Infections During Pregnancy

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KEYWORDS

• Congenital infection • Pregnancy complications • Vertical transmission • Zika
• TORCH

KEY POINTS

- Some common infections affect pregnant women differently and treatment options must be chosen keeping safety in pregnancy in mind.
- Certain infections can be transmitted vertically and pregnancies affected by these infections must be monitored and managed to decrease transmission.
- Some infections can be acquired in utero and can cause congenital infections in newborns that lead to developmental anomalies, affect growth, and lead to significant neonatal morbidity and mortality.

INTRODUCTION

In pregnancy, potential effects of infections on both mother and fetus must be considered. Pregnant women are at increased risk of some infections due to physiologic changes of pregnancy. Infections may cause complications with the pregnancy, and some maternal infections are transmissible to the fetus. When determining treatment, potential effects on the fetus and the pregnancy must be taken into consideration including different effects by trimester. In this article, the authors discuss common infections that require special considerations in pregnancy, infections that can be vertically transmitted, and infections that can cause in utero and perinatal infection leading to birth defects (including the classic TORCH infections).

PREGNANCY CONSIDERATIONS WITH COMMON INFECTIONS

Urinary Tract Infections

Recurrent bacteriuria and pyelonephritis are more common in pregnancy. Smooth muscle relaxation and dilation of ureters with pregnancy increases the propensity for ascending infection. Screening and treatment of urinary tract infections (UTIs)

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are more intensive in pregnancy than in the general population. Infectious Disease Society of America guidelines recommend universal screening of pregnant women for asymptomatic bacteriuria with urine culture in early pregnancy and periodic rescreening in women with positive culture during pregnancy.[1] Diagnosis is made if greater than or equal to 10^5 colony-forming units of uropathogen or greater than or equal to 10^4 of Group B Streptococcus (GBS) is present in urine culture.[2,3] Pyelonephritis in pregnancy typically requires inpatient empirical intravenous antibiotics, with the patient switched to an oral regimen once improving and afebrile for 24 to 48 hours.[4] Appropriate antibiotics are given for 10 to 14 days followed by suppressive therapy for the remainder of pregnancy to prevent recurrence.[4] GBS growing in any amount in urine culture during pregnancy indicates significant anogenital colonization and therefore qualifies the woman for intrapartum antibiotics to prevent neonatal GBS disease.[5]

The pregnancy and trimester need to be considered when prescribing antibiotics. Penicillins, cephalosporins, and aztreonam are considered safe in pregnancy. Antibiotics with high protein binding, such as ceftriaxone, may cause hyperbilirubinemia in newborns if used within a day of delivery. Nitrofurantoin is associated with birth defects[6,7] and hemolytic anemia[8] and, therefore, is avoided in the first trimester and at term. Trimethoprim-sulfamethoxazole should be avoided in the first trimester and at term because trimethoprim is a folic acid antagonist and sulfonamides can displace plasma binding of bilirubin in newborns. Tetracyclines are avoided in pregnancy due to fetal bone and teeth developmental defects[9,10] and fluoroquinolones are avoided due to developmental defects of cartilage in animal experiments.[11]

Chlamydia and Gonorrhea

Chlamydia and gonorrhea are common infections that can affect pregnancy outcomes. Prevalence of chlamydia in pregnancy is 2% to 20% depending on the population.[12–14] Newborns born vaginally to women with chlamydia are at increased risk of chlamydia conjunctivitis and pneumonia. Signs of chlamydia conjunctivitis include swelling, eye discharge, and chemosis appearing 5 to 14 days after delivery. Signs of chlamydia pneumonia include staccato cough, nasal discharge, tachypnea, and rales without fever presenting at 4 to 12 weeks of life.

Rates of gonorrhea are highest in adolescents and young adults, particular racial minorities, and in the southeastern United States.[15] Gonorrhea has been associated with premature rupture of membranes, preterm birth, chorioamnionitis, small-for-gestational-age infants, and spontaneous abortion.[16–19] Newborns born to women with gonorrhea are at increased risk of gonococcal conjunctivitis, scalp abscesses (with fetal scalp electrode placement), and disseminated gonococcal infections, which may include arthritis, sepsis, or meningitis. Gonococcal conjunctivitis causes profuse purulent exudate and swelling 2 to 5 days after birth and can cause visual impairment if left untreated.

