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Handbook of Clinical Neurology, Vol. 172 (3rd series)
Neurology and Pregnancy: Neuro-Obstetric Disorders
E.A.P. Steegers, M.J. Cipolla and E.C. Miller, Editors
https://doi.org/10.1016/B978-0-444-64240-0.00005-2

Chapter 5

Neurologic infections during pregnancy

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Abstract

Neurologic infections during pregnancy represent a significant cause of maternal and fetal morbidity and mortality. Immunologic alterations during pregnancy increase the susceptibility of the premature brain to damage. This chapter summarizes the epidemiology, pathophysiology, and clinical manifestations in the pregnant woman and the infant, and the diagnosis, treatment, and prevention of the major viral, parasitic, and bacterial infections known to affect pregnancy. These organisms include herpes virus, parvovirus, cytomegalovirus, varicella, rubella, Zika virus, toxoplasmosis, malaria, group B streptococcus, listeriosis, syphilis, and tuberculosis. There is an emphasis on the important differences in diagnosis, treatment, and fetal outcome between trimesters. An additional overview is provided on the spectrum of neurologic sequelae of an affected infant, which ranges from developmental delay to hydrocephalus and seizures.

INTRODUCTION

Infectious diseases of the nervous system during pregnancy can cause considerable maternal and fetal morbidity and mortality. There is now an evolving understanding of the immunologic alterations during pregnancy that likely play a key role in susceptibility to infection. Evidence shows that adaptive immune responses are reduced, leading to impaired pathogen clearance with advancing pregnancy and, possibly, increased susceptibility to severe infection (Priddy, 1997; Zoller et al., 2007; Forbes et al., 2012; Kraus et al., 2012; Pazos et al., 2012; Sappenfield et al., 2013). There is also evidence that the hormonal environment during pregnancy contributes to local suppression of cell-mediated immunity at the maternal–fetal interface (Sappenfield et al., 2013). Thus, although pregnant women are not immunosuppressed by standard definitions, immunologic changes during pregnancy may induce a state of increased susceptibility to severe infections, including neurotropic pathogens.

Here we discuss major neurotropic pathogens and their maternal and fetal impact during pregnancy, with a discussion of the epidemiology, pathophysiology, clinical presentation, and management of significant organisms (Table 5.1).

VIRUSES

Herpes virus

EPIDEMIOLOGY

Herpes simplex virus type-1 and type-2 (HSV-1 and HSV-2) are a part of *Herpesviridae* family, of which eight viruses are infectious to human hosts (Silasi et al., 2015). Genital HSV-2 is the leading sexually transmitted infection (STI) in women in the United States. According to the Center for Disease Control and Prevention (CDC), over 750,000 people in the United States are infected with genital herpes annually. HSV-2 is more common

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Table 5.1

Specific causes of fetal and neonatal neuro-infections in pregnancy

Viruses	HSV, Parvo, CMV, Varicella, Zika, Rubella
Bacteria	Listeria, group B streptococcus, syphilis, TB
Protozoa	Toxoplasma, malaria

among women and non-Hispanic blacks (34.6%), as compared to non-Hispanic whites (8.1%) (Centers for Disease Control and Prevention, 2017). Independent risk factors for HSV-2 infection include ethnicity, poverty, cocaine abuse, sexual activity at a young age, a higher number of partners, and concurrent STIs (Gottlieb et al., 2002).

HSV is the leading cause of sporadic encephalitis, primarily due to type-1 HSV. Eighteen cases of HSV encephalitis in pregnant women have been reported in the literature (Whitley and Gnann, 2002; Dodd et al., 2015). The majority of HSV-1 encephalitis in pregnant women were identified in the third trimester, to a lesser extent in the second trimester, and rarely in the first trimester. This is speculated to be related to estrogen and progesterone rise during late second and third trimester in pregnancy, which modulates an immunologic shift (Dodd et al., 2015).

Both HSV-1 and HSV-2 during pregnancy can result in congenital infection. Neonatal HSV is associated with significant morbidity and, if left untreated, high rates of mortality. HSV increases the risk of spontaneous abortion, premature birth, and stillbirth with an OR of 3.81, 3.83, and 1.78, respectively (Shi et al., 2018). Central nervous system (CNS) associated infection accounts for 30% of neonatal HSV. The frequency of neonatal HSV infection ranges from 8 to 60 per 100,000 live births (Pascal et al., 2012). Primary genital HSV infection in late pregnancy is associated with a 30%–50% risk of neonatal infection, whereas the risk is less than 1% in early pregnancy. In late acquisition of infection, HSV antibodies are not present during labor to suppress the replication cycle (Silasi et al., 2015).

Pathophysiology

HSV transmission occurs across epithelial mucosal cells and via skin breakdown, after which the virus migrates to nerve tissues primarily via the olfactory tract and remains latent within the CNS (Pascal et al., 2012; Silasi et al., 2015). Thus, the virus accesses the CNS intraneuronally. HSV-1 is predominantly located in the trigeminal ganglia, whereas HSV-2 is in the lumbosacral ganglia.

Neonatal HSV infection is often from direct contact of either HSV-1 or HSV-2 from an asymptomatic mother during vaginal delivery (Brown et al., 1997). In utero and postnatal infection occasionally occur.

Signs and symptoms in the pregnant woman

HSV-1 encephalitis in a pregnant woman presents as it would in a nonpregnant woman with headaches, fever, altered mental status, and seizures. Eighty-nine percent of pregnant women in a case review had fever, 67% had headache, and 45% had seizures (Dodd et al., 2015). Other etiologies for seizures in a pregnant woman should be investigated and treated, including hyperemesis gravidarum, which results in vomiting, electrolyte imbalances, and potentially secondary seizures, and eclampsia, a hypertensive disorder of pregnancy. If seizures are preceded by a headache and features of increased intracranial pressure, cerebral sinus venous thrombosis should also be excluded.

Magnetic resonance imaging (MRI) of the brain is the preferred imaging method if maternal meningoencephalitis is suspected, as its use of nonionizing radiation is safe throughout pregnancy. In mothers diagnosed with HSV during pregnancy with completed MRI of the brain, 80% were abnormal (Dodd et al., 2015). Findings were similar to nonpregnant immunocompetent patients and included increased T2 signal with and without edema at the temporal lobes, while some also had increased signal in the parietal region and cerebral peduncle.

During pregnancy, HSV can be asymptomatic in the mother either because of disease reactivation or newly acquired genital herpes. Often, primary genital infections in pregnancy are misdiagnosed (Corey and Wald, 2009). Pregnant women sometimes have nonspecific prodromal symptoms of HSV-1 and HSV-2 with viral symptoms and tingling at the skin, and some can present with painful urogenital blisters and ulcerations.

Prenatal diagnosis

Pregnant women can be diagnosed with HSV during pregnancy with serologic testing (Piskin et al., 2008). PCR analysis of HSV-1 and HSV-2 is the quickest and most sensitive measure of diagnosis in serum (Corey and Wald, 2009) and in cerebrospinal fluid (CSF; Pascal et al., 2012). Herpes virus screening in pregnant women is not recommended by the CDC or by the prevention from sexually transmitted disease treatment guidelines, and the American and Royal Colleges of Obstetricians and Gynecologists do not recommend universal screening (Urato and Caughey, 2006). These recommendations are based on the lack of benefit in identifying women who are HSV negative without successful means of preventing transmission, the unknown complications associated with treatment of HSV positive pregnant women, and multiple cost-effectiveness studies that do not support screening (Glass and Huffman, 2005).

Signs and symptoms in the infant

Transmission of HSV infection during pregnancy is associated with spontaneous abortion, intrauterine growth restriction (IUGR), prematurity, and herpes infection in the newborn. Untreated neonatal disseminated HSV carries a mortality rate of approximately 80% (Silasi et al., 2015). After birth, neonates with CNS HSV infection can present with seizures and tremors, altered mental status (lethargy, irritability, poor feeding), and temperature instability. On exam, the infants may have a bulging fontanelle, microcephaly, chorioretinitis, microphthalmia, and hydranencephaly (Sloan et al., 2017). Long-term effects include neurodevelopmental disability, focal neurologic deficits, blindness, and seizures. In a large prospective study, among nine infants born to women with newly acquired genital HSV infection around the time of labor, neonatal HSV infection occurred in four infants. Of those affected infants, one died and one had lifelong neurologic disability (Brown et al., 1997).

Fetal brain MRI can show brain infarcts, ventriculomegaly, and edema. In a case report in 2017, new-onset in utero ventriculomegaly was identified by ultrasound at 33 weeks, after the mother was found to have a primary HSV infection at 17 weeks of gestation and subsequently treated with acyclovir. New-onset ventriculomegaly on prenatal ultrasound of an HSV-infected mother is considered a diagnostic indicator of antenatal CNS herpes simplex infection (Sloan et al., 2017).

Treatment and prevention

If a mother develops HSV-1 encephalitis during pregnancy, intravenous acyclovir is the mainstay of treatment at a dose of 10 mg per kg every 8 h for 14–21 days. Acyclovir crosses the placenta, concentrates in the amniotic fluid, and results in similar drug levels between mother and fetus (Pascal et al., 2012). Treatment of seizures in pregnant women should be done carefully, avoiding polytherapy and potentially teratogenic drugs (Dodd et al., 2015).

Infants infected with HSV (disseminated or CNS infection) should receive intravenous acyclovir 20 mg per kg every 8 h for 21 days. Antiviral therapy reduces mortality in infants with CNS disease from 50% to 6% (Corey and Wald, 2009), and reduces further progression of infection from mucosal surfaces to the CNS.

In women with a known history of HSV-2 genital lesions, suppressive therapy can be given during the last month of pregnancy to reduce asymptomatic viral shedding and clinical recurrence (Silasi et al., 2015). Cesarean delivery is recommended in the presence of genital lesions or when women experience prodromal symptoms to minimize risk of vaginal viral exposure, regardless of suppressive therapy.

Parvovirus

Epidemiology

Parvovirus B19 is a single-stranded DNA virus identified by Anderson et al. in 1983 as the cause of a common viral exanthema in children, erythema infectiosum or fifth disease (Anderson et al., 1984). This virus, which exclusively infects humans, is common in childhood and up to 60% of children become seropositive by adulthood (Douvoyiannis et al., 2009). Most women are immune to parvovirus B19 prior to pregnancy. Parvovirus B19 newly affects 1%–5% of pregnant women (Ornoy and Ergaz, 2017). The highest risk of fetal loss and adverse fetal outcome is after primary infection in weeks 9–16, is lower in the second trimester, and rare in the third trimester (Ornoy and Ergaz, 2017).

