higher congenital syphilis rates are linked to inadequate prenatal care, black or Hispanic race, and lack of treatment (Su, 2016). Similarly, syphilis remains a significant global health problem, with many countries reporting high numbers of new infections (Newman, 2015; World Health Organization, 2012).

Pathogenesis and Transmission

Syphilis is caused by the spirochetal bacterium *Treponema pallidum*. Minute abrasions on the vaginal mucosa provide an entry portal, and cervical eversion, hyperemia, and friability raise transmission risk. Spirochetes replicate and then disseminate through lymphatic channels within hours to days. The incubation period is 3 to 4 weeks depending on host factors and inoculum size.

The early stages of syphilis include primary, secondary, and early latent syphilis. These are associated with high spirochete loads, and partner transmission

rates approximate 30 to 60 percent (Garnett, 1997; Singh, 1999). In late-stage disease, transmission rates decline because of smaller inoculum sizes.

Maternal syphilis can cause fetal infection by several routes. Spirochetes readily cross the placenta to cause congenital infection. Although transplacental transmission is the most common route, neonatal infection may follow after contact with spirochetes through lesions at delivery or across the placental membranes. Fetal infection develops in >50 percent of untreated early syphilis cases and in 10 percent of late latent disease (Fiumara, 1975; Hollier, 2001).

Clinical Manifestations

Maternal Syphilis

This is staged according to clinical features and disease duration.

1. Primary syphilis is diagnosed by its characteristic chancre, which develops at the inoculation site. This solitary, painless lesion typically has a raised, firm border and a red, smooth ulcerated base without significant pus (Fig. 65-1). Nonsuppurative lymphadenopathy may develop. A chancre will usually resolve spontaneously in 2 to 8 weeks, even if untreated. Multiple lesions, if found, are predominantly in HIV-1 co-infected women.

FIGURE 65-1 Primary syphilis. Photograph of a chancre with a raised, firm border and smooth, red base.

2. Secondary syphilis stems from dissemination of spirochetes to affect multiple organ systems. Manifestations develop 4 to 10 weeks after the chancre appears and include dermatological abnormalities in up to 90 percent of women. A diffuse macular rash, plantar and palmar targetlike lesions, patchy alopecia, and mucous patches may be seen (Fig. 65-2). Condylomata lata are flesh-colored papules and nodules found on the perineum and perianal area (Fig. 65-3).

These papules are teeming with spirochetes and are highly infectious. Most women with secondary syphilis also express constitutional symptoms such as fever, malaise, headache, and myalgias. Hepatitis, nephropathy, ocular changes, anterior uveitis, and periostitis can also develop.

FIGURE 65-2 Secondary syphilis. A. Target lesions on the palms. B. Mucous patches around the nose and mouth. (Used with permission from Dr. Devin Macias.)

FIGURE 65-3 Condyloma lata. (Reproduced with permission from Horsager R, Roberts S, Roger V, et al (eds): Williams Obstetrics 24th Edition Study Guide, New York, McGraw Hill Education, 2014; Photo contributor: Dr. Jonathan Willms.)

3. Latent syphilis develops when primary or secondary syphilis is not treated but clinical manifestations still resolve. It is identified instead by serological testing. Early latent syphilis is subclinical disease acquired within the preceding 12 months. Disease diagnosed beyond 12 months is either late latent syphilis or latent syphilis of unknown duration.

4. Tertiary syphilis is a slowly progressive disease affecting any organ system but is rarely seen in reproductive-aged women.

Congenital Syphilis

Without screening and treatment, approximately 70 percent of infected women will have an adverse pregnancy outcome (Hawkes, 2011). Maternal infection can lead to preterm labor, fetal death, fetal-growth restriction, or fetal infection (Gomez, 2013). Because of immune incompetence prior to midpregnancy, the fetus generally does not manifest the immunological inflammatory response characteristic of clinical disease before this time (Silverstein, 1962). Once fetal

syphilis develops, however, it manifests as a continuum. Fetal hepatic abnormalities are followed by anemia and thrombocytopenia, then ascites and hydrops (Hollier, 2001). Stillbirth remains a major complication (Lawn, 2016; Su, 2016). The newborn may have jaundice with petechiae or purpuric skin lesions, lymphadenopathy, rhinitis, pneumonia, myocarditis, nephrosis, or long-bone involvement (Fig. 65-4).

FIGURE 65-4 Congenital syphilis. A. Fetogram of a stillborn infant infected with syphilis showing the “moth-eaten” appearance of the femurs (arrow). B. Enlarged hydropic placenta of a syphilis-infected neonate.

With syphilitic infection, the placenta becomes large and pale (see Fig. 65-4). Microscopically, villi lose their characteristic arborization and become thicker and clubbed. Sheffield and colleagues (2002c) described these villi in more than 60 percent of syphilitic placentas. Blood vessels markedly diminish in number, and in advanced cases, they almost entirely disappear as a result of endarteritis and stromal cell proliferation. Likely related, Lucas and coworkers (1991) demonstrated increased vascular resistance in uterine and umbilical arteries of infected pregnancies. The cord may also show evidence of infection. In a study of 25 untreated women, Schwartz and associates (1995) reported that necrotizing funisitis was present in a third.