The Center for Disease Control (CDC) and US Preventative Services Task Force (USPSTF) recommend universal screening of pregnant women younger than 25 years and older than or equal to 25 years at increased risk for sexually transmitted infections (STIs) (**Box 1**) at the first prenatal visit for chlamydia and gonorrhea.[20–22] Retesting during the third trimester should be performed for women who remain at high risk.[20]

Pregnant women diagnosed with chlamydia should have a test of cure collected at least 3 weeks after treatment as cure rates are decreased in pregnancy and because continued infection places infants at risk of infection.

Rising antibiotic resistance makes treatment of gonorrhea more complicated. The CDC currently recommends single doses of ceftriaxone, 250 mg, intramuscularly

Box 1
Women at increased risk of sexually transmitted infections

Personal history of sexually transmitted infections (STI)

New sexual partner

Multiple sexual partners or a sexual partner with multiple partners

Sexual partner diagnosed with STI

Inconsistent condom use if not in a mutually monogamous relationship

Contact with sex workers or trading sex for money or drugs

Admission into a correctional facility

Data from LeFevre ML, U.S. Preventive Services Task Force. Screening for Chlamydia and gonorrhea: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;161:902–10.

and azithromycin, 1gm, orally.[20] Doxycycline (potential alternative to azithromycin) should be avoided in pregnancy. Desensitization should be pursued for pregnant women with gonorrhea who have severe allergy to cephalosporins. Dual therapy with gentamicin and azithromycin is an alternative if desensitization is not possible. If alternative regimens are used, a test of cure is recommended. Culture with susceptibility testing is ideally used for test of cure starting at 7 days after treatment. If nucleic acid amplification testing is used for test of cure, it should be performed 14 days after treatment to avoid false-positive results.[23,24] The American Academy of Pediatrics (AAP) and the CDC recommend erythromycin ophthalmic ointment be given within 2 hours of birth to all newborns to prophylactically prevent gonococcal ophthalmia.[20,25]

Influenza

Pregnant women tend to have more severe illness and mortality from influenza than the general population.[26] This is theorized to be due to physiologic changes of pregnancy including decreased lung capacity, increased oxygen consumption, and decreased cell-mediated immunity. Infection in the first trimester increases risk of birth defects,[27] and maternal influenza has been associated with increased risk of miscarriage, preterm labor, small-for-gestational-age infants, and fetal death.[28–31]

Influenza vaccination is recommended for all pregnant women during influenza season.[32] Vaccination during pregnancy confers protection to a newborn for several months after birth[33–35] and antiinfluenza immunoglobulins are transferred to newborns through breast milk.[36] Pregnant women should not receive the live-attenuated influenza vaccine.

Pregnant women with suspected influenza should receive empirical antiviral treatment because it decreases morbidity and mortality. Although treatment within 2 days of symptom onset has the best data, benefit has still been shown after 2 days.[37] Neuraminidase inhibitors can be used in pregnancy and dosing and durations are the same as nonpregnant adults. Oseltamivir is preferred in pregnancy due to systemic absorption and more experience in pregnancy.

Vaginitis

The 3 main causes of vaginitis include bacterial vaginosis (BV), yeast vulvovaginitis, and trichomoniasis.

BV increases the risk of preterm labor.[38] However, screening and treatment of asymptomatic BV does not seem to reduce preterm birth and the American College of Obstetricians and Gynecologists (ACOG), USPSTF, and CDC recommend against routine screening for asymptomatic BV to prevent preterm birth.[20,39,40] Studies are currently being conducted to determine high-risk subpopulations (ie, women with history of preterm birth or with genetic polymorphisms affecting cytokine release) that may benefit from screening, but data are still lacking to determine which patients would benefit. Testing is recommended for symptomatic pregnant women and recommended treatment is with oral metronidazole or clindamycin for 7 days.