The seroconversion rate in pregnant women varies drastically from 3% to 34%, and is higher during parvovirus epidemics, which tend to occur in late winter and early spring (Koch and Adler, 1989). In some studies, the risk of a new infection in pregnancy correlates with the number of children in the household, as mothers often contract the illness by respiratory secretions of younger children. Overall there is a high incidence of vertical transmission, up to 30%–50% of cases, but a low fetal infectivity rate of 1%–2% (Ornoy and Ergaz, 2017).

Pathophysiology

Parvovirus B19 belongs to the *Parvoviral* family, in the genus *Erythrovirus* that require erythroid cells to replicate. Viral transmission is primarily by respiratory droplets but can be spread hematogenously, and transplacentally in pregnancy. When the virus enters the fetus, it preferentially infects rapidly dividing cells in the liver. In the second trimester, the liver is the main source of hematopoietic activity, making the fetus particularly vulnerable to infection at that time.

Signs and symptoms in the pregnant woman

Pregnant women, similar to nonpregnant women, have nonspecific flu-like symptoms during primary infection with Parvovirus B19, including fever, malaise, myalgia, and pruritis. Approximately 20%–30% of all people infected with the virus have no symptoms. The classic “slapped cheek” or reticular rash is reported more often among immunocompetent individuals than those with altered immunity, and particularly in children (Douvoyiannis et al., 2009). Arthralgia and arthritis are often the presenting symptoms of parvovirus B19 in adults. Other symptoms of primary infection can include thrombocytopenia, hepatitis, lymphadenopathy, myocarditis, vasculitis, and a transient aplastic crisis in patients

with hemoglobinopathies (Douvoyiannis et al., 2009; Feldman et al., 2016). CNS symptoms have been reported in nonpregnant patients, and include encephalopathy, meningoencephalitis, stroke, seizures, chorea, cerebellar ataxia, and opsoclonus. CNS involvement occurs more often in children and young adults; in one study 81% of CNS cases were less than 20 years old (Douvoyiannis et al., 2009).

MRI features of CNS parvovirus infection include increased white matter signal abnormalities on T2-weighted or fluid-attenuated inversion recovery images of the frontal or parietal lobes, or, periventricularly, in the gray matter, brainstem, basal ganglia, or corpus callosum (Douvoyiannis et al., 2009).

Prenatal diagnosis

Pregnant women are diagnosed with acute infection by serologic testing. B19-specific IgM antibodies rise 10–12 days after infection, peak with viral levels, and last from 3 to 6 months following primary infection. IgG production follows IgM, and can last for life (Giorgio et al., 2010; Ornoy and Ergaz, 2017). If B19 IgM antibodies are present in the absence of a B19 IgG, this could represent a recent infection or a false-positive result, and should be repeated 1–2 weeks later. If immunity is documented (IgG+ and IgM−), the fetus is not at risk of prenatal infection.

Congenital parvovirus B19 is diagnosed by performing PCR of amniotic fluid or fetal cord blood, or by identifying viral particles by electron microscopy. The fetus does not make IgM antibodies until 22 weeks of gestation, thus fetal IgM may remain negative and be falsely reassuring. Diagnosis can be difficult in a fetus as viral particles can only be identified during the viremic stage. Ultrasound can also be used to identify evidence of fetal anemia and hydrops. Middle cerebral artery peak systolic velocity is a highly sensitive marker for fetal anemia.

Signs and symptoms in the infant

Most infants born to mothers infected with parvovirus B19 have a favorable prognosis. Less commonly, when detrimental effects occur, parvovirus B19 infection can cause significant harm to a developing fetus. This is primarily a concern in the second and third trimesters. B19 infection can result in severe fetal anemia, secondary to destruction of erythropoietic stem cells, heart failure, and nonimmune hydrops fetalis, and even death (Koch and Adler, 1989; Giorgio et al., 2010; Ornoy and Ergaz, 2017).

There are case reports of CNS, craniofacial, and ophthalmologic anomalies in the developing fetus, yet there are no proven associations between infection and congenital anomalies. Specifically there are case reports of neurologic anomalies from congenital parvovirus B19 infection, including hydrocephalus, cerebellar hemorrhage, and polymicrogyria (Ornoy and Ergaz, 2017). In a retrospective review of 27 fetuses infected with parvovirus B19 who required at least 1 intrauterine transfusion for severe anemia, 26% had abnormal cerebral imaging in the third trimester, such as cerebellar biometry below the third percentile and uni- or bilateral cerebellar hemorrhage (Maisonneuve et al., 2018). Viral load in fetal blood correlated with the presence of brain lesions, suggesting that there is direct brain injury caused by the virus. Children with abnormal findings seen at follow-up had a normal neurodevelopmental course. Controversy exists about the incidence of developmental delay; most studies report no association with parvovirus infection, yet small studies do (Rodis et al., 1998; Feldman et al., 2016).

Postmortem neuropathologic examination of fetal brains affected by parvovirus B19 demonstrate multinucleated giant cells of macrophage and microglia lineage, containing B19 genome DNA, and small perivenular calcifications, particularly in the cerebral white matter (Isumi et al., 1999). This suggests that parvovirus B19 infection in the fetal brain may cause neurologic sequelae. Despite this postmortem finding, the majority of infants with transplacental parvovirus infection have a normal outcome.

Treatment

There is no specific treatment or prophylaxis against parvovirus B19 infection acquired during pregnancy. Intrauterine blood transfusion is sometimes necessary to manage fetuses with anemia or hydrops. Transfusions often decrease the speed of systolic peak flow of the middle cerebral artery and improve or eliminate the sonographic signs of anasarca, thus improving overall outcome (Subtil et al., 2015).

Cytomegalovirus

Epidemiology

Cytomegalovirus (CMV) is a highly prevalent DNA herpes virus. The ubiquitous virus is estimated to infect 60% of women of reproductive age in developed countries and closer to 90% in developing countries (Silasi et al., 2015). Seroprevalence of CMV is highest among minorities (ethnic, racial, socioeconomic), multiparous women, those of advanced maternal age, and women coinfected with HIV (Davis et al., 2017). Women with younger children are exposed by child-to-child transmission at daycare. Healthcare workers are not at increased risk due to routine precautions, i.e., hand washing and wearing personal protective equipment; their annual seroconversion risk is similar to pregnant women at 2.3% (Hyde et al., 2010).

CMV is the most common infection in the developing fetus, and the principal cause of congenital sensorineural hearing loss (SNHL). In live infants, CMV prevalence ranges from 0.3% to 2.4% in the United States and other developed countries (Bale Jr., 2014), with higher rates seen in certain regions of Africa and Latin America. Primary maternal CMV infection is seen in 0.7%–4.1% of pregnancies, and reactivation may occur in 10% of seropositive women (Silasi et al., 2015). The rate of CMV vertical transmission in pregnant women with a primary maternal infection is reported as 32%, and in those with recurrent infection as 1.4% (Kenneson and Cannon, 2007). The overall rate of transmission increases with advancing gestational age with 30% in the first trimester, 38% in the second, and 72% in the third. Conversely, first and early second trimester transmission increases the risk of symptomatic infants, with up to 32% having SNHL and/or neurologic manifestations (Silasi et al., 2015; Faure-Bardon et al., 2018).

Pathophysiology

CMV persists latent for a person's lifetime and can be reactivated during transient immunosuppression (Kagan and Hamprecht, 2017). Viral transmission is by contact with infected body fluids, including nasopharyngeal secretions, semen, cervical or vaginal secretions, saliva, urine, blood products, or breast milk. CMV excretion can occur over months to years. There are two main routes of primary maternal CMS infection: (1) via sexual activity and (2) via saliva of children, on their hands or toys. Congenital CMV occurs by the following mechanisms of transmission: (1) transplacentally by virus infecting the placenta, (2) ingestion or aspiration of secretions in the vaginal canal, (3) postpartum via breastfeeding, and rarely (4) ascending virus from the genital tract (Silasi et al., 2015).

In the developing fetus, CMV has a predilection for the walls of the ventricles, organ of Corti, and the neurons of the eighth cranial nerve (Silasi et al., 2015).

Signs and symptoms in the pregnant woman

Primary CMV infection is asymptomatic in 75%–95% of mothers, but can present with flu-like symptoms such as fever, fatigue, myalgias, rhinitis, pharyngitis, and headache. Due to nonspecific symptoms, most maternal CMV infections remain undiagnosed.

CMV encephalitis primarily occurs in immunocompromised patients and is rare in pregnant women. An immunocompetent pregnant woman with probable CMV encephalitis was described in the literature, and presented with diffuse headache, drowsiness, and an acute confusional state (Saliba et al., 2004). The infant was born asymptomatically at 39 weeks gestation and had a urine culture positive for CMV. A second case described life-threatening acute disseminated encephalomyelitis in an immunocompetent pregnant woman found to have PCR-positive CSF for CMV (Saliba et al., 2004; Macerollo et al., 2016).

Prenatal diagnosis

Screening pregnant women for CMV is not routinely recommended in most countries. Serologic testing of the pregnant woman is pursued if suspicious findings are seen on ultrasound (Davis et al., 2017). Recent or prior infection with CMV can be confirmed by the presence of CMV-specific IgM and IgG antibodies. CMV IgM persists for months following a primary infection and can be detected in reactivation of latent disease; thus, its presence can be a false-positive result (Davis et al., 2017). Primary infection in the prior 2–4 months can be confirmed by IgG avidity testing, with very low avidity of antibody binding to the antigen. Diagnosis of fetal CMV can be made by amniocentesis 6 weeks after the presumed infection and safely, with regard to procedure-related iatrogenic miscarriage, after 21 weeks gestation.

Although the sensitivity and positive predictive value is low, early signs of congenital CMV can be appreciated on the 20-week fetal anatomy ultrasound, with an echogenic bowel being the first indication of in utero infection, along with developmental brain abnormalities, IUGR, amniotic fluid abnormalities, placental enlargement, hepatosplenomegaly, hepatic calcifications, or hydrops fetalis. MRI has a higher sensitivity in detecting brain abnormalities than ultrasound (92% compared to 38%) and predicting symptomatic infants (83% compared to 33%). Abnormal brain MRI findings include periventricular calcifications, ventriculomegaly, microcephaly, intraventricular septa, temporal pole lesions, and cortical anomalies (Doneda et al., 2010).

For diagnosis of symptomatic or asymptomatic congenital CMV infection, culture of the urine or saliva or urine PCR is recommended, both with high sensitivity and specificity (Bale Jr., 2014).