Diagnosis

The United States Preventative Services Task Force recommends that clinicians screen all pregnant women for syphilis to prevent congenital infection (Wolff, 2009). Testing is ideally performed at the first prenatal visit. In populations with a high prevalence of syphilis, serological testing is repeated in the third trimester and again at delivery (Workowski, 2015).

Treponema pallidum cannot be cultured from clinical specimens. However, direct diagnosis of early-stage disease from lesion exudate, tissue, or body fluid can be completed by dark-field microscopic examination, by polymerase chain reaction (PCR), or by direct fluorescent antibody tests for *T. pallidum* (DFA-TP) (Tsang, 2015). These methods are not widely available and are less sensitive for blood specimens (Grange, 2012; Henao-Martínez, 2014). Thus, in practice, diagnoses are mainly derived from clinical findings coupled with serological blood testing.

Serological testing is used for diagnostic and for screening purposes. There are two types. If the first of these is positive, then the second type is also performed. This combination identifies infection and clarifies disease stage. Traditionally, the first type is nontreponemal testing, and either the Venereal Disease Research Laboratory (VDRL) or the rapid plasma reagin (RPR) is selected. Both tests measure patient immunoglobulin M and G (IgM and IgG) antibodies formed against cardiolipin that is released from damaged host cells and possibly also from treponemes. Notably, these same antibodies can also be produced in response to other acute events that include recent vaccination, febrile illness, and pregnancy itself or in response to chronic conditions such as intravenous drug abuse, systemic lupus erythematosus, aging, leprosy, or cancer. As such, these all serve as potential sources of false-positive results (Larsen, 1995). Conversely, seroconversion occurs at around 3 weeks, but can take up to 6 weeks (Peeling, 2004). Thus, women with very early primary syphilis can have initially false-negative serological test results. With positive nontreponemal test results, findings are quantified and expressed as titers. Because titers reflect disease activity, they increase during early syphilis and often exceed levels of 1:32 in secondary syphilis. Following treatment of

primary and secondary syphilis, serological testing at 3 to 6 months usually confirms a fourfold drop in VDRL or RPR titers (Rac, 2014a). Because VDRL titers do not correspond directly to RPR titers, consistent use of the same test for surveillance is recommended. Those with treatment failure or reinfection may lack this expected decline. Importantly, some successfully treated patients may still exhibit persistently low-level positive titers, which are referred to as “serofast.” This state is more likely in older individuals, those with lower initial nontreponemal antibody titers, and those with later stages of syphilis (Seña, 2015).

The second type of serological testing is treponemal-specific. It seeks patient antibodies formed specifically against *T pallidum*. The antibodies detected by treponemal assays appear up to a few weeks earlier than those detected by nontreponemal tests (Levett, 2015). Tests include the fluorescent treponemal antibody absorption tests (FTA-ABS), the *T pallidum* passive particle agglutination (TP-PA) test, and various immunoassays (Association of Public Health Laboratories, 2015). Of note, these treponemal-specific tests generally remain positive throughout life.

Each of the serological tests has limitations including false-positive and -negative results. Traditionally, nontreponemal tests have been used for screening in the United States, and results are then confirmed by a specific treponemal test. Within the past several years, some laboratories have implemented a reverse screening algorithm, namely, screening first with a treponemal-specific test (Binnicker, 2012; Centers for Disease Control and Prevention, 2011). Both approaches are effective if there is a program for appropriate screening, follow-up, and treatment.

In contrast to these tests, rapid “point-of-care” (POC) syphilis screening of

blood or serum samples is being developed (Singh, 2015; Tucker, 2010). These may be best used for women with limited prenatal care. Most tests are treponemal specific, and positive POC results can then be confirmed by a laboratory nontreponemal test. In hard-to-reach populations, some countries immediately treat women with positive POC results. This practice, however, risks overtreating previously cured women who still have residual persistent treponemal antibodies. This limitation may be overcome by newer POC dual tests, which simultaneously assess nontreponemal and treponemal antibodies (Causer, 2015).

Following maternal diagnosis, sonographic evaluation is performed for fetuses >20 weeks' gestation to search for signs of congenital syphilis. Rac and associates (2014b) noted that 31 percent of infected women diagnosed at ≥ 18 weeks' gestation had abnormal fetal sonographic findings. Hepatomegaly, placental thickening, hydramnios, ascites, hydrops fetalis, and elevated middle cerebral artery Doppler velocimetry measurements are indicative of fetal infection. Before 20 weeks, treatment is highly successful, and sonographic findings are rare (Nathan, 1997).

For fetuses of viable age with sonographic findings, antepartum fetal heart rate monitoring prior to treatment is recommended. Spontaneous late decelerations or a nonreactive tracing likely reflects an extremely ill fetus that may poorly tolerate a Jarisch-Herxheimer reaction, described next. In this extreme case, consultation with a neonatologist regarding a plan of delaying treatment, pursuing delivery, and then treating in the nursery is a consideration (Wendel, 2002).

Treatment

Syphilis therapy during pregnancy is given to eradicate maternal infection and to prevent or treat congenital syphilis. Parenteral penicillin G remains the preferred

treatment for all stages of syphilis during pregnancy (Table 65-1). During pregnancy, authorities recommend that a second dose of benzathine penicillin G be given 1 week after the initial dose. Such treatment is also given for women with concomitant HIV infection (Workowski, 2015).