Yeast vulvovaginitis causes no pregnancy complications.[41] Vaginal treatment for 7 days with clotrimazole 1% cream or miconazole 2% cream or 100 mg suppositories is recommended over oral therapy due to potential risks of oral azoles in pregnancy. Oral azole use, particularly in the first trimester, may be associated with increased risk of miscarriage[42] and high doses may be associated with birth defects.[43,44]

Trichomoniasis is associated with premature rupture of membranes, preterm delivery, and low birth weight infants.[45,46] Newborns can become infected with trichomonas during delivery causing fever, nasal discharge, respiratory difficulty, UTIs, and vaginal discharge in female infants.[47–50] Routine screening for trichomonas in pregnancy is not recommended. A single oral dose of 2gm metronidazole is a preferred treatment in pregnancy, but 500 mg orally twice daily for 5 to 7 days is also acceptable if nausea/vomiting prevents 2g regimen.[51]

Vertically Transmissible Infections

These infections can be transmitted mother-to-child and therefore monitoring and, in some cases, treatment is warranted to prevent transmission to the newborn.

Hepatitis B

Hepatitis B can cause acute and chronic infections. Universal screening of pregnant women for chronic hepatitis B is recommended at the first prenatal visit with HBsAg testing. HBsAg-positive women should have testing for HBeAg, anti-HBe antibody, HBV DNA level, and aminotransferases. For pregnant women with chronic hepatitis B, antivirals are offered if HBV DNA is high to prevent mother-to-child transmission.[52] Tenofovir disoproxil fumarate is the preferred antiviral due to rare resistance and safety during pregnancy.[53,54] Women with chronic hepatitis B who do not require antiviral treatment should have repeat viral load tested at 26 to 28 weeks to determine if antiviral therapy is indicated to prevent mother-to-child transmission.

Pregnant women diagnosed with acute hepatitis B should be monitored for seroconversion indicating recovery instead of chronic infection. Recovery is indicated by disappearance of HBV DNA and seroconversion of HBeAg and HBsAg to anti-HBe and anti-HBs antibodies, respectively.

Cesarean delivery does not decrease risk of vertical transmission of hepatitis B.[55–57] Newborns born to women with positive HBsAg should receive their first dose of hepatitis B vaccine and HBIG within 12 hours of delivery.

Hepatitis C

Rates of hepatitis C have been increasing in young adults.[58,59] Chronic infection may not cause adverse pregnancy or newborn complications. However, newborns born to women with chronic hepatitis C are more likely to be low birth weight, small for gestational age, and require assisted ventilation or neonatal intensive care unit admission.[60] Antiviral therapy should not be used as safety and efficacy in pregnancy has not been established. In hepatitis C-infected pregnant women, invasive prenatal testing,

prolonged rupture of membranes, and obstetric procedures (ie, fetal scalp electrode) should be avoided to decrease vertical transmission.[61,62] Hepatitis C is not an indication for cesarean delivery because it does not decrease vertical transmission.[63,64] Newborns born to women with hepatitis C should have HCV antibody checked after 18 months to test for vertical transmission.

Human Immunodeficiency Virus

Women make up an increasing percentage of AIDS cases in the United States.[65] Minority women have disproportionately higher rates of human immunodeficiency virus (HIV)/AIDS.[65,66] In the United States, an estimated 8700 women with HIV give birth yearly.[67] Perinatal transmission of HIV has significantly decreased to 2% or less in the United States with current recommendations for screening, treatment, and obstetric management.[68,69]

Universal screening for HIV is recommended in pregnancy.[70] For women with HIV, a CD4 count is measured at the initial prenatal visit and at least every 3 months. Viral load is measured at the initial prenatal visit, when antiretrovirals (ARVs) are initiated, 2 to 4 weeks after initiation of or change in ARVs, monthly until complete suppression achieved, then at least every 3 months during pregnancy. Resistance testing is measured before initiating or changing ARV regimens. Pregnant HIV-infected women should be screened for latent tuberculosis, Hepatitis C, and toxoplasmosis and immunity against Hepatitis A.[71]

All pregnant women with HIV should be treated with ARVs regardless of CD4 count to decrease vertical transmission.[71] Opportunistic infection prophylaxis should be prescribed at the same CD4 count cutoffs as nonpregnant patients. Pneumococcal, hepatitis A and B vaccination is indicated for pregnant women with HIV if they have not already received them.