Signs and symptoms in the fetus and infant

Approximately 90% of neonates with congenital CMV infection are asymptomatic but carry a long-term risk of sequelae (Kagan and Hamprecht, 2017). CMV infection during pregnancy is a risk factor for spontaneous abortion, prematurity, and stillbirth, with an OR of 1.61, 1.86, and 5.74, respectively (Shi et al., 2018). Permanent deafness, vision impairment, and neurologic disability are the most severe sequelae in surviving infants (Davis et al., 2017). About 8%–15% of these children develop a uni- or bilateral SNHL, typically within the

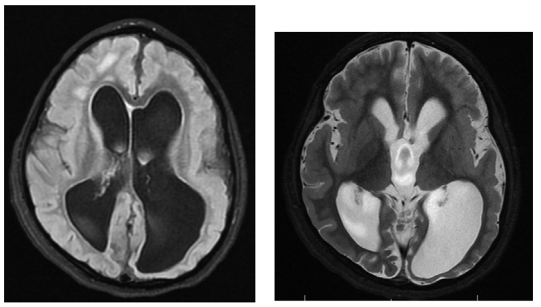

Fig. 5.1. (A) Axial T2 FLAIR MRI brain without contrast of 5-year-old patient with congenital CMV. This image demonstrates severe ventriculomegaly with enlargement of the lateral and third ventricles. There is abnormal FLAIR signal seen throughout the subcortical white matter particularly in the bilateral frontal and parietal regions, right more than left cerebral hemisphere. (B) Axial T2 MRI brain without contrast of 5-year-old patient with congenital CMV. There is evidence of severe polymicrogyria seen throughout the bilateral frontal, parietal, and temporal lobes. Additionally the cerebellar vermis appears abnormally rotated. Sagittal images (not shown) demonstrated severe dysgenesis of the left cerebellar hemisphere and a large posterior fossa cyst.

first 3 years of life, though SNHL has been reported up to adolescence (Faure-Bardon et al., 2018). Of the 10% of neonates who have symptomatic CMV infection, their clinical manifestations include petechiae (76%), jaundice (67%), hepatosplenomegaly (60%), microcephaly (53%), IUGR (50%), SNHL (35%–50%), chorioretinitis, and optic atrophy (20%). Neurologically affected infants often have hypotonia and poor feeding, but can also experience seizures (Bale Jr., 2014). Common brain MRI findings in affected infants include periventricular calcifications, ventriculomegaly, and microcephaly. A neurodevelopmental disorder develops in 30%–40% of children later in life (Davis et al., 2017; Kagan and Hamprecht, 2017) (Fig. 5.1).

Treatment

Antiviral treatment of CMV in pregnancy is not recommended at this time, and mothers are typically offered supportive care. However, current studies suggest that treatment of moderately symptomatic fetuses in utero can be helpful. Case reports demonstrate that valacyclovir given to affected mothers decreases fetal CMV viral loads and reaches therapeutic concentrations in utero (Codaccioni et al., 2019). A nonrandomized phase II study of oral valacyclovir (8 g daily) given to pregnant women with a moderately infected fetus, defined by abnormal cerebral ultrasound findings, increased the proportion of asymptomatic neonates compared to a historical cohort (82% with treatment vs 43% without) (Leruez-Ville et al., 2016). High-dose valacyclovir was tolerated by pregnant women in this study, and there were no major safety concerns to the mother or the fetus. Because of the findings being limited by open-label design, valacyclovir is not standard of care in the obstetrics community. In immunocompromised adults (i.e., HIV-infected women or transplant recipients), antiviral medications are used in the prevention of CMV; however, they have not been proven to be effective. Another therapy, hyperimmune globulin (HIG), has been studied for treatment of CMV infected mothers; however, phase II studies have not shown significant differences in the rates of congenital infection in those treated with HIG compared to controls (Revello et al., 2014). Several studies are now being conducted on developing a CMV vaccine due to the large number of infants affected and the economic burden of disease (Inoue et al., 2018).

Varicella

Epidemiology

Varicella zoster virus (VZV), known to cause chickenpox, is a part of *Herpesviridae* family. It is a common and highly contagious disease. The incidence of varicella in pregnancy is low and is estimated at 0.7 per 1000 (Silasi et al., 2015). Most women are immune before pregnancy due to infection during childhood or vaccination. Prior VZV infection is 97%–99% predictive of seropositivity and offers lifelong immunity to the mother (Bialas et al., 2015). The risk of transplacental infection by the teratogenic virus is 0.4%–2%, if maternal infection occurs in the first 20 weeks of gestation, and is more commonly seen after reactivation of the virus rather than as a primary infection.

Herpes zoster, or the reactivation of dormant varicella zoster, in pregnancy is exceedingly rare, as antibodies prevent transplacental viral transmission. VZV meningitis has been reported in an HIV-positive pregnant woman, presenting as a painful vesicular rash in an L3 dermatome and subsequently developing meningitis symptoms of headache, fever, neck stiffness, and photophobia (Jayakrishnan et al., 2008).

Pathophysiology

VZV transmission occurs by contact with respiratory droplets, with skin lesions, and transplacentally. The virus is contagious starting 2 days before the rash onset until the vesicles have crusted or disappeared (Silasi et al., 2015). VZV can remain dormant in ganglion cells; if reactivated, the resultant infection is known as herpes zoster.

Signs and symptoms in the pregnant woman

Classically, infection with VZV causes a disseminated maculopapular to vesicular rash that primarily involves the face and trunk.

Prenatal diagnosis

Fetal ultrasound can detect some anomalies associated with congenital varicella syndrome.

Signs and symptoms in the fetus and infant

Symptoms of congenital varicella syndrome include microcephaly, hydrocephaly, cerebellar hypoplasia, intellectual disability, limb hypoplasia, cataracts, and IUGR (Silasi et al., 2015). Most of these malformations can be detected on prenatal ultrasound.

Neonatal infection can also occur if a mother becomes acutely infected with VZV 5 days before and up to 2 days after delivery, due to hematogenous spread of virus across the placenta (Bialas et al., 2015). The infant is exposed to a high viral load but does not produce sufficient protective antibodies in time. Infants become symptomatic between 5 and 10 days of life with symptoms ranging from isolated skin lesions to disseminated infection.

Treatment

Chickenpox is a vaccine-preventable infectious disease. If a primary infection occurs during pregnancy, there is no known effective treatment to reduce the rate of vertical transmission. A recent review article described the safety and pregnancy outcomes in women who received varicella zoster immune globulin (VZIG) as prophylaxis after exposure to either VZV or herpes zoster. The incidence of varicella was 29% in a randomized control trial after VZIG and 7.3% in an open-label, expanded access program. This study further supports CDC recommendations to provide postexposure prophylaxis to nonimmune pregnant women exposed to VZV (Centers for Disease Control and Prevention, 2013; Swamy and Dotters-Katz, 2019). In the United States, VZIG is recommended for exposed newborns and prevent approximately 50% of symptomatic cases (Blumental and Lepage, 2019).

Vaccination to VZV is contraindicated during pregnancy, and women should avoid becoming pregnant within 28 days of vaccine, as the Zostavax vaccine contains a live-attenuated virus and could potentially affect the fetus.

In the rare cases of VZV meningoencephalitis, acyclovir has been used as treatment, including its use in one immunocompromised pregnant woman (Jayakrishnan et al., 2008).

Rubella

Epidemiology

While rubella has been eliminated in the United States with vaccination, occasional imported cases are reported. In developing countries, women of reproductive age are more prone to rubella infection because of the scarcity of vaccines. Transmission of infection occurs via nasopharyngeal secretions, and the transmission rate is 80% to susceptible individuals. Peak incidence is in late winter and spring. In pregnancy, however, rubella infection can result in congenital rubella syndrome (CRS). This syndrome consists of the classical triad of cataracts, cardiac malformation, and SNHL.

The risk and severity of congenital infection depends mainly on the gestational age at infection (Miller et al., 1982). In up to 85% of cases, pregnant women with rubella infection and a rash during the first 12 weeks of gestation have a fetus with CRS. This incidence reduces to 65% and 25% at 13–14 weeks' gestation and second trimester, respectively (Miller et al., 1982). Defects tend to be rare after 20 weeks. Teratogenic infections have been reported in pregnancies where the rubella rash appeared 3–6 weeks after the first day of the last menstrual period.

Pathophysiology

The disease is caused by a togavirus (enveloped by a single-stranded RNA genome). CRS pathogenesis is multifactorial. At a cellular level, noninflammatory necrosis of chorionic epithelium and endothelial cells occurs (Bouthry et al., 2014). Necrotic cells travel through the fetal circulation and cause thrombotic and ischemic lesions in the eyes, ears, brain, and heart. Other effects of infection include direct or indirect inhibition of actin assembly that leads to inhibition of cell mitosis and hinders development of organ precursor cells.

Signs and symptoms in the pregnant woman

Infectious symptoms in the pregnant women are usually mild and can present as a febrile illness with a generalized maculopapular rash that begins on the face and spreads to the trunk and extremities. Other less frequent symptoms include arthralgias, head and neck lymphadenopathy, and conjunctivitis. The incubation period is approximately 12–23 days. Clinical signs are usually preceded by a phase of viremia for about a week and the infectious period lasts from time of onset of viremia through a week after the rash. Most maternal infections are subclinical (Bouthry et al., 2014).

Prenatal diagnosis

Rubella may be isolated from body fluids such as urine, blood, nasopharynx, and CSF for up to 2 weeks from the time of onset of rash. Serologic analysis confirms the diagnosis by Rubella-specific IgM (RV-IgM) antibody detection using enzyme-linked immunoassay (ELISA). RV-IgM can be tested starting from 4 to 5 days after onset of disease and can be present for up to 6 weeks after appearance of the rash (Reef et al., 2006). RV-IgG detected by ELISA peak 1–2 weeks after the onset of the rash, and persists throughout life. An RV-IgG-positive result with a negative IgM is reassuring, as it implies that there is no active infection.

Signs and symptoms in the fetus

Rubella is one of the most severe teratogens, and associated with poor outcomes when acquired during organogenesis (Adams Waldorf and McAdams, 2013). While sensorineural deafness is the most common single defect from disease, congenital rubella infection can also result in the following abnormalities: (1) ophthalmologic defects (microphthalmia, cataracts, retinopathy), (2) heart defects (patent ductus arteriosus and pulmonary artery stenosis), (3) neurologic deficits (microcephaly, developmental delay, intellectual disability, and meningoencephalitis), (4) hepatosplenomegaly and jaundice, and (5) radiolucent bone disease.

Neonates with CRS may be a threat to other infants and to susceptible adults because of the shedding of virus during early infancy. Chronic fetal nonlytic infections may affect any organ. Delayed presentation includes the extended rubella syndrome, which presents as progressive panencephalitis and type 1 diabetes, in the second or third decade of life (Webster, 1998).

Treatment

No specific treatment for rubella exists. Droplet precautions for a week after the onset of rash are recommended in suspected cases. MMR vaccine should be offered to nonpregnant women of childbearing age who lack evidence of immunity whenever they come in contact with the healthcare system. Vaccination should be avoided 1 month before pregnancy and for the duration of pregnancy, as the vaccine contains live-attenuated virus that might be harmful to the developing fetus. Prevention of CRS is the major goal of rubella vaccination development (McLean et al., 2013).