TABLE 65-1. Recommended Treatment for Pregnant Women with Syphilis

Benzathine penicillin G is highly effective for early maternal infection. In a study of 340 pregnant women so treated, Alexander and associates (1999) reported six cases—1.8 percent—of congenital syphilis. Four of these six neonates were from a group of 75 women with secondary syphilis. The other two were identified in those delivered from a group of 102 women with early latent syphilis.

Congenital syphilis was generally confined to neonates of women treated after 26 weeks and is likely related to the duration and severity of fetal infection. Sheffield and coworkers (2002b) reported that high maternal serological titers, preterm delivery, and delivery shortly after antepartum therapy are all risks for failure of maternal treatment to prevent neonatal infection.

There are no proven alternatives to penicillin therapy during pregnancy.

Erythromycin and azithromycin may be curative for the mother, but because of limited transplacental passage, these drugs do not prevent all congenital disease (Berman, 2004; Wendel, 1988; Zhou, 2007). Moreover, in several countries, macrolide-resistant strains of *T pallidum* are now prevalent (Stamm, 2015).

Cephalosporins may prove useful, but data are limited (Liang, 2016).

Tetracyclines, including doxycycline, are effective but generally not recommended during pregnancy, because of the risk for fetal deciduous-teeth discoloration.

All women with syphilis are offered counseling and testing for HIV and other STDs. Following syphilis treatment, serological testing to detect treatment failures

is done at 3 to 6 months and usually confirms a fourfold drop in VDRL or RPR titers. During pregnancy, serological titers can be checked monthly in women at high risk for reinfection (Workowski, 2015).

In some instances, a woman may present without symptoms but describes recent sexual contact with a person who has been diagnosed with syphilis. She should be evaluated clinically and serologically. If her partner is diagnosed and their sexual contact occurred within the preceding 90 days, the gravida is treated presumptively for early syphilis, even if serological test results are negative. This accounts for early infection but before seroconversion. If contact was earlier than 90 days ago, treatment is based on serological results (Workowski, 2015).

Penicillin Reactions

Women with a history of penicillin allergy should have either an oral stepwise penicillin-dose challenge or skin testing performed to confirm the risk of immunoglobulin E (IgE)-mediated anaphylaxis. If confirmed, penicillin desensitization, shown in Table 65-2, is recommended and then followed by benzathine penicillin G treatment (Wendel, 1985).

TABLE 65-2. Penicillin Allergy—Oral Desensitization Protocol for Patients with a Positive Skin Test

Distinct from allergy, a Jarisch-Herxheimer reaction develops following penicillin treatment in most women with primary syphilis and approximately half with secondary infection. Uterine contractions, mild maternal temperature elevation, decreased fetal movement, and fetal heart rate decelerations are findings.

Reaction treatment is supportive with antipyretics as needed, hydration, and oxygen supplementation (Klein, 1990). In a study of 50 gravidas who received benzathine penicillin for syphilis, Myles and associates (1998) reported a 40-

percent incidence of Jarisch-Herxheimer reactions. Of the 31 women monitored electronically, 42 percent developed regular uterine contractions, and 39 percent developed variable decelerations. All contractions resolved within 24 hours of therapy. Accordingly, for fetuses of viable age, some recommend administering the first dose of antibiotic in labor and delivery and with continuous fetal monitoring for at least 24 hours (Rac, 2017). Others recommend this only if sonographic signs of fetal syphilis, described earlier, are found (Duff, 2014; Wendel, 2002). If this second plan is elected, patients are counseled on reaction signs and encouraged to seek evaluation if they develop.

Varicella-Zoster Virus

Maternal Infection

Varicella–zoster virus (VZV) is a double-stranded DNA herpesvirus acquired predominately during childhood, and 90 percent of adults have serological evidence of immunity (Whitley, 2015). The incidence of adult varicella declined by 82 percent after the introduction of varicella vaccination, and this has resulted in a drop in maternal and fetal varicella rates (American College of Obstetricians and Gynecologists, 2017). In the United States between 2003 and 2010, the incidence of maternal varicella among 7.7 million pregnancy admissions was 1.21 per 10,000 (Zhang, 2015).

Primary infection—varicella or chickenpox—is transmitted by direct contact with an infected individual, although respiratory transmission has been reported. The incubation period is 10 to 21 days, and a nonimmune woman has a 60- to 95-percent risk of becoming infected after exposure (Whitley, 2015). Primary varicella presents with a 1- to 2-day flulike prodrome, which is followed by pruritic vesicular lesions that crust after 3 to 7 days. Infection tends to be more severe in

adults (Marin, 2007). Affected patients are then contagious from 1 day before the onset of the rash until the lesions become crusted.

Mortality is predominately due to VZV pneumonia, which is thought to be more severe during adulthood and particularly in pregnancy. Although the incidence was once thought to be higher, only 2 to 5 percent of infected pregnant women develop pneumonitis (Marin, 2007; Zhang, 2015). Risk factors for VZV pneumonia include smoking and having more than 100 cutaneous lesions. Maternal mortality rates with pneumonia have decreased to 1 to 2 percent (Chandra, 1998).

Symptoms of VZV pneumonia usually appear 3 to 5 days into the course of illness. Fever, tachypnea, dry cough, dyspnea, and pleuritic pain are characteristic. Nodular infiltrates are similar to other viral pneumonias (Chap. 51, p. 994). Although resolution of pneumonitis parallels that of skin lesions, fever and compromised pulmonary function may persist for weeks.