Viral load should be measured at 34 to 36 weeks to assist with decisions regarding delivery as women with viral loads greater than or equal to 1000 copies/mL should be scheduled for cesarean delivery at 38 weeks.[71] Management of ARVs at delivery are reviewed in **Table 1**. Interventions including fetal scalp electrode placement and operative vaginal delivery should be avoided to decrease perinatal transmission. Breastfeeding is not recommended in resource-rich countries.

All newborns born to women with HIV should receive ARVs to reduce perinatal transmission. Exposed newborns should be tested with virologic tests (HIV RNA or DNA) at 2 to 3 weeks of life, 1 to 2 months of life, and 4 to 6 months of life.[71]

TORCH Infections

The classic group of perinatal infections known as the TORCH infections includes toxoplasmosis, other (syphilis), rubella, cytomegalovirus (CMV), and herpes simplex

Table 1
Peripartum management of HIV positive patients by viral load

Viral Load	IV Zidovudine at Delivery	Delivery Management
Undetectable: 49 copies/mL	Not indicated	Vaginal delivery safe unless obstetrically contraindicated
50–999 copies/mL	Can be considered	Vaginal delivery safe unless obstetrically contraindicated
≥1000 copies/mL	Given 3 h before cesarean	Cesarean delivery before labor at 38 wk recommended[71]

virus (HSV). This group has common presenting features of rash and ocular abnormalities.[72] Varicella-zoster virus and parvovirus B19 and Zika virus can also be grouped in this category.[73]

TOXOPLASMOSIS

Organism and Epidemiology

Toxoplasma gondii is a protozoan parasite spread through cat feces, contaminated soil, or by consuming undercooked meats. *T gondii* preferentially invades neural tissues (brain and retina), skeletal muscle, and/or cardiac muscle forming cysts that destroy host cells.[74] Approximately 201,000 cases of congenital toxoplasmosis are reported worldwide yearly with highest prevalence in tropical regions. Toxoplasmosis affects between 10 and 33/100,000 of live births in the United States.[75] Risk of fetal infection after maternal infection increases from 15% if infected at 13 weeks gestation to greater than 70% if infected at 36 weeks.[76]

Clinical Presentation

Maternal infections are predominately asymptomatic but symptoms can include fever, night sweats, cervical lymphadenopathy, myalgias, malaise, and hepatosplenomegaly.[77] Similarly, 70% to 90% of infants are asymptomatic at birth. The classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications is rare. Fetal manifestations can present early (**Box 2**) or late (**Box 3**).[74]

Testing

There is no recommendation for universal screening of pregnant women.[77] When toxoplasma is suspected, maternal antibody testing is recommended. Immunoglobulin G (IgG) is the most sensitive test, because IgM antibodies have a high false-positive rate. IgM can remain elevated for up to 2 years following infection.[79]

Fetal testing either based on positive maternal tests or ultrasound findings can be done via polymerase chain reaction (PCR) analysis of the amniotic fluid after 18 weeks. At birth, affected infants should have repeat PCR or serology; a computed tomographic (CT) scan of head; and comprehensive eye, ear, and neurologic examinations.

Management

Before 18 weeks, pregnant women are treated with spiramycin until the diagnosis can be confirmed with ultrasound and PCR. Once the diagnosis is confirmed, patients are treated with a regimen of spiramycin, pyrimethamine, sulfadiazine, and folinic acid. Infected infants are treated for a total of 12 months with a regimen of pyrimethamine, sulfadiazine and folinic acid. One month after treatment the infant should be retested including serology, head CT, and detailed eye/ear/neuro examinations.[76]

Box 2
Early manifestation of fetal toxoplasmosis infection

- Maculopapular rash
- Fevers
- Jaundice
- Hepatosplenomegaly
- Thrombocytopenia
- Microcephaly

Box 3
Late manifestation of fetal toxoplasmosis infection

Chorioretinitis (occurs in 90% of cases)[78]

Cerebellar or motor dysfunction

Intellectual delay

Sensorineural hearing loss

Seizures

SYPHILIS

Organism and Epidemiology

Syphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum*. In 2016 there were 628 cases of congenital infection in the United States, rates being highest in the southern states and in minority populations.[80] Lack of adequate prenatal care carries the highest risk of congenital infection.