Zika virus

Epidemiology and overview

Zika virus is an arthropod-borne flavivirus related to dengue and West Nile Virus. In utero exposure to Zika virus is associated with the development of congenital Zika syndrome (CZS), which can lead to a variety of manifestations. Although sporadic cases were described throughout the 20th century in Africa and Southeast Asia, the first major recognized outbreak occurred in the Yap Islands of Micronesia in 2007 where more than 70% of the population was infected (Lanciotti et al., 2008; Dyer, 2015; Cauchemez et al., 2016). Another larger outbreak occurred in French Polynesia in 2013–14, which affected about two-thirds of the population (Duffy et al., 2009; Hayes, 2009). A major outbreak then occurred throughout Central and South America in 2014–15, where a significant number of neurologic complications occurred, including congenital birth defects. The risk of maternal-to-fetal transmission is greatest in the first trimester, though neurologic sequelae due to Zika virus has been identified in fetuses exposed during the second and third trimester as well (Besnard et al., 2014; Brasil et al., 2016; Cauchemez et al., 2016; Hennessey et al., 2016; Pacheco et al., 2016; Petersen et al., 2016; Ventura et al., 2016; Halai et al., 2017; Shapiro-Mendoza et al., 2017). The frequency is difficult to define given that testing may be negative in exposed infants.

Pathophysiology

Maternal infection leads to placental infection and injury, with the virus crossing the placenta with neurotropism for the fetal brain (Adams Waldorf et al., 2016; Costello et al., 2016; Cugola et al., 2016; Jurado et al., 2016; van der Linden et al., 2016; Miner et al., 2016; Quicke et al., 2016; Tabata et al., 2016; Vouga and Baud, 2016; Sheridan et al., 2017; Walker et al., 2019). In the fetal brain, neuronal growth, proliferation, migration, and differentiation are disrupted. Early gestational age and the Zika virus strain likely impact vulnerability to severe infection.

Signs and symptoms in the pregnant woman

Only approximately 20% of people with Zika virus are symptomatic. The most common symptoms including rash, arthralgias, conjunctivitis, and fever (5–6). In those who have symptoms, they typically occur approximately 1 week after exposure to the virus.

Prenatal diagnosis

Ultrasound is the major modality used to screen for congenital Zika virus infection, though sensitivity and

specificity is variable (Pereira Jr et al., 2018). Ultrasound is recommended in pregnant women who have tested positive for Zika virus, though the optimal timing of testing is unknown. MRI is more sensitive for diagnosis of fetal brain abnormalities (Griffiths et al., 2017), though it is not accessible in many Zika endemic settings (Driggers et al., 2016). Ideally in patients with possible exposure, though testing negative, ultrasound should be done for routine care. Features to assess include microcephaly, cerebral calcifications, ventriculomegaly, and other brain abnormalities (Fig. 5.2) (Soares de Oliveira-Szejnfeld et al., 2016; Society for Maternal–Fetal Medicine (SMFM) Publications Committee, 2016). Zika virus rRT-PCR positivity in amniotic fluid is diagnostic of fetal viral exposure, though it does predict whether there will be CZS (Petersen et al., 2016). Decisions regarding amniocentesis should be tailored to individual clinical circumstances (Besnard et al., 2014). Amniocentesis may be considered for women who have fetal ultrasound findings suggestive of CZS and/or positive or inconclusive maternal laboratory test results for Zika virus infection, and when this information will impact decisions about pregnancy termination or ongoing pregnancy and delivery management. Timing and route of delivery are determined according to routine obstetric policies and standards.

Signs and symptoms in the fetus/infant

The principal clinical features of CZS include microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, seizures, irritability, arthrogryposis, ocular abnormalities, and SNHL (Costello et al., 2016; de Fatima Vasco Aragao et al., 2016; Miranda-Filho Dde et al., 2016; Meneses et al., 2017). The full spectrum of the syndrome is still evolving and more subtle manifestations of Zika virus infection may become apparent as infants age (Table 5.3).

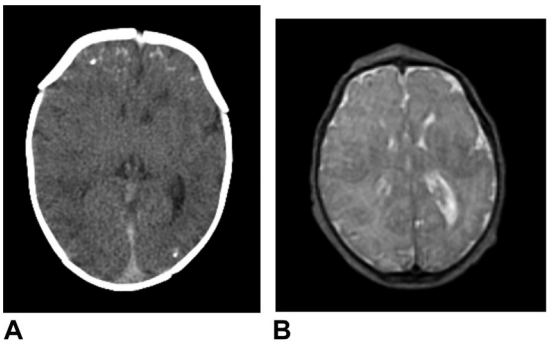

Fig. 5.2. (A) Noncontrast head CT of 4-day-old patient with congenital Zika. This motion degraded head CT demonstrates bifrontal and left parietal cortical and subcortical calcifications. Not shown is the T1 MRI brain with corresponding hyperintense signal. (B) Axial T2 MRI brain of 1-day-old patient with congenital Zika. The left cerebral hemisphere is mildly decreased in volume compared to the right; there are abnormal sulci and broadened gyri in the left frontoparietal regions suggesting pachygyria; there is an abnormally thickened and irregular cortex in the posterior left sylvian fissure suggesting cortical migration anomaly.

Treatment and prevention

There is no specific treatment for Zika virus infection and management is supportive. The key to preventing infection is avoiding exposure to the virus by preventing mosquito bites. A past Zika virus infection is likely to provide protection from future infection. Although there is no evidence that women who have had a past Zika virus infection are at risk of birth defects in future pregnancies, the possibility cannot be definitively excluded. To protect against Zika virus infection, pregnant women should avoid travel to areas with mosquito transmission, adhere to mosquito protective measures, and protect against sexual transmission (CDC Zika website).

Novel coronavirus (COVID-19)

Neurologic complications in pregnancy

There is a scarcity of published data on the effect of the novel coronavirus (COVID-19) on pregnant women and the developing fetus. Even less is known about neurologic complications in these unique populations.

Similar to nonpregnant women, the majority of symptoms in pregnant women are mild or absent (95.6% of women in a systematic review), and when present include fever (67–75%), cough (65–73%), and less often dyspnea, sore throat, fatigue, diarrhea, and myalgia (Elshafeey et al., 2020; Chen et al., 2020b). Less than 5% of women experienced headache or other neurologic symptoms. Pregnant women do not appear to have a higher risk of severe disease based on most recent data from China (Chen et al., 2020b).

Maternal viremia is reportedly low (1%) and transient, both suggestive of a low risk of intrauterine transmission (Wang et al., 2020). The virus has been identified by real-time reverse transcriptase-polymerase chain reaction tests in maternal nasopharyngeal samples, as well as in the placenta (Baud et al., 2020), of which the latter is associated with increased risk of miscarriage. Premature birth and stillbirths after maternal COVID-19 infection have been reported in various studies, although they were described as having similar rates to that in non-COVID infected mothers (Elshafeey et al., 2020; Yan et al., 2020; Yang et al., 2020). There is little to no evidence of vertical transmission in late trimester pregnancies; in one particular study, amniotic fluid, cord blood, neonatal throat swabs, and breast milk were all negative for virus

(Chen et al., 2020a). However there is a single report of a newborn that tested positive for COVID-19 by nasopharyngeal PCR testing at 16 h after delivery, without maternal contact, raising the concern for possible vertical transmission (Alzamora et al., 2020). There have been no reported neurologic manifestations of newborns or mothers with COVID-19. To date CSF has not been tested for COVID-19 infection in newborns or mothers.

As more women who were infected during their first and second trimester progress in their pregnancy, and as the newborns with COVID-19 infection develop, physicians will gain a better understanding of the neurologic effects of this novel virus. Neurologists should be on high alert for strokes and vasculitis, given the hypercoagulable state induced by the virus and the emergence of the COVID-19-associated pediatric inflammatory syndrome akin to toxic shock and Kawasaki disease. But for now, we can be reassured that intrauterine vertical transmission during third trimester pregnancies is highly unlikely and neurologic sequelae in the short term have not been observed in mothers or neonates.

PARASITIC INFECTIONS

Toxoplasmosis

Epidemiology and risk factors

Toxoplasmosis is caused by the obligate intracellular parasite *Toxoplasma gondii*. In the United States, the seroprevalence of *T. gondii* in women of reproductive age is estimated to be 15%, with an estimated incidence of 400–4000 cases per year (Jones et al., 2001; Paquet and Yudin, 2018).

Ninety percent of pregnant women with *T. gondii* infection do not exhibit symptoms. If symptomatic, pregnant women have symptoms similar to nonpregnant women with an influenza-like illness after 5–18 days of incubation (Paquet and Yudin, 2018; Sadiqui et al., 2018). Immunocompetent women rarely have neurologic manifestations during primary infection with *T. gondii*, whereas immunocompromised women are at risk of cerebral disease. The overall incidence of maternal cerebral toxoplasmosis during pregnancy is low, and only case reports exist on cerebral toxoplasmosis in immunocompetent women (Alapatt et al., 2009).

Acute infection of *T. gondii* during pregnancy can hematogenously spread to the placenta and can lead to severe neurologic complications in the fetus. The prevalence of congenital infection is 0.1–0.3 per 1000 live births (Kieffer and Wallon, 2013). Congenital transmission occurs almost exclusively in seronegative immunocompetent pregnant women who develop a primary infection, with the exception of women with immunosuppression who have reactivation of latent *T. gondii* (i.e., those with HIV coinfection with a reduction of CD4 count $<200 \times 10^6$ cells/L, those with immunosuppression from cancer, or transplant recipients on antirejection medications) (Halonen and Weiss, 2013). The rate of transmission from mother to child increases as gestational age at the time of infection increases, from 15% at 13 weeks, 44% at 26 weeks, and 71% at 36 weeks (Thiebaut et al., 2007; Kieffer and Wallon, 2013). In pregnant women with HIV coinfection, the incidence of congenital toxoplasmosis is low (0.72%), but can occur in those with normal CD4 cell counts. However, in an estimated 50% of women coinfected with HIV and toxoplasmosis, vertical transmission occurs with both diseases (O'Riordan and Farkas, 1998).

Pathophysiology

The intracellular parasite has three phases: the oocyst, which can remain infectious in soil and cat feces for more than 1 year; the tachyzoite, which divides rapidly and destroys infected cells throughout the host before transforming into the bradyzoite; and the viable cyst, which contains the bradyzoite and permanently remains within high affinity tissues (i.e., skeletal and cardiac muscle, brain, retina, and lymphoid tissue) (Halonen and Weiss, 2013). In an immunocompromised host, cyst rupture may reactivate the parasitic infection, which converts bradyzoites back to tachyzoites, leading to tissue injury. This differs from an immunocompetent host that can invoke a rapid immune response that limits damage, in the rare occasion when the cyst ruptures (Halonen and Weiss, 2013).