If primary varicella is reactivated years later, it causes herpes zoster or shingles (Whitley, 2015). This presents as a unilateral dermatomal vesicular eruption associated with severe pain. Zoster does not appear to be more frequent or severe in pregnant women. Congenital varicella syndrome rarely develops in cases of maternal herpes zoster (Ahn, 2016; Enders, 1994). Zoster is contagious if blisters are broken, although less so than with primary varicella.

Fetal and Neonatal Infection

In women with varicella during the first half of pregnancy, the fetus may develop congenital varicella syndrome. Some features include chorioretinitis, microphthalmia, cerebral cortical atrophy, growth restriction, hydronephrosis, limb hypoplasia, and cicatricial skin lesions as shown in Figure 64-3 (Ahn, 2016; Auriti, 2009). Enders and coworkers (1994) evaluated 1373 pregnant women with

varicella. When maternal infection developed before 13 weeks, only two of 472 pregnancies—0.4 percent—had neonates with congenital varicella syndrome. The highest risk was between 13 and 20 weeks, during which time seven of 351 exposed fetuses—2 percent—had evidence of congenital varicella. After 20 weeks' gestation, the researchers found no clinical evidence of congenital infection. Ahn and colleagues (2016) recently described similar findings. That said, sporadic reports have described CNS abnormalities and skin lesions in fetuses who developed congenital varicella in weeks 21 to 28 of gestation (Lamont, 2011a; Marin, 2007).

If the fetus or neonate is exposed to active infection just before or during delivery, and therefore before maternal antibody has been formed, the newborn faces a serious threat. Attack rates range from 25 to 50 percent, and mortality rates approach 30 percent. In some instances, neonates develop disseminated visceral and CNS disease, which is commonly fatal. For this reason, varicella-zoster immune globulin (VZIG) should be administered to neonates born to mothers who have clinical evidence of varicella 5 days before and up to 2 days after delivery.

Diagnosis

Maternal varicella is usually diagnosed clinically. Infection may be confirmed by NAAT of vesicular fluid, which is very sensitive. The virus may also be isolated by scraping the vesicle base during primary infection and performing a Tzanck smear, tissue culture, or direct fluorescent antibody testing. Congenital varicella may be diagnosed using NAAT analysis of amniotic fluid, although a positive result does not correlate well with the development of congenital infection (Mendelson, 2006). A detailed anatomical sonographic evaluation performed at least 5 weeks after maternal infection may disclose abnormalities, but the sensitivity is low

(Mandelbrot, 2012).

Management

Maternal Viral Exposure. Several aspects of maternal VZV exposure and infection in pregnancy affect management. Exposed gravidas with a negative history for chickenpox should undergo VZV serological testing. At least 70 percent of these women will be seropositive, and thus immune. Exposed pregnant women who are susceptible (seronegative) should be given varicella-zoster immune globulin (VarizIG). Although best given within 96 hours of exposure, its use is approved for up to 10 days to prevent or attenuate varicella infection (Centers for Disease Control and Prevention, 2012, 2013d). Passive immunization appears to be highly effective (Jespersen, 2016). In women with known history of varicella, VarizIG is not indicated.

Maternal Infection. Any patient diagnosed with primary varicella infection or herpes zoster should be isolated from pregnant women. Because VZV pneumonia often presents with few symptoms, a chest radiograph is recommended by many. Most women require only supportive care, but those who require intravenous (IV) fluids and especially those with pneumonia are hospitalized. IV acyclovir therapy is given to women requiring hospitalization—500 mg/m² or 10 to 15 mg/kg every 8 hours.

Vaccination. An attenuated live-virus vaccine is recommended for nonpregnant adolescents and adults with no history of varicella. Two doses of Varivax are given 4 to 8 weeks apart, and the seroconversion rate is 98 percent (Marin, 2007). Importantly, vaccine-induced immunity diminishes over time, and the breakthrough infection rate approximates 5 percent at 10 years (Chaves, 2007). The vaccine is not recommended for pregnant women or for those who may

become pregnant within a month following each vaccine dose. That said, a registry of more than 1000 vaccine-exposed pregnancies reports no cases of congenital varicella syndrome or other associated congenital malformations (Marin, 2014; Wilson, 2008). The attenuated vaccine virus is not secreted in breast milk. Thus, postpartum vaccination should not be delayed because of breastfeeding (American College of Obstetricians and Gynecologists, 2016c).

Rubella Virus

This RNA togavirus causes rubella, also called German measles, which is of minor importance in the absence of pregnancy. Rubella infection in the first trimester, however, poses significant risk for abortion and severe congenital malformations. Transmission occurs via nasopharyngeal secretions, and the transmission rate is 80 percent to susceptible individuals. The peak incidence is late winter and spring in endemic areas (Lambert, 2015).

Maternal rubella is usually a mild febrile illness with a generalized maculopapular rash beginning on the face and spreading to the trunk and extremities. That said, 25 to 50 percent of infections are asymptomatic. Other symptoms may include arthralgias or arthritis, head and neck lymphadenopathy, and conjunctivitis. The incubation period is 12 to 23 days. Viremia usually precedes clinical signs by about a week, and adults are infectious during viremia and through 7 days after the rash appears. Up to half of maternal infections are subclinical despite viremia that may cause devastating fetal infection (McLean, 2013).