Clinical Presentation

Syphilis infection manifests over time in several stages. Primary syphilis presents 3 to 6 weeks after exposure with painless chancres in the genital areas at the site of infection. These may go unnoticed and resolve spontaneously. Secondary syphilis presents 6 to 8 weeks later with an erythematous papular rash on the palms and soles, condyloma lata in the mouth or groin, and systemic symptoms such as fever, lymphadenopathy, sore throat, muscle aches, weight loss, and fatigue. Again, these symptoms will typically resolve spontaneously. Syphilis may then remain latent from months to years before progressing to tertiary syphilis, which can affect the central nervous system, cardiovascular system, musculoskeletal system, or liver. Neurosyphilis and ocular syphilis can occur at any stage of infection.[74,80]

Most of the infants with congenital infection are asymptomatic at birth. Severe infections can result in hydrops fetalis, premature birth, and stillbirth. The clinical manifestations are categorized as early (age <2 years) or late (age >2 years) findings and are outlined in **Table 2**. Abnormalities in the placenta and umbilical cord include the placenta appearing enlarged and pale and the umbilical cord appearing inflamed with focal necrosis within the Wharton jelly.

Testing

Universal screening of pregnant women is recommended in the first trimester with repeat testing in the third trimester in high-risk areas/populations.[81] There are several different tests available including the following:

- Nontreponemal tests—Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR)
- Treponemal tests—fluorescent treponemal antibodies and direct treponemal antibodies
- Treponemal culture, which requires dark field microscopy

The VDRL and RPR are fast and inexpensive but have higher false positives than treponemal-specific tests and thus these are used for confirmation and following treatment.

Fetal testing for treponemal antibodies can be performed after 18 to 22 weeks. After delivery, infants with suspected congenital syphilis are tested using the same 2-step

Table 2
Clinical manifestation of congenital syphilis infection

Organ System	Early Manifestations	Late Manifestations
Mucocutaneous	• Persistent rhinitis ("snuffles") • Maculopapular rash on palms and soles • Pemphigus syphiliticus • Condylomata lata	• Hutchinson teeth • Perforation of hard palate • Gummas • Rhagades
Neurologic (including eyes and ears)	• Meningitis • Hydrocephalus	• Chorioretinitis • Glaucoma • Sensorineural hearing loss • Intellectual/developmental delay • Seizures

Skeletal	• Symmetric long bone lesions
	• Periostitis
	• Metaphyseal serration
	• Pseudoparalysis
		• Abnormal facies:
		  ○ Frontal bossing
		  ○ Saddle nose
		  ○ Short maxilla
		  ○ Protuberant mandible
		• Saber shins
		• Clutton joints

Reticuloendothelial	• Fever • Anemia • Leukopenia or leukocytosis • Thrombocytopenia • Hepatosplenomegaly • Jaundice • Generalized lymphadenopathy	

Data from Follett T, Clarke DF. Resurgence of congenital syphilis: diagnosis and treatment. Neonatal Netw 2011;30:320–8.

approach. The placenta and umbilical cord can be sent for pathologic evaluation including dark field microscopy.

Management

Primary, secondary, and early latent syphilis is treated with 2.4 million units of benzathine penicillin G given as a single dose intramuscularly. If the duration of latent infection is unknown, then 3 doses are given at 1-week intervals. Neurosyphilis and ocular syphilis are treated with 3 to 4 million units of aqueous crystalline penicillin G intravenously every 4 hours for 10 to 14 days. There is limited data on nonpenicillin alternatives. Pregnant women with penicillin allergy should be desensitized. Women should be retested and antibody titers followed throughout pregnancy to ensure effective treatment.[80]

Congenital infection is treated with intravenous aqueous penicillin G, 50,000 units/kg, every 12 hours (<1 week old) or every 8 hours (>1 week old) for 10 days. Intramuscular procaine penicillin G, 50,000 units/kg, daily for 10 days can also be used. If treatment is interrupted for more than 24 hours the course should be repeated. For more details regarding the evaluation and management of congenital syphilis, please refer to the AAP 2012 Report of the Committee on Infectious Diseases.[82]

RUBELLA

Organism and Epidemiology

Rubella is a single-stranded RNA virus spread via inhalation of infected particles. Routine vaccination worldwide has led to a 95% decrease in cases from 2000 to