Humans are infected by cyst ingestion in undercooked or raw meat, mostly pork and lamb, or in the oocyst stage by direct contact with contaminated food, soil, or water, or handling of infected cat feces (Kieffer and Wallon, 2013). Following ingestion of oocysts, *T. gondii* then enters the blood stream via the intestinal epithelium. Pregnant women are advised to wear gloves when handling a litter with cat feces, although the risk of infection by domestic animals is fairly low. Cats become contaminated by ingesting other animals infected by *T. gondii*, and shed noninfectious oocysts in their feces 1–2 weeks after exposure. In a warm and humid environment, these oocysts can be infectious for many months. Thus the seroprevalence of *T. gondii* is higher where people regularly consume raw meat (e.g., France has a seroprevalence of 54%) and in Latin America or Sub-Saharan Africa where cats are more numerous and/or the climate is ideal for oocysts (Jones et al., 2001).

Congenital toxoplasmosis is due to primary infection with *T. gondii* during pregnancy. Transplacental passage of the trachyzoite via vertical transmission infects the fetus (Halonen and Weiss, 2013; Kieffer and Wallon,

2013). Whereas the risk of transmission increases with gestational age, the severity of disease decreases with gestational age, with first trimester infections often leading to spontaneous abortion or serious complications as alluded to in the following test. Primary infection in immunocompetent individuals may affect the CNS of the developing fetus, or cause opportunistic infection in immunosuppressed individuals (Pittella, 2013).

Signs and symptoms in the pregnant woman

Immunocompetent pregnant women will commonly be asymptomatic during acute infection with toxoplasmosis, or will exhibit flu-like symptoms of fevers, malaise, cough, and congestion.

Cerebral toxoplasmosis

Cerebral toxoplasmosis with necrotizing encephalitis can occur if latent infection is reactivated in the brain of an immunosuppressed pregnant woman. Cerebral toxoplasmosis is considered the most common opportunistic infection in AIDS. Clinical manifestations include headache, fever, focal deficits, seizures, confusion, ataxia, lethargy, and visual alterations (Halonen and Weiss, 2013). It often causes multifocal intracranial lesions that appear as T2 hyperintense and T1 hypo- or isointense signals, with perilesional edema and ring-enhancement on T1-postcontrast sequences. Single cerebral lesions can be present in 14%–17% of patients (da Cunha Correia et al., 2012). In pregnancy, the risk of intracranial hemorrhage increases because of increased cardiac output, blood volume, vasodilation, and other hormone related changes. Hemorrhages secondary to toxoplasmosis may be larger. A favorable clinical response is expected within 14 days of treatment of cerebral toxoplasmosis; thus, early recognition and diagnosis is essential.

Prenatal diagnosis

Pregnant women are diagnosed with acute infection by serologic testing. There is no consensus regarding universal screening of pregnant women for toxoplasmosis, yet there are reported associations between early treatment and reduction in the vertical transmission of toxoplasmosis (de Oliveira Azevedo et al., 2016). In the United States, where there is a low incidence of *T. gondii*, prenatal testing is not routinely done. This compares to other countries, such as Morocco and France, with a higher incidence that screen pregnant women for *T. gondii* infection during the first trimester then monthly or every subsequent trimester.

In the first 2 weeks of an acute infection, *T. gondii*-specific IgM and IgG antibody levels rise, with the latter lagging in time. A positive IgG and negative IgM is suggestive of an infection of at least 6 months duration. IgM antibodies can persist for up to 18 months after infection and can be nonspecific; thus, IgM antibodies alone cannot be considered a reliable marker of acute disease (Halonen and Weiss, 2013; Kieffer and Wallon, 2013). In a study conducted in Pakistan, where the authors found a high prevalence of toxoplasmosis (24.8%), 54 patients were seropositive for toxoplasma IgG, 40 cases for Toxo-IgM, and 30 cases for both IgG and IgM antibodies. A high percentage of IgM seropositivity was seen in the first trimester, indicating a predilection to infection early in pregnancy (Sadiqui et al., 2018). An IgG avidity test was developed to help determine the timing of infection by measuring the strength of IgG binding to the organism. Low avidity IgG antibodies are consistent with an acute infection. This is helpful for counseling mothers, as infection before pregnancy does not result in transmission in utero. If acute infection is confirmed in the pregnant mother, fetal infection can be confirmed by amniocentesis after 18 weeks of gestation, and at least 4 weeks after primary maternal infection (Halonen and Weiss, 2013). Real-time PCR for the detection of *T. gondii* can predict poor prognosis in early infections when parasite quantification is greater than 100/mL (Kieffer and Wallon, 2013). The global sensitivity of the PCR test as reported by a meta-analysis was 87% and the specificity was 99% when tested up to 5 weeks after maternal diagnosis (de Oliveira Azevedo et al., 2016).

Signs and symptoms in the fetus

Congenital toxoplasmosis is classically a triad of chorioretinitis, hydrocephalus, and intracranial calcifications, described by Sabin (1942) and Sabin and Feldman (1949). If contracted early in pregnancy, maternal toxoplasmosis can also lead to spontaneous abortion or severe neurologic complications. Third trimester infections are usually subclinical, and some infected individuals develop chorioretinitis or neurologic disability later in life. The incidence of brain lesions have been reported as: 30% at 5 weeks gestation, 10% at 20 weeks gestation, and less than 5% at 28 weeks (Thiebaut et al., 2007; Kieffer and Wallon, 2013).

Antenatal ultrasound scans are normal in two-thirds of newborns, unless the infection occurred early in pregnancy. Hydrocephalus is thought to be secondary to the sloughing of periventricular necrotic tissue and subsequent obstruction of the aqueduct of Sylvius and/or the foramen of Monroe (Kieffer and Wallon, 2013). Chorioretinitis, the most common ocular lesion seen in toxoplasmosis, is because of necrosis and inflammation in the retinal tissue. Systemic manifestations often noted occur in the newborn, including fever, hepatosplenomegaly, jaundice, lymphadenopathy, anemia, and abnormal

spinal fluid (Kieffer and Wallon, 2013; Maldonado and Read, 2017). Infants can also develop seizures and other serious neurologic sequelae, such as intellectual disability or blindness.

Treatment and prevention

Parasitostatic spiramycin is started in pregnant women with acute infection with *T. gondii*, to prevent vertical transmission. Spiramycin concentrates in but does not readily cross the placenta (Paquet and Yudin, 2018). It is given at a dose of 1 g (3 million U) every 8 h. If fetal infection is confirmed, spiramycin is replaced by parositocidal pyrimethamine and sulfadiazine with folinic acid. This combination is thought to reduce the risk of clinical manifestations in the fetus, though the evidence is controversial. In a European systemic review, which included 550 infected liveborn infants, the authors found no evidence that prenatal treatment significantly reduced the risk of clinical manifestations (Thiebaut et al., 2007). Folinic acid is used specifically for the side effect of reversible, dose-dependent bone marrow depression. Pyrimethamine is potentially tetratogenic and is not recommended for use in the first trimester. In immunocompromised pregnant women with CD4 < 200 cells/mm^3, primary prophylaxis is recommended.

Malaria

Epidemiology and risk factors

Malaria is a protozoan disease caused by four species of the genus. Malaria is endemic in most countries, except the United States, Canada, Europe, and Russia. It is responsible for 1.5–2.7 million deaths annually, mainly from cerebral malaria and multiorgan dysfunction. Cerebral malaria is a life-threating complication of the disease caused primarily by *Plasmodium falciparum*, occasionally by *Plasmodium vivax* (Murthy et al., 2014). Cerebral malaria occurs in approximately 1% of infected individuals and causes 15%–20% mortality despite appropriate treatment. Patients who survive often recover fully with little-to-no long-term consequences. Worldwide, cerebral malaria occurs mostly in African children younger than 5 years of age and Asian adults. Children have a more rapid onset of neurologic symptoms, with coma, seizures, and focal neurologic deficits, whereas adults tend to have multiorgan failure in conjunction with neurologic dysfunction (Postels and Birbeck, 2013).

Pregnant women have a three times higher risk of severe malaria compared to nonpregnant women (Seal et al., 2010; Kovacs et al., 2015). Young maternal age and lower immunity (i.e., exposure to) malaria are both independent risk factors for severe disease (Kovacs et al., 2015; Bauserman et al., 2019). In one prospective observational study over a 5-year period, pregnant women had a statistically significant increase in incidence of anemia, cerebral malaria, renal failure, hepatic failure, hypoglycemia, hypotension, and death compared to nonpregnant women. Twelve maternal deaths in the case series were secondary to cerebral malaria (Seal et al., 2010). According to a recent CDC Malaria Surveillance in the United States, 32 pregnant women were diagnosed with malaria in 2015, 27 (84.4%) of whom were hospitalized, 12 with severe malaria. All women in this report recovered after appropriate treatment, though it was not stated if any had cerebral malaria (Mace et al., 2018).

Congenitally acquired malaria is seldom reported in the United States, and occurs primarily in children of recently immigrated mothers (Mace et al., 2018). The true prevalence of congenital malaria is undetermined, but thought to be anywhere from <1% to up to 33% in highly endemic areas (Bauserman et al., 2019). The incidence of congenital malaria has been reported from 0.3% in immune mothers to 7.4% in nonimmune mothers. Maternal antimalarial antibodies transferred to the fetus and the placenta themselves decrease the frequency of congenital infection. Congenital malaria is thus more commonly seen in newborns of women who have low immunity (i.e., mothers raised in nonendemic areas or mothers who migrated to malaria-free areas with subsequent loss of immunity) (Bauserman et al., 2019). Malaria acquired during pregnancy is a significant contributor to spontaneous abortion, stillbirth, prematurity, and early neonatal mortality.

Pathophysiology

Humans are infected by the bite of a female *Anopheles* mosquito, which inoculates the plasmodial sporozoite into the body. This sporozoite enters the hepatocyte, multiplying and releasing merozoites. Merozoites go onto invade the RBCs and continue to divide every 48 h through the erythrocyte cycle.

Malaria parasites change RBC membrane characteristics, including new membrane protuberances that appear after 12–15 h of *P. falciparium* invasion and export proteins (PfEMP1, VAR2CSA) that are involved in cytoadherence to endothelial cells (Murthy et al., 2014). Intracellular adhesion molecule 1 is an important vascular ligand for cytoadherence found in the brain. Parasitized RBCs adhere to capillary endothelium, and release cytokines that lead to vasodilation, edema, and ischemia (Rasalkar et al., 2011). Cerebral damage in malaria is due to vascular sequestration of parasitized erythrocytes and cerebral toxicity by cytokines.