Diagnosis

Rubella virus may be isolated from the urine, blood, nasopharynx, and cerebrospinal fluid for up to 2 weeks after rash onset. The diagnosis is usually

made, however, with serological analysis. In one study, 6 percent of nonimmune women seroconverted to rubella virus during pregnancy (Hutton, 2014). Specific IgM antibody can be detected using enzyme-linked immunoassay for 4 to 5 days after onset of clinical disease, but antibody can persist for up to 6 weeks after appearance of the rash. Importantly, rubella virus reinfection can give rise to transient low levels of IgM. With this, fetal infection can rarely occur, but no adverse fetal effects have been described. Serum IgG antibody titers peak 1 to 2 weeks after rash onset. This rapid antibody response may complicate serodiagnosis unless samples are initially collected within a few days after the onset of the rash. If, for example, the first specimen was obtained 10 days after the rash, detection of IgG antibodies would fail to differentiate between very recent disease and preexisting immunity to rubella. IgG avidity testing is performed concomitant with the serological tests above. High-avidity IgG antibodies indicate an infection at least 2 months in the past.

Fetal Effects

The rubella virus is one of the most complete teratogens, and effects of fetal infection are worst during organogenesis (Adams Waldorf, 2013). Pregnant women with rubella and a rash during the first 12 weeks of gestation have an affected fetus with congenital infection in up to 90 percent of cases (Miller, 1982). At 13 to 14 weeks' gestation, this incidence is 50 percent, and by the end of the second trimester, it is 25 percent. Defects are rare after 20 weeks' gestation. Features of congenital rubella syndrome amenable to prenatal diagnosis are cardiac septal defects, pulmonary stenosis, microcephaly, cataracts, microphthalmia, and hepatosplenomegaly (Yazigi, 2017). Other abnormalities include sensorineural deafness, intellectual disability, neonatal purpura, and radiolucent bone disease.

Neonates born with congenital rubella may shed the virus for many months and thus be a threat to other infants and to susceptible adults who contact them.

Reports of delayed morbidities associated with congenital rubella syndrome may include a rare, progressive panencephalitis, insulin-dependent diabetes mellitus, and thyroid disorders (Sever, 1985; Webster, 1998).

Management and Prevention

There is no specific treatment for rubella. Droplet precautions for 7 days after the onset of the rash are recommended. Postexposure passive immunization with polyclonal immunoglobulin may be of benefit if given within 5 days of exposure (Young, 2015).

Although large epidemics of rubella have virtually disappeared in the United States because of immunization, up to 10 percent of women in the United States are susceptible. Cluster outbreaks during the 1990s mainly involved persons born outside the United States, as congenital rubella is still common in developing nations (Centers for Disease Control and Prevention, 2013f). To eradicate rubella and prevent congenital rubella syndrome completely, a comprehensive approach is recommended for immunizing the adult population (Grant, 2015).

MMR vaccine should be offered to nonpregnant women of childbearing age who do not have evidence of immunity whenever they make contact with the health-care system. Vaccination of all susceptible hospital personnel who might be exposed to patients with rubella or who might have contact with pregnant women is important. Rubella vaccination should be avoided 1 month before or during pregnancy because the vaccine contains attenuated live virus. No observed evidence links the vaccine and induced malformations, although the overall theoretical risk is up to 2.6 percent (McLean, 2013; Swamy, 2015). MMR

vaccination is not an indication for pregnancy termination.

Prenatal serological screening for rubella is indicated for all pregnant women.

Women found to be nonimmune are offered the MMR vaccine postpartum.

Cytomegalovirus

Several viruses cause severe maternal infections, and some can also cause devastating fetal infections. Of these, cytomegalovirus (CMV) is a ubiquitous DNA herpes virus that eventually infects most humans. CMV is also the most common perinatal infection in the developed world. Specifically, some evidence of fetal infection is found in 0.2 to 2.2 percent of all neonates (American College of Obstetricians and Gynecologists, 2017). The virus is secreted into all body fluids, and person-to-person contact with viral-laden saliva, semen, urine, blood, and nasopharyngeal and cervical secretions can transmit infection. The fetus may become infected by transplacental viremia, or the neonate is infected at delivery or during breastfeeding. Moreover, acquisition continues to accrue. Day-care centers, for example, are a frequent source. Revello and coworkers (2008) reported that amniocentesis in women whose blood is positive for CMV DNA does not result in iatrogenic fetal transmission.

Up to 85 percent of women from lower socioeconomic backgrounds are seropositive by the time of pregnancy, whereas only half of women in higher income groups are immune. Following primary CMV infection, and in a manner similar to other herpesvirus infections, the virus becomes latent with periodic reactivation characterized by viral shedding. This occurs despite high serum levels of anti-CMV IgG antibody. These antibodies do not prevent maternal recurrence, reactivation, or reinfection, nor do they totally mitigate fetal or neonatal infection.

Maternal Infection

Women who are seronegative before pregnancy, but who develop primary CMV infection during pregnancy, are at greatest risk to have an infected fetus. It is estimated that 25 percent of congenital CMV infections in the United States are from primary maternal infection (Wang, 2011). Most CMV infections are clinically silent, but they can be detected by seroconversion, and this may be as high as 1 to 7 percent annually (Hyde, 2010). Conversely, diagnosis of CMV nonprimary infection is a challenge (Picone, 2017).

Pregnancy does not increase the risk or severity of maternal CMV infection.