2014 and The Pan American Health Organization declaring rubella eliminated from the Americas in 2015. The US National Congenital Rubella Registry does report 5 to 6 cases of congenital infection yearly, primarily in infants of mothers who emigrated from countries without adequate vaccine programs. Risk of congenital rubella is highest when primary infection occurs in the first trimester (80%–100%), decreases in the second trimester (10%–20%), and increases again in the third trimester (60%).[83]

Clinical Presentation

Maternal symptoms are mild and often go unrecognized. The primary manifestation is a diffuse maculopapular rash lasting around 3 days. Patients may have fever, sore throat, arthralgia, and fatigue. Fetal infection can result in miscarriage, stillbirth, or congenital rubella syndrome (CRS) (**Box 4**).[74]

Other findings include low birth weight, hepatosplenomegaly, thrombocytopenia, bone lesions, and a purpuric "Blueberry Muffin" rash. Late manifestations of CRS include diabetes mellitus, thyroid dysfunction, hypertension, intellectual and behavioral disorders, and panencephalitis.

Testing

Proof of rubella immunity should be documented at the first prenatal visit either through serologic testing or through documentation of immunization. Guidelines for fetal testing in suspected cases were developed by the CDC in 2009 and include the following:

- Viral PCR or culture
- Reverse transcription PCR for viral RNA from blood, cerebrospinal fluid, urine, or nasal swab
- Rubella IgM (usually positive at birth to 3 months in congenital infection)
  - Confirm with stable or rising IgG levels over first 7 to 11 months of age due to false-positive test results

Management

Women found to be nonimmune should be vaccinated immediately following delivery. No specific treatments are available for infants born with CRS. All cases should be reported to the National Congenital Rubella Registry at the CDC. Infants born with CRS are considered contagious through the first year of life unless serial cultures are negative after 3 months of age.[82]

CYTOMEGALOVIRUS

Organism and Epidemiology

CMV is the most common congenital viral infection, affecting up to 2% of live births.[84,85] In the United States, congenital CMV is the leading cause of long-term disabilities in children and is the most common cause of nonhereditary hearing loss worldwide.[86] Risk of vertical transmission is between 30% and 40% for a primary

Box 4
Clinical manifestations of congenital rubella syndrome

Sensorineural hearing loss

Ocular defects, including cataracts, glaucoma, retinopathy, and microphthalmia

Heart defects, including patent ductus arteriosus, pulmonary artery stenosis, and coarctation

infection; this risk increases with each trimester; however, more serious sequelae are typically seen with earlier infection.[77]

Clinical Presentation

Maternal infection with CMV is almost always asymptomatic, only about 5% will experience symptoms, including fever, myalgias, and lymphadenopathy. Between 12% and 18% of newborns will exhibit signs and symptoms at birth[77] (**Box 5**), and[87] the rest remain asymptomatic.

Late sequelae develop in up to 25% by 2 years of life and include hearing loss and intellectual delay. Severe infections have up to a 30% mortality rate.[77]

Testing

Routine testing is not recommended due to lack of effective treatment.[88] Serologic testing is the most common method with viral culture and PCR testing also available. Less than 30% of primary CMV infections will show a positive IgM with a high false-positive rate; thus IgG testing is performed in serial samples 3 to 4 weeks apart. Test result is positive if there is seroconversion from negative to positive or if the IgG titer increases more than 4-fold. Fetal infection may be suspected with ultrasound findings, such as intrauterine growth restriction, microcephaly, ventriculomegaly, liver calcifications, echogenic bowel, ascites, and/or fetal hydrops. Confirmation of infection can be made using CMV PCR testing of amniotic fluid at greater than 20 weeks gestation.[89]

Management

There are currently no approved treatments for either maternal or fetal CMV infection. One study of valganciclovir did demonstrate improvement at 6 months of age in neurodevelopmental and hearing measures.[90] Use of CMV hyperimmune globulin has also shown some initial promise but further study is needed.[91]

HERPES SIMPLEX VIRUS

Organism and Epidemiology

HSV is a sexually transmitted, double-stranded DNA virus that exists as 2 distinct subtypes, HSV-1 and HSV-2. A common infection, the prevalence of HSV-1 is higher (54%) when compared with HSV-2 (16%) in the United States amongst all individuals aged 14 to 49 years.[92] Despite a high prevalence, neonatal infections in the United