In transplacental infection, there is preferential accumulation of parasites in the placental intervillous space

(Bauserman et al., 2019). The VAR2CSA erythrocyte membrane protein adheres to the ligand chondroitin-sulfate A on placental tissue, which activates mononuclear cells and mediates the effects on the fetus. Maternal antibodies against VAR2CSA are protective. *P. vivax* infection can also lead to placental changes; however, no studies have demonstrated the evidence of *P. vivax* infected cells in the placenta.

Signs and symptoms in the pregnant woman

The natural immune suppression during pregnancy can induce a relapse of malaria. Most women with primary or relapsed malaria infection during pregnancy report a febrile illness.

Cerebral malaria

Cerebral malaria is defined as "unarousable coma (Glasgow Coma Scale (GCS) </10 or Blantyre scale </3) with presence of asexual parasites in blood and in which locally prevalent encephalitis and meningitis has been ruled out by appropriate tests" (Murthy et al., 2014). Clinical features are variable, and can include encephalopathy, focal or generalized seizures and status epilepticus, hypertonicity, extensor plantar reflexes, neck stiffness, and/or cranial nerve involvement. In advanced stages, decerebrate and decorticate rigidity are frequently observed. Disease is often severe in children, nonimmune travelers, and pregnant women.

Classically in cerebral malaria, T1 and T2 MRI imaging shows significant hemorrhage or infarction with edema. SWI sequences are more sensitive in the detection of petechial hemorrhages in various locations (cerebral white matter, corpus callosum, brain stem, and cerebellum) (Murthy et al., 2014). Several case reports describe the MRI findings of cerebral malaria, with increased brain volume being the most common finding. In a report of four adults with cerebral malaria, all patients had bilateral thalamic involvement (Gupta and Patel, 2008; Rasalkar et al., 2011). CNS vasculopathy has also been a reported consequence of cerebral malaria, with magnetic resonance angiography (MRA) evidence of multifocal segmental narrowing of cerebral arteries (Yamamoto et al., 2018). It is not known if this is due to direct infectious vasculitis, reversible cerebral vasoconstriction, or postinfectious inflammatory vasculopathy.

Prenatal diagnosis

Malaria is primarily a clinical diagnosis and can be confirmed by the presence of parasites on the peripheral smear or immunologic tests for parasite-derived proteins. Microscopic examination of stained thick and thin peripheral blood smear is the gold standard for confirmation of malaria, as it is cost effective, fairly sensitive, and highly specific. PCR, which has a high sensitivity and can detect one parasite per mL of blood (Murthy et al., 2014), can also be used for diagnosis. In a case report of cerebral malaria in a pregnant Spanish woman who presented with a febrile illness and progressed to GCS 7, a second blood smear during a febrile peak was required for diagnosis (i.e., revealed abundant malarial protozoa) after a negative initial blood smear for *P. falciparum* (Curiel Balsera et al., 2008).

Signs and symptoms in the fetus

Malaria is an important cause of stillbirth pregnancy in endemic areas, and contributes to 12%–20% of stillbirths in sub-Saharan Africa (Bauserman et al., 2019). Malaria also increases the risk of low birth weight (LBW) secondary to IUGR and prematurity. LBW independently is associated with a 3–20-fold increase in the probability of infant mortality in Africa. Up to 36% of preterm births in endemic areas are attributed to *P. falciparum* infection in pregnancy and incomplete or inadequate treatment.

Congenital malaria is diagnosed in the first 7 days of life by peripheral blood smear. Although symptoms typically become apparent between 10 and 30 days of life or later, it is important to recognize and treat the infant early as congenital malaria progresses rapidly and has the potential to be fatal (Bauserman et al., 2019).

Treatment and prevention

In malaria-endemic areas, mefloquine is the only approved chemoprophylaxis, and mefloquine and quinine with clindamycin are prescribed to treat uncomplicated malaria in pregnancy. In areas with chloroquine sensitive malaria, pregnant women with uncomplicated disease can use chloroquine for preventative chemoprophylaxis.

Severe malaria, including cerebral malaria in pregnant women is considered life-threatening. If diagnosis is delayed, specific antimalarial treatment should be empirically started based on clinical suspicion. All patients with severe malaria, including pregnant women, should be treated with parenteral artemisinin derivatives or quinine. Although artemisinin are embryotoxic and teratogenic in animal studies, the World Health Organization (WHO) recommends their use in the first trimester for severe malaria because of a high risk of maternal mortality (Bauserman et al., 2019). Data in the use of artemisinin in the first trimester in humans has shown no increased risk of adverse pregnancy outcomes. Intravenous (IV) artesunate is preferred in adults and is administered in the dose of 2.4 mg/kg body weight, at 12 and 24 h, then once a day for 7 days. Once the patient can take oral therapy, switch treatment to artemisinin-based combination therapy for 3 days. Alternatively, quinine with

clindamycin is given (Murthy et al., 2014; Kovacs et al., 2015; Bauserman et al., 2019). Quinine is used less often because of the low tolerability of side effects (prolonged cardiac QT interval, tinnitus, headache, blurred vision, nausea, diarrhea, and rarely hemolysis).

Hypoglycemia is common in pregnant women and should be treated by IV 25% glucose. There is also a high incidence of pulmonary edema and hypoglycemia in pregnant women. In uncomplicated (i.e., non-cerebral) *P. falciparum* infection during pregnancy, IV artesunate is preferred in the second and third trimesters, whereas a 7-day course of quinine and clindamycin are the drugs of choice for the first trimester.

In all areas with moderate to high malaria transmission in Africa, the WHO recommends intermittent preventive treatment starting in the second trimester of pregnancy with sulfadoxine–pyrimethamine (World Health Organization, 2018; Bauserman et al., 2019). Dapson crosses the placenta and has also been safely used as prophylaxis for malaria in pregnancy, except in the case of G6PD deficiency because of the risk of maternal and fetal hemolytic anemia.

For newborns less than 5 kg with congenital malaria, there are no specific treatment recommendations and many of the standard antimalarial medications are restricted in their use at this age (World Health Organization, 2015). In newborns, specific treatments are advised against because of known side effects of sulfadoxine–pyrimethamine, primaquine, and tetracyclines. Artemisinins are thought to be safe in children, though again the doses and formulations are difficult to determine without sufficient evidence and, thus, rarely used.

BACTERIA

Group B streptococcus (GBS)

Epidemiology

The incidence of GBS colonization in pregnancy is 10%–30% (Verani et al., 2010). With the use of intrapartum prophylaxis, it has decreased to 0.35 cases per 1000 live births from around 1.7 cases per 1000 live births in the 1990s (Verani et al., 2010). Most cases of early-onset GBS occur in infants older than 37 weeks gestation. Risk factors include young maternal age, African American race, maternal fever during labor, prolonged rupture of membranes (>18 h), and preterm labor (Schuchat et al., 2000).

Pathophysiology

Vertical transmission to the fetus takes place either through the vagina during labor or as a result of an ascending infection into the amniotic fluid with or without membrane rupture (Schrag and Verani, 2013).

Signs and symptoms in the pregnant woman

GBS in pregnant women is primarily asymptomatic, and only 0.5%–1% of mothers who test positive develop any signs or symptoms of the disease. GBS may present as amnionitis, endometritis, cystitis, or stillbirth, and rarely as endocarditis or meningitis. GBS may also lead to urinary tract infection or pelvic abscesses in the postpartum period (Smith and Basistha, 2018).

Prenatal diagnosis

In the United States, current recommendations are to obtain vaginal and rectal swab screening for GBS culture in all pregnant women at 35–37 weeks gestation (Centers for Disease Control and Prevention, 2013).

Signs and symptoms in the fetus

The onset of GBS in the fetus can be classified as either early (infection less than 7 days) or late (infection more than 7 days after birth). The incidence of late-onset disease is higher compared to early-onset disease. Neonatal sepsis is the most common manifestation of early-onset GBS. Late-onset GBS usually presents as meningitis approximately 1 week to 3 months after birth (Verani et al., 2010). The decision to provide treatment is based on the Bacterial Meningitis Score (Dubos et al., 2008). It consists of positive CSF gram stain, CSF absolute neutrophil count (ANC) $\geq$ 1000/μL, CSF protein level $\geq$80 mg/dL, peripheral blood ANC $\geq$10,000/μL, and history of seizures. CT and MRI may reveal signs of increased intracranial pressure such as ventriculomegaly and sulcal effacement. Long-term sequelae are loss of hearing or vision and learning disabilities.

Treatment and prevention

In a GBS positive pregnant woman, the preventative regimen is to administer 5 million U of IV Penicillin G (or 2 g of IV Ampicillin) as a loading dose to the mother followed by 3 million U of IV Penicillin G (or 1 g IV Ampicillin) every 4 h until delivery (American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2011). The treatment of GBS meningitis in infants is the administration of IV cefotaxime for at least 2 weeks (NICE CG, 2012). Several ongoing clinical trials are involved in developing vaccines to prevent GBS infection.

Listeriosis

Epidemiology

Listeriosis is caused by *Listeria monocytogenes*, which is a facultative, intracellular, and Gram-positive bacillus. Infection is acquired by consuming contaminated food (dairy products, deli meat, raw vegetables, smoked fish, etc.) (Centers for Disease Control and Prevention, 2019b). Pregnant women are more commonly affected than nonpregnant women, with an incidence of 17% in pregnancy (Silk et al., 2012).

Pathophysiology

Listeria is transmitted to the fetus through the transplacental route while in utero or by contamination during delivery. Nosocomial transmission in the newborn nursery is also common. Early infection in the neonate occurs in the first 5 days following delivery while late infection develops more than 5 days after delivery (Mylonakis et al., 2002). The CNS infections can present up to 2–3 weeks after delivery.

Signs and symptoms in the pregnant woman

Listeriosis in a pregnant woman may be asymptomatic or lead to a febrile illness. Diagnosis is confirmed based on positive blood cultures. Premature labor, miscarriage, stillbirth, chorioamnionitis, and maternal sepsis have been reported from clinical as well as occult infection during pregnancy (Boucher and Yonekura, 1986).

Prenatal diagnosis

Diagnosis is based on isolating the organism from the amniotic fluid, blood, or CSF.

Signs and symptoms in the fetus

Disseminated granulomatous lesions with micro abscesses may be seen. Granulomatosis infantisepticum occurs less frequently, and the classic syndrome includes granulomatous pneumonia and granulomas in skin, liver, and other locations (Mylonakis et al., 2002; Janakiraman, 2008). Long-term neurologic sequelae include hydrocephaly, delayed neurologic development, and other symptoms.