Most infections are asymptomatic, but 10 to 15 percent of infected adults have a mononucleosis-like syndrome characterized by fever, pharyngitis, lymphadenopathy, and polyarthrititis. Immunocompromised women may develop myocarditis, pneumonitis, hepatitis, retinitis, gastroenteritis, or meningoencephalitis. Nigro and associates (2003) reported that most women in a cohort with primary infection had elevated serum aminotransferases or lymphocytosis. Reactivation disease usually is asymptomatic, although viral shedding is common.

Transmission rates for primary infection are 30 to 36 percent in the first trimester, 34 to 40 percent in the second, and 40 to 72 percent in the third trimester (American College of Obstetricians and Gynecologists, 2017; Picone, 2017). In contrast, recurrent maternal infection infects the fetus in only 0.15 to 1 percent of cases. Naturally acquired immunity during pregnancy results in a 70-percent risk reduction of congenital CMV infection in future pregnancies (Fowler, 2003; Leruez-Ville, 2017). However, as noted earlier, maternal immunity does not prevent recurrences, and maternal antibodies do not prevent fetal infection (Ross, 2011).

Fetal Infection

Newborns with apparent sequelae of in-utero-acquired CMV infection are described as having symptomatic CMV infection. Congenital infection is a syndrome that may include growth restriction, microcephaly, intracranial calcifications, chorioretinitis, mental and motor retardation, sensorineural deficits, hepatosplenomegaly, jaundice, hemolytic anemia, and thrombocytopenic purpura (Cheeran, 2009). An example of periventricular calcifications is shown in Figure 64-1. Of the estimated 40,000 infected neonates born each year, only 5 to 10 percent demonstrate this syndrome (Fowler, 1992). Thus, most infected infants are asymptomatic at birth, but some develop late-onset sequelae. Complications may include hearing loss, neurological deficits, chorioretinitis, psychomotor retardation, and learning disabilities. Infections in dichorionic twins most likely are nonconcordant (Egaña-Ugrinovic, 2016).

Routine prenatal CMV serological screening is currently not recommended by the Society for Maternal–Fetal Medicine (2016). An algorithm for management is shown in Figure 64-2. Pregnant women should be tested for CMV if they present with a mononucleosis-like illness or if congenital infection is suspected based on abnormal sonographic findings. Primary infection is diagnosed using CMV-specific IgG testing of paired acute and convalescent sera. CMV IgM does not accurately reflect timing of seroconversion because IgM antibody levels may be elevated for more than a year (Stagno, 1985). Moreover, CMV IgM may be found with reactivation disease or reinfection with a new strain. Thus, specific CMV IgG avidity testing is valuable in confirming primary CMV infection. High anti-CMV IgG avidity indicates primary maternal infection >6 months before testing (Kanengisser-Pines, 2009). Finally, viral culture may be useful, although a

minimum of 21 days is required before findings are considered negative.

FIGURE 64-2 Algorithm for evaluation of suspected maternal primary cytomegalovirus (CMV) infection in pregnancy. EIA = enzyme immunoassay; IgG = immunoglobulin G; IgM = immunoglobulin M.

Several fetal abnormalities associated with CMV infection may be seen with sonography, computed tomography, or magnetic resonance imaging. In some cases, they are found at the time of routine prenatal sonographic screening, but in others they are part of a specific evaluation in women with CMV infection.

Findings include microcephaly, ventriculomegaly, and cerebral calcifications; ascites, hepatomegaly, splenomegaly, and hyperechoic bowel; hydrops; and oligohydramnios (Society for Maternal-Fetal Medicine, 2016). Abnormal sonographic findings seen in combination with positive findings in fetal blood or amniotic fluid are predictive of an approximate 75-percent risk of symptomatic congenital infection (Enders, 2001).

CMV nucleic acid amplification testing (NAAT) of amniotic fluid is considered the gold standard for the diagnosis of fetal infection. Sensitivities range from 70 to 99 percent and depend on amniocentesis timing. Sensitivity is highest when amniocentesis is performed at least 6 weeks after maternal infection and after 21 weeks' gestation (Azam, 2001; Guerra, 2000). A negative result from amniotic fluid polymerase chain reaction (PCR) testing does not exclude fetal infection and may need to be repeated if suspicion for fetal infection is high.

Management and Prevention

The management of the immunocompetent pregnant woman with primary or recurrent CMV is limited to symptomatic treatment. If recent primary CMV infection is confirmed, amniotic fluid analysis should be offered. Counseling

regarding fetal outcome depends on the gestational age during which primary infection is documented. Despite the high infection rate with primary infection in the first half of pregnancy, most fetuses develop normally. However, pregnancy termination may be an option for some.

Currently, no proven treatments are available for CMV infection (Society for Maternal–Fetal Medicine, 2016). Leruez-Ville and associates (2016) recently reported that oral treatment with valganciclovir, 8 g daily, apparently mitigated adverse outcomes in eight of 11 affected fetuses treated beginning at median of 25.9 weeks' gestation. Kimberlin and colleagues (2015) previously showed that intravenous valganciclovir administered for 6 weeks to neonates with symptomatic central nervous system (CNS) disease prevented hearing deterioration at 6 months and possibly later. Passive immunization with CMV-specific hyperimmune globulin may lower the risk of congenital CMV infection when given to pregnant women with primary disease (Nigro, 2005, 2012; Visentin, 2012). The Maternal–Fetal Medicine Units Network currently is conducting a randomized trial designed to address this.