Box 5
Clinical manifestations of congenital cytomegalovirus infection

- Microcephaly
- Intracranial calcifications
- Sensorineural hearing loss
- Chorioretinitis
- Seizures
- Growth restriction
- Jaundice
- Thrombocytopenia
- Hepatosplenomegaly
- Petechial rash

States are uncommon occurring in around 1 out of every 3200 births.[93] In utero transmission is even more rare at 1 in 300,000 births.[94]

Infection with HSV-1 or HSV-2 in a patient seronegative to both HSV-1 and HSV-2 is known as a primary infection. A secondary infection occurs when a patient is seropositive to one type and acquires the other. The risk of vertical transmission is highest with primary infection (**Table 3**).[93,95–97]

Clinical Presentation

Up to two-thirds of women with genital infection are asymptomatic. Symptomatic infection presents with painful, erythematous, grouped, papular lesions on the external genitalia, which quickly convert to vesicles, then rupture forming small ulcerated lesions that resolve spontaneously. Burning or shooting pain often precedes the rash.[98] Congenital herpes infection only accounts for 5% of cases and presents with a characteristic triad of findings.[94]

- Cutaneous—vesicular rash, ulcerations, scarring, aplasia cutis
- Ocular—chorioretinitis, microphthalmia
- Neurologic—intracranial calcifications, microcephaly, hydranencephaly

Most cases of neonatal herpes are acquired in the peripartum or postpartum period during symptomatic maternal outbreak. There are 3 categories of clinical manifestations: skin/eyes/mouth (SEM), central nervous system (CNS), and disseminated disease, which account for 45%, 30%, and 25% of cases, respectively.[99] As many as two-thirds of cases of disseminated disease will have CNS involvement. The clinical findings for each category are outlined in **Table 4**.

Testing

Universal screening is not recommended. Viral culture of vesicular fluid is the gold standard for diagnosis of acute infection. Newer immunofluorescent and PCR tests are also available. Serologic testing for HSV-1 and HSV-2 antibodies is also useful for determining primary and secondary infection.

Management

Oral acyclovir and valacyclovir are the mainstays of treatment for active infection and can be used for suppression of recurrence during pregnancy. Suppressive therapy has been shown to decrease viral detection and active lesions at the time of delivery and thus the need for cesarean section but has not been shown to fully prevent neonatal disease.[98] Despite this, ACOG recommends women with known recurrent infection be offered suppressive therapy starting at 36 weeks.[100] Any patient with signs or symptoms of infection, whether primary or recurrent, should be delivered by cesarean section ideally before rupture of membranes to decrease the risk of transmission to the newborn.[100] Women with a history of infection but no signs of recurrence at delivery can safely deliver vaginally.

Table 3
Risk of maternal infection and vertical transmission of herpes simplex virus

	Risk During Pregnancy	Risk of Vertical Transmission
First episode, primary infection	4%	57%
First episode, secondary infection	2%[a]	25%
Recurrence	75%	2%

[a] Women with prior HSV-1 infection acquiring HSV-2.

Table 4
Clinical findings of neonatal herpes simplex virus infection

	Clinical Picture	Laboratory Findings
SEM Disease	• Vesicular rash • Conjunctivitis • Ulcerated lesions in oral mucosa	• Typically normal
CNS Disease	• Poor feeding, lethargy, irritability • Temperature instability • Bulging fontanelles • Tremor • Seizure • Skin lesions seen in up to 70% of cases	• CSF analysis: ○ Mononuclear cell pleocytosis ○ Normal or low glucose ○ Mildly elevated protein • Focal or multifocal periodic epileptiform discharges on EEG • Edema, hemorrhage, or lytic lesions on CT/MRI
Disseminated Disease	• Septic appearance • Hyper/hypothermia • Respiratory distress • Hepatitis and liver failure • DIC • CNS findings in two-thirds of cases • Skin lesions seen in up to 80% of cases	• Elevated transaminases • Thrombocytopenia • CSF, EEG, and CT/MRI findings as mentioned earlier

Abbreviations: CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulation; EEG, electroencephalogram.

Data from American Academy of Pediatrics. Committee on infectious diseases. Red book: 2012 report of the committee on infectious diseases. Elk Grove Village, (IL): American Academy of Pediatrics; 2012.