Treatment

The first-line treatment for bacteremia is Ampicillin 6 g/day IV for 7–14 days. In acute meningitis, gentamicin should be added and the duration of treatment is 3 weeks (Janakiraman, 2008). The second-line treatment for meningitis is trimethoprim (TMP) 200 mg and sulfamethoxazole (SMX) 320 mg for 3 weeks. Brain abscesses are treated with Ampicillin 14 g/d IV plus gentamicin 2.5 mg/kg/d for 4–6 weeks or an alternative regimen is TMP/SMX 200–320 mg for 4–6 weeks (Temple and Nahata, 2000; Janakiraman, 2008). Currently no vaccine is available and prevention in pregnant women is by washing raw vegetables and cooking all raw food.

Syphilis

Epidemiology

Syphilis is a significant global health problem. The incidence rate of syphilis in 2012 globally was 1.5 cases per 1000 females (World Health Organization, 2016). Maternal syphilis has been associated with substance abuse, especially crack cocaine, inadequate prenatal care, and screening and treatment failures leading to reinfection.

Pathophysiology

Syphilis is a STI due to *Treponema pallidum* (*T. pallidum*). It is acquired by 50% of people after unprotected sex with an infected person with early syphilis. *T. pallidum* replicates in vaginal mucosa and then spreads through lymphatic channels within hours to days. Incubation period averages 3 weeks based on host factors and size of inoculum.

The fetal infection occurs through several routes. Transplacental transmission is the most common route and the spirochetes can infect the fetus from about 14 weeks gestation, and the risk of fetal infection increases with gestational age (Goldenberg and Thompson, 2003). Other routes of neonatal infection include direct contact with spirochetes.

Signs and symptoms in the pregnant woman

Maternal syphilis can lead to preterm labor, stillbirth, IUGR, and significant neonatal infection (Krakauer et al., 2012). Maternal syphilis is classified as primary or secondary based on clinical features and duration of disease. In primary syphilis, a chancre develops at the inoculation site. Chancres are painless, red, raised lesions with firm border and smooth base, and are characteristic of the disease. Chancres usually resolve in 2–8 weeks even when untreated. Multiple lesions and nonsuppurative lymphadenopathy may also be noted, especially in women coinfected with HIV.

Secondary syphilis results from disseminated disease and affects multiple organ systems. Signs and symptoms develop 4–10 weeks after the appearance of chancre and consist predominantly of dermatologic signs in up to 90% of women. A diffuse macular rash, plantar and palmar target-like lesions, patchy alopecia, and mucous patches are commonly noted. Condyloma lata, which are flesh-colored papules and nodules in perineum and

perianal area may develop as well. CSF abnormalities are noted in up to 40% of infected individuals although only 1%–2% will present with clinically apparent meningitis. Hepatitis, nephropathy, ocular changes, anterior uveitis, and periostitis are other forms of clinical presentation. Latent syphilis develops as a result of untreated primary or secondary syphilis. While the clinical signs and symptoms have resolved, the serologic testing is still reactive. Early latent syphilis is disease acquired within the preceding 12 months, whereas syphilis diagnosed beyond 12 months is either late or of unknown duration. Tertiary syphilis is a slowly progressive disease rarely observed in women of reproductive age. Infiltrative tumors of bone, liver, and skin (gummata) (15%), neurosyphilis (7%), and cardiovascular problems (10%) can be seen in tertiary syphilis approximately 3–15 years after the initial infection (De Santis et al., 2012).

Prenatal diagnosis

As per the United States Preventative Services Task Force recommendations, all pregnant women must be tested for syphilis to prevent congenital infection. All US states mandate testing at the first prenatal visit. Screening for infection is done quantitatively either by Venereal Disease Research Laboratory (VDRL) or the rapid plasma reagin test. As titers reflect disease activity, the titers are high during early syphilis and, often, more than 1:32 in secondary syphilis. Following treatment, serologic testing at 3–6 months usually confirms a fourfold drop in VDRL titers. Other options for diagnosis are treponemal-specific tests, such as the fluorescent treponemal-antibody absorption test (FTA-ABS), the micro hemagglutination assay for antibodies to *T. pallidum* (MHATP), or the treponema pallidum passive particle agglutination (TP-PA) test. These treponemal-specific tests tend to remain positive throughout life.

Signs and symptoms in the fetus

Congenital syphilis is difficult to diagnose on prenatal ultrasound as the infected fetus does not have any specific abnormal sonographic signs. However, sonographic findings suggestive of disease include hydrops fetalis, hepatomegaly, ascites, placental thickening, and elevated middle cerebral artery Doppler velocimetry measurements (Rac et al., 2014). Polymerase chain reaction detects *T. pallidum* in amniotic fluid, and treponemal DNA has been found in 30% of pregnancies infected before 20 weeks (Nathan et al., 1997).

Congenital neurosyphilis may be symptomatic or asymptomatic. CSF findings suggestive of neurosyphilis include more than 25 WBC/mm^3 and protein greater than 150 mg/dL (170 mg/dL in premature infants). Increased levels of CSF tau protein may be a useful adjunct in differentiating neurosyphilis from syphilis without nervous system involvement. It is also important to note that normal CSF indices do not exclude neurosyphilis. Neurologic manifestations of late congenital syphilis include intellectual disability, hydrocephalus, seizures, and cranial nerve abnormalities. Hutchinson's triad is a pattern recognized in children with congenital syphilis and consists of Hutchinson's teeth (notched, small, widely spaced teeth), eighth nerve deafness, and interstitial keratitis.

Treatment

Penicillin G, administered parenterally, is the preferred drug for treating persons in all stages of syphilis. The preparation, dosage, and duration of treatment depend on clinical manifestations and stage of the disease (Centers for Disease Control and Prevention, 2016). Children with symptomatic congenital syphilis should undergo a complete blood count, lumbar puncture, and long bone radiography before treatment initiation. If these tests are normal, a single intramuscular dose of benzathine Penicillin G (50,000 units/kg up to the adult dose of 2.4 million units in a single dose) is recommended. With abnormal test results or concerns for noncompliance, a 10-day course of either aqueous crystalline Penicillin G (50,000 units/kg IV every 12 h for the first 7 days of life, and then every 8 h for the next 3 days) or procaine penicillin (50,000 units/kg/day IM) should be administered. Parenteral Penicillin G is the only documented therapy efficacious in syphilis during pregnancy. Pregnant women with penicillin allergy should be desensitized and treated with penicillin (Centers for Disease Control and Prevention, 2016).

Tuberculosis

Epidemiology

In 2011, more than 200,000 cases of active TB were estimated worldwide among pregnant women, with the greatest burden in Africa and Southeast Asia (Sugarman et al., 2014). In North America, the incidence of TB reported in pregnancy was 26.6 per 100,000 births (El-Messidi et al., 2016).

Pathophysiology

Transmission to the child may occur in utero by hematogenous spread through the umbilical vein, aspiration, or swallowing of infected amniotic fluid, or at the time of labor by contact with infected amniotic fluid or genital secretions (Saramba and Zhao, 2016). Postpartum infection happens far more often. It is via aerosol spread, or through infected breast milk from an active tuberculous lesion in the breast. Postnatal contamination from a

family member or close contact is also possible. Transmission of disease through breast milk otherwise does not occur (Baquero-Artigao et al., 2015).

Signs and symptoms in the pregnant woman

One of the most severe clinical forms of TB occurs when the organism infects the CNS. Neurologic involvement is seen in 5%–10% of extrapulmonary TB cases, and 1% of all patients with TB (Cherian and Thomas, 2011). Lesions (Rich foci) may develop in the meninges, subpial or subependymal surfaces of the brain, or the spinal cord, and may sometimes remain dormant for years. When active, the disease course evolves over 1–2 weeks. The degree of CNS involvement depends on the proximity to subarachnoid space. Meningitis develops as a result of rupture into the subarachnoid space, whereas deep parenchymal infiltration can lead to tuberculomas or abscesses. Cranial nerve involvement is common in tubercular involvement of the base of brain. Acute hydrocephalus might ensue, secondary to infiltration of blood vessels from thick exudate, leading to inflammation, obstruction, and infarction, and may require a shunt as treatment.

Head CT or brain MRI that shows basal meningeal enhancement with hydrocephalus is strongly suggestive of TB meningitis. Other neuroimaging findings include cerebral edema, infarction, tuberculoma, and ventriculitis.

In advanced disease in the puerperium as well as in those with HIV coinfection, the prognosis is very poor. A higher rate of spontaneous abortion, small for gestational age, LBW, preterm labor, and suboptimal weight gain in pregnancy are other complications (Ormerod, 2001).

Prenatal diagnosis

Two main tests are available to detect latent or active tuberculosis. Tuberculin skin test is one of the most common tests used globally. A positive test result measures $\geq$5 mm in diameter and requires evaluation for active disease, including a chest radiograph (Taylor et al., 2005). Interferon-gamma release assay (IGRA) is now becoming the preferred testing method (Horsburgh Jr. and Rubin, 2011). IGRAs measure interferon-gamma release in blood in response to tuberculosis antigens. For those who have received bacilli Calmette-Guerin (BCG; i.e., the vaccine against TB), IGRA testing is preferred (Mazurek et al., 2010).

Diagnosis of tuberculosis in pregnancy is sometimes challenging due to the nonspecific symptoms of lassitude, loss of appetite, nausea, vomiting, and low-grade fever, which may be erroneously attributed to the pregnancy, and the normal weight changes in pregnancy may mask the associated weight loss seen in active TB.

Lumbar puncture is used to diagnose tubercular meningitis. CSF findings include elevated leucocyte count with a lymphocytic predominance, elevated protein (100–800 mg/dL), and decreased glucose concentration (20–40 mg/dL). CSF smear is positive in only 10% cases and CSF culture (gold standard) in 25%–70% of cases. A high adenosine deaminase value indicates tubercular etiology. TB PCR when available may also aid in diagnosis (Singh et al., 2015).

Signs and symptoms in the fetus

The diagnostic criteria for neonatal tuberculosis developed by Cantwell includes presence of a primary hepatic caseating granuloma on liver biopsy at birth, tuberculosis infection of the maternal genital tract or placenta, and the presence of tuberculous lesions during the first week of life (Cantwell et al., 1994).

Treatment

See Table 5.2 for the standard treatment regimens for tuberculosis in pregnancy.

Table 5.2

Standard treatment of tuberculous in pregnancy

Latent TB infection in pregnant woman	Isoniazid (INH) daily or twice weekly for 9 months, with pyridoxine supplementation
TB in pregnant woman	INH, rifampin (RIF), and ethambutol daily for 2 months, followed by INH and RIF daily, or twice weekly for 7 months (total of 9 months)
HIV-related TB disease in pregnant woman	Same as for nonpregnant women but with attention to considerations like drug interactions
Additional for meningitis in pregnant woman	Dexamethasone should be given in HIV negative patients for 3 weeks, tapered over next 3 weeks
All infants of mothers with TB	6 months of INH followed by BCG vaccination

References: Singh (2015); Centers for Disease Control and Prevention, 2016. Emergency preparedness and response: recognizing, managing, and reporting Zika virus infections in travelers returning from Central America, South America, the Caribbean, and Mexico. http://emergency.cdc.gov/han/han00385.asp (accessed on January 18, 2016); Mittal, H., Das, S., Faridi, M.M., 2014. Management of newborn infant born to mother suffering from tuberculosis: current recommendations & gaps in knowledge. Indian J Med Res 140, 32–39.