There is no CMV vaccine, although several clinical trials are underway (Arvin, 2004; Schleiss, 2016). Prevention of congenital infection relies on avoiding maternal primary infection, especially in early pregnancy. Basic measures such as good hygiene and hand washing have been promoted, particularly for women with toddlers in day-care settings (Fowler, 2000). CMV may be sexually transmitted among infected partners, but no data address the efficacy of preventive strategies.

HERPES SIMPLEX VIRUS

This virus poses a disproportionately higher risk to the newborn than to the mother. Thus, strategies in pregnancy aim to curb rates of vertical transmission.

Adult Disease

Two types of herpes simplex viruses are distinguished based on immunological differences. Yet, the two viruses have significant DNA sequence homology, and thereby, prior infection with one type attenuates a primary infection with the other. Type 2 HSV is recovered almost exclusively from the genital tract and is usually transmitted by sexual contact. Type 1 is responsible for most nongenital infections and typically is acquired in childhood. However, more than half of new cases of genital herpes in adolescents and young adults are now caused by HSV-1 infection (Bernstein, 2013). This rise in the prevalence of HSV-1 genital disease is thought to stem from an increase in oral-genital sexual practices. Another explanation is that HSV-1 acquisition has declined in childhood as a result of improved living conditions and hygiene (Bradley, 2014; Xu, 2007). Without prior exposure, this renders young people without HSV-1 antibodies susceptible to genital acquisition of HSV-1 or -2.

Genital herpes simplex virus affects an estimated 50 million adolescents and adults (Workowski, 2015). Most women are unaware of their infection, but HSV-2 seroprevalence among non-Hispanic white females in the United States was 15.3 from 2007 to 2010 and among black females, it was 53 percent (Fanfair, 2014; Schulte, 2014). In one study of nearly 16,000 pregnant women from 2000 to 2010, the overall seroprevalence of HSV-2 was 16 percent, and for HSV-1, it was 66 percent (Delaney, 2014). Seronegative pregnant women have a 4 to 5 percent risk to acquire HSV-1 or -2 during pregnancy (Brown, 1997; Kulhanjian, 1992). For those who are HSV-1 seropositive, acquisition risk for HSV-2 approximates 2 percent (Brown, 1997).

Clinical Manifestations

Once transmitted by contact, HSV-1 or -2 replicates at the entry site. Following mucocutaneous infection, the virus moves retrograde along sensory nerves. It then remains latent in cranial nerves or dorsal spinal ganglia, but recurrences are common. HSV infections may be categorized into three groups. First episode primary infection describes the case in which HSV-1 or 2 is isolated from a lesion in the absence of HSV-1 or -2 serological antibodies. The typical incubation period of 6 to 8 days (range 1 to 26 days) may be followed by a papular eruption with itching or tingling, which then becomes painful and vesicular. Multiple vulvar and perineal lesions may or may not coalesce, and then ulcerate (Fig. 65-5). Associated inguinal adenopathy can be severe. Many women do not present with typical lesions. Instead, a pruritic or painful abraded area or knife-cut may be found. Cervical involvement is common, although it may be inapparent clinically. Transient systemic influenza-like symptoms are frequent and are presumably caused by viremia. Some cases are severe enough to require hospitalization. Hepatitis, encephalitis, or pneumonia infrequently develop, and disseminated disease is rare. After 2 to 4 weeks, all signs and symptoms of infection disappear. Instead of these classic symptoms, the percentage of asymptomatic primary HSV-2 genital infections may be as high as 90 percent (Fanfair, 2013).

First episode nonprimary infection is diagnosed when one HSV type is isolated from a lesion in a woman who has only the other serological HSV-type antibody present. In general, compared with primary infection, nonprimary infections are characterized by fewer lesions, less pain, fewer systemic

manifestations, and briefer duration of lesions and viral shedding. This is likely because of some immunity from cross-reacting antibodies, for example, from childhood-acquired HSV-1 infection.

Recurrent disease is characterized by isolation of HSV-1 or -2 from the genital tract in women with the same serotype antibodies. During the latency period, in which viral particles reside in nerve ganglia, reactivation is common and mediated through poorly understood stimuli. The resulting lesions generally are fewer in number, are less tender, and shed virus for a shorter period than those of primary infection. Typically, they recur at the same sites. Genital disease recurrences are more frequently caused by HSV-2 compared with HSV-1. Recurrences are most frequent in the first year after initial infection, and rates slowly decline subsequently (Benedetti, 1999). Gravidas with a known prior history of genital HSV often experience recurrences (Sheffield, 2006).

Asymptomatic viral shedding is defined by the absence of clinical findings. Most infected women shed virus intermittently over time, and most HSV transmission to a partner occurs during these periods of asymptomatic viral shedding.

Vertical Transmission

The virus can be passed to the fetus/neonate by three routes: (1) peripartum in 85 percent, (2) postnatal in 10 percent, or (3) intrauterine in 5 percent (James, 2015).

As discussed in Chapter 18 (p. 347), evidence does not suggest an obvious link between HSV infection and miscarriage (Zhou, 2015).

Peripartum transmission is by far the more frequent route of infection, and the fetus is exposed to virus shed from the cervix or lower genital tract. HSV-1 or -2 invades the uterus following membrane rupture or is transmitted by contact at delivery. The newborn is mainly infected, but rare cases of maternal endometritis have been described (Hollier, 1997; McGill, 2012). Neonatal manifestations vary.