Neonatal infections are treated with intravenous acyclovir for 14 days in SEM disease and 21 days in CNS/disseminated disease followed by 6 months of suppressive therapy.[101] Guidelines for the testing and treatment of asymptomatic infants born vaginally during active infections have been developed by the AAP, the details of which are discussed elsewhere.[102]

VARICELLA-ZOSTER VIRUS AND PARVOVIRUS B19

Varicella-zoster virus is sometimes included with TORCH infections. The annual incidence of infection during pregnancy is low (0.4–0.7/1000) due to high rates of natural and acquired immunity. Between 10% and 20% of women infected during pregnancy develop pneumonia with a mortality rate up to 40%.[77] Manifestations of congenital varicella syndrome are shown in **Box 6**.[103]

Box 6
Manifestations of congenital varicella syndrome

Intrauterine growth restriction

Skin lesions or scarring in a dermatomal distribution

Chorioretinitis, congenital cataracts, and/or microphthalmos

Horner syndrome and/or nystagmus

Hypoplastic limbs

Cortical atrophy

Seizures

Intellectual disability

ACOG recommends oral acyclovir for treatment because it may reduce morbidity and mortality in patients with pneumonia; however, it does not prevent transmission to the fetus or treat the congenital manifestations.[77]

Parvovirus B19 is a common childhood infection with an annual incidence of new infections during pregnancy of 1% to 2%. Most fetal infections are self-limited and cause no harm to the fetus, but infection can cause spontaneous abortion, stillbirth, and hydrops fetalis.[74,77]

ZIKA

Organism and Epidemiology

Zika virus is a single-stranded RNA flavivirus transmitted to humans by Aedes mosquitoes. Person-to-person transmission is possible through sexual and mother-to-child transmission. Zika virus was first detected in the Western Hemisphere in 2014 and an outbreak has been ongoing in the Americas, Pacific, and Caribbean.[104–107] Between 2015 and February 2018, 5653 cases of symptomatic Zika virus have been reported in the United States with 95% of these in travelers to affected areas.[108]

Clinical Presentation

Acute maternal infection is characterized by fever, maculopapular rash, conjunctivitis, and arthralgia, but some patients may be asymptomatic. The manifestations of congenital Zika syndrome are shown in **Box 7**.[109–112]

Testing

All pregnant women should be questioned about potential exposure before and during the pregnancy and about symptoms of Zika virus. No testing is recommended for pregnant women with possible prior exposure without symptoms and without ongoing exposure. Testing algorithms are available from the CDC (https://www.cdc.gov/pregnancy/zika/testing-follow-up/testing-and-diagnosis.html), which includes testing pregnant women with possible exposure with symptoms and asymptomatic pregnant women with possible ongoing exposure.[113] Placental testing can be considered if diagnosis is unclear or if the newborn has possible Zika-associated birth defects.[114]

Management

Symptomatic treatment is provided for acute Zika infection in pregnancy. If Zika infection is suggested by maternal testing, serial ultrasounds are performed to evaluate for congenital infection. Recommendations exist for the first ultrasound 4 weeks after possible exposure, then every 4 weeks.[115,116] If ultrasound is concerning, amniocentesis can be considered to diagnose fetal infection. The timing and route of delivery is unchanged for affected pregnancies. Breastfeeding seems to be safe.[117]

Box 7
Manifestations of congenital Zika syndrome

- Microcephaly
- Central nervous system abnormalities (hypertonia, seizures)
- Facial disproportion
- Ocular abnormalities
- Arthrogryposis
- Sensorineural hearing loss

DISCUSSION

Some infections are highlighted in pregnancy due to having unique effects on the mother-child dyad. Research often lags or is lacking on the effects of diseases and medications in pregnancy. Research is constantly evaluating ways to decrease risk of vertical transmission. Some novel treatments such as direct-acting antivirals for hepatitis C have not yet been studied in pregnancy and may provide new options. Infections, such as Zika virus, that can cause in utero infection are emerging and being recognized as causing congenital syndromes. As more infections are recognized and studied for their effects on pregnancy, we may find more answers to causes of syndromes that are currently poorly defined, such as cerebral palsy.

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