First, infection may be localized to the skin, eye, or mouth—SEM disease—in approximately 40 percent of cases. Second, central nervous system disease with encephalitis is seen in 30 percent. Last, disseminated disease with involvement of multiple major organs is found in 32 percent. Localized infection is usually associated with a good outcome. Conversely, even with acyclovir treatment, disseminated infection has a mortality rate of nearly 30 percent (Corey, 2009;

Kimberlin, 2011). Of disseminated or cerebral infection survivors, serious developmental and central nervous system morbidity is seen in 20 to 50 percent. The neonatal infection rate is 0.5 to 1 per 10,000 births in the United States (Flagg, 2011; Mahnert, 2007). Most infected newborns are born to mothers with no reported history of HSV infection (Gardella, 2010). The risk of neonatal infection correlates with the presence of HSV in the genital tract, the HSV type, invasive obstetrical procedures, and stage of maternal infection (Brown, 2005, 2007). For example, neonates born to women who acquire genital HSV near the time of delivery have a 30- to 50-percent risk of infection. This is attributed to higher viral loads and the lack of transplacental protective antibodies (Brown, 1997, 2000). Women with recurrent HSV have less than a 1-percent risk of neonatal infection (Pasternak, 2010; Prober, 1987).

Postpartum transmission is uncommon and passed to the newborn by contact with an infected mother, family member, or health-care worker. The clinical presentation mirrors that with peripartum transmission.

In utero transmission of HSV-1 or HSV-2 is rare and is part of the TORCH (toxoplasmosis, other, rubella, cytomegalovirus, herpes virus) collection of infections. Intrauterine HSV infection classically leads to disease involving the skin (blisters, scarring), the central nervous system (hydranencephaly, microcephaly, intracranial calcification), or the eyes (chorioretinitis, microphthalmia) (Hutto, 1987). Bone and viscera can be involved (Marquez, 2011). If seen sonographically, findings should prompt viral serological testing as described next. PCR analysis of an amniocentesis sample is another potential tool (Diguët, 2006).

Diagnosis

Several organizations recommend against routine serological HSV screening in asymptomatic gravidas (American College of Obstetricians and Gynecologists, 2016b; Workowski, 2015; U.S. Preventive Services Task Force, 2016). However, for those with a clinically suspicious lesion, a diagnosis should be confirmed by laboratory testing. Available HSV tests are either virological or type-specific serological tests.

Direct virological tests can be performed on a specimen from the mucocutaneous lesion. PCR or culture of the sample is a testing option. Of the two, PCR assays are more sensitive, the results generally are available in 1 to 2 days, and specimen handling is easier. In contrast, for viral culture, the sensitivity of HSV isolation is relatively low as vesicular lesions ulcerate and then crust. Also, results sometimes are not available for 7 to 14 days (Strick, 2006). Regardless of the test performed, HSV viral types should be differentiated (LeGoff, 2014). Importantly, a negative culture or PCR result does not exclude infection. In contrast, false-positive results are rare.

Serological assays are available to detect antibodies produced against specific HSV glycoproteins, G1 and G2. These proteins evoke type-specific antibody responses to HSV-1 and HSV-2 infection, respectively, and they reliably differentiate the two. IgG antibodies develop 1 to 2 weeks after a primary infection and then persist. This permits confirmation of clinical infection and identification of asymptomatic carriers. Providers should request type-specific glycoprotein G-based assays when serology is being performed. Sensitivity approaches 90 to 100 percent, and specificity is 99 to 100 percent (Wald, 2002). IgM antibody detection is not a useful test.

Management

In nonpregnant patients, antiviral therapy with acyclovir, valacyclovir, or famciclovir is used to treat first-episode genital herpes. Oral or parenteral preparations attenuate clinical infection and viral shedding duration. Suppressive therapy is also an option to limit recurrent infections and to reduce heterosexual transmission (Corey, 2004).

In pregnant women, acyclovir is safe (Briggs, 2015). Through 1999, the manufacturers of acyclovir and valacyclovir maintained a registry of outcomes following exposure to these drugs during pregnancy. More than 700 neonates exposed during the first trimester were evaluated, and there were no adverse effects attributable to acyclovir (Stone, 2004). At this time, data are insufficient regarding famciclovir exposure, although a pregnancy registry is being maintained (1-888-669-6682).

For a primary outbreak during pregnancy, women may be given antiviral therapy to attenuate and decrease the duration of symptoms and viral shedding (Table 65-4). Women with HIV co-infection may require a longer duration of treatment. Those with severe or disseminated HSV are given IV acyclovir, 5 to 10 mg/kg every 8 hours for 2 to 7 days until clinically improved. This is followed by oral antiviral drugs to complete at least 10 days of total therapy (Workowski, 2015). For intense discomfort, oral analgesics and topical anesthetics may provide some relief, and comorbid urinary retention is treated with an indwelling bladder catheter.

During pregnancy, amniocentesis, percutaneous cord blood sampling, or transabdominal chorionic villus sampling may be performed even with active genital lesions. With active lesions, however, internal electronic monitoring during labor is not recommended. Transcervical procedures may best be delayed until lesions have resolved (American College of Obstetricians and Gynecologists, 2016b).