OVERVIEW OF SEQUELAE OF INFECTION DURING PREGNANCY

Maternal-to-fetal transmission of infection as delineated in the discussion on specific pathogens, can manifest with a variety of abnormalities in fetuses/infants. The extent of injury is dependent on the timing of the damage during fetal development and the cellular population affected in the nervous system. In this section, we describe some common neurologic manifestations of CNS infections acquired during pregnancy (Table 5.3).

Hydrocephalus

Fetal and neonatal hydrocephalus can occur as a result of perinatal infection with toxoplasma, syphilis, CMV, and other diseases, or as a result of intraventricular hemorrhage due to premature delivery. Because babies have a distensible skull due to nonfusion of the sutures, hydrocephalus most often presents with increased head circumference and fullness of the anterior fontanelle (Aquilina, 2015). Assessment of treatment of the hydrocephalus is complex and depends largely on whether CSF resorption can normalize with time. In cases where intraventricular hemorrhage is the driving factor resulting in impaired resorption of CSF, several interventions have been trialed. Randomized controlled trials have shown that neither early and repeated lumbar punctures (Ventriculomegaly Trial Group, 1990) nor addition of furosemide and acetazolamide (Kennedy et al., 2001) impacts need for permanent shunt insertion. An invasive process called "drainage, irrigation and fibrinolytic therapy," has been associated with lower incidence of death or severe disability at 2 years postintervention, though the original study was stopped early because of rebleeding episodes in two patients in the treatment arm (Whitelaw et al., 2007, 2010). The desire to avoid ventriculoperitoneal shunts (VPS) is due to several factors. Premature neonates cannot tolerate VPS until they are at least 2 kg in weight, and they may need to be temporized with a ventriculosubgaleal shunt or a ventricular access device with repeated percutaneous taps (Limbrick Jr et al., 2010). Once placed, a VPS often requires frequent revisions to prevent overdrainage as the child grows, as well as to deal with malfunctions, infections, obstructions, and the child's growth (Couldwell et al., 1996; Drake et al., 1998). Further, as a child grows hydrocephalus ex vacuo can also develop due to cerebral atrophy, which can complicate the assessment of whether shunting is still required (McAllister II and Chovan, 1998). VPS cannot be placed in situations where there is an active CSF infection, very elevated CSF protein, significant blood within the ventricular system, peritoneal inflammation, or infection because of risk of shunt superinfection or obstruction of the shunt tubing (Aquilina, 2015). In situations where CSF resorption will likely not improve and VPS is contraindicated, an alternative to VPS is endoscopic third ventriculostomy, though its efficacy has been called into question in neonates and infants (Drake and Canadian Pediatric Neurosurgery Study Group, 2007; Ogiwara et al., 2010).

Seizures

Neonatal seizures can occur as a result of intracranial calcifications, meningoencephalitis, or encephalomalacia. Neonates with first time seizure need to be fully worked up with infectious screens (Bui et al., 2002). Using EEG to detect subclinical or subtle clinical seizure activity, which can ultimately affect cerebral development (Massey et al., 2018), is a strong consideration. In neonates, paroxysmal events may be incorrectly identified as seizures as the majority of electrographic seizures do not have clinically apparent correlates (Murray et al., 2008). Seizures should be treated with antiseizure medications, and if a single cerebral lesion that can be surgically resected is identified, consideration should be given to a surgical cure for refractory seizures.

Blindness

Visual loss can be due to a myriad of abnormalities including keratitis, conjunctivitis with corneal scarring, cataracts, chorioretinitis, retinal coloboma, retinal detachments, and optic hypoplasia or atrophy. Notably, even if asymptomatic at birth, children with congenital toxoplasmosis can develop blindness in adolescence or adulthood as a result of delayed chorioretinitis (Koppe et al., 1986). Some visual impairment can improve with surgery or aggressive infectious treatment, while others are fixed or progressive despite treatment.

Hearing loss

SNHL can occur with several infections and may often manifest as poor development of speech. The timing of the hearing loss can occur after birth so neonatal hearing screening programs may not identify babies at risk for developing hearing loss in the future. Antimicrobials directed at the underlying infection may help slow the rate of hearing loss or even improve hearing depending on the infection. Otherwise patients may need hearing aids or cochlear implants and early intervention (Korver et al., 2017).

Developmental delay

Developmental delay can result as the long-term sequelae of cortical hypoplasia, calcifications, or

Table 5.3

Major fetal and neonatal characteristics of CNS infections in pregnancy

Organism	Route of transmission to fetus	Trimester with highest rates of transmission[a]	Neurologic signs and symptoms of congenital or neonatal infection	Fetal brain imaging	Treatment of neonatal CNS infection[b]
Viruses					
Herpes simplex virus	Direct or indirect contact in vaginal canal of infected mothers	3rd ≫ 2nd	Seizures, tremors, altered mental status, temperature instability; bulging fontanelle, microcephaly, chorioretinitis, microphthalmia, and hydranencephaly; long-term neurodevelopmental disability	Ventriculomegaly on US; infarcts, hydrocephalus, edema on MRI	Acyclovir
Parvovirus	Primarily respiratory droplets, also by blood, and transplacental	1st ≫ 2nd	Rare neurologic effects on fetus (hydrocephalus, cerebellar hemorrhage, polymicrogyria)	No known imaging findings	Supportive
Cytomegalovirus	Transplacental, contact with infected cervicovaginal fluids during birth, ascending from genital tract	3rd ≫ 2nd > 1st	SNHL, microcephaly, chorioretinitis, hypotonia, poor feeding, rare seizures; long-term neurodevelopmental disability	Periventricular calcifications, ventriculomegaly, microcephaly, cortical anomalies, intraventricular septa, temporal pole lesions on MRI	Supportive
Varicella zoster virus	Reactivation of latent virus, respiratory droplets, skin lesions, transplacental	1st = 2nd	Microcephaly, hydrocephaly, cerebellar hypoplasia, intellectual disability	Microcephaly, hydrocephaly, cerebellar hypoplasia on US	VZIG to exposed neonates
Zika virus	Transplacental	1st	Microcephaly, cerebral calcifications, ventriculomegaly, seizures, hyperreflexia, irritability, SNHL	Microcephaly, calcifications, ventriculomegaly on US	Supportive
Rubella virus	Transplacental	$1^{st} \gg 2^{nd}$ Risk of CRS highest in 1st trimester	SNHL, microphthalmia, cataracts, retinopathy; patent ductus arteriosus, pulmonary artery stenosis; microcephaly, developmental delay, intellectual disability, meningoencephalitis; hepatosplenomegaly and jaundice; radiolucent bone disease	Microcephaly, no specific findings	No specific treatment

Continued

Table 5.3

Continued

Organism	Route of transmission to fetus	Trimester with highest rates of transmission[a]	Neurologic signs and symptoms of congenital or neonatal infection	Fetal brain imaging	Treatment of neonatal CNS infection[b]
Parasites					
Toxoplasmosis	Transplacental	3rd > 2nd > 1st	Chorioretinitis, hydrocephalus, intracranial calcifications, spontaneous abortions, prematurity	Normal US in 2/3 of newborns; hydrocephalus	Supportive
Malaria	Transplacental		Spontaneous abortion, prematurity, stillbirth, low birth weight, intrauterine growth restriction	No known imaging findings	Supportive
Bacteria					
Group B streptococcus (GBS)	Vertical transmission during labor		Early infection—neonatal sepsis; late infection meningitis	Ventriculomegaly sulcal effacement	IV cefotaxime for at least 2 weeks in neonatal meningitis
Listeria monocytogenes	Transplacental, ascending from a colonized vaginal canal, nosocomial in nursery		Sepsis or meningitis	Nonspecific findings	IV ampicillin +aminoglycoside for neonatal meningitis
Treponema pallidum (syphilis)	Transplacental, direct contact with spirochetes	3rd > 2nd > 1st	Intellectual disability, hydrocephalus, seizures and cranial nerve abnormalities	Nonspecific findings, elevated middle cerebral artery Doppler velocimetry measurements	IV Penicillin G
Mycobacterium tuberculosis (TB)	Hematogenous spread through the umbilical vein, aspiration or swallowing of infected amniotic fluid, or by contact with amniotic fluid or secretions during labor, postpartum through aerosol spread		Meningitis, hydrocephalus, cranial nerve abnormalities	Basal meningeal enhancement with hydrocephalus, cerebral edema, infarction, tuberculoma, ventriculitis	All infants of mothers with TB: 6 months of INH followed by BCG vaccination

[a]Transmission is rare but reported in trimesters not otherwise indicated on chart.

[b]This treatment section does not include non-CNS treatment that may contribute to overall clinical picture (e.g., intrauterine blood transfusions for fetal anemia in parvovirus, which may improve cerebral blood flow).

MRI, magnetic resonance imaging; *SNHL*, sensorineural hearing loss; *US*, ultrasound; *VZIG*, varicella zoster immune globulin.

inappropriately treated hydrocephalus. Children may have delayed onset of milestones as well as spasticity or hypotonia that prevents normal motor function from developing (Embree and Alfattoh, 2015). The development of seizure disorders and hearing loss can also delay or prevent development of normal milestones. Early identification of underlying treatable causes of developmental delay such as hydrocephalus and subclinical seizures can mitigate long-term effects on cognition and development. Comprehensive early intervention services can be helpful if available (Guralnick, 2017).

POLIOVIRUS, CLOSTRIDIUM TETANI, AND HUMAN IMMUNODEFICIENCY VIRUS

This review does not comprehensively cover poliovirus, clostridium tetani or HIV. Briefly, poliovirus can cause neurologic disease in the form of aseptic meningitis or paralytic disease (Centers for Disease Control and Prevention, 2000). Pregnancy itself is a risk factor for paralytic disease, and pregnant women at high risk of infection can receive the inactivated poliovirus vaccine. Tetanus is caused by the bacterial infection clostridium tetani and leads to painful muscle spasms, and often death in the newborn (World Health Organization, 2019b). Neonatal tetanus is seen in developing countries and is caused by neurotoxin production during nonsterile deliveries. Tetanus vaccine in the form of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) is recommended for all women during pregnancy, and it is administered from 27 through 36 weeks' gestation (Liang et al., 2018). HIV is a life-threatening condition if untreated (World Health Organization, 2019a). Maternal HIV is highly prevalent in sub-Saharan Africa in which 91% of HIV-positive pregnant women reside (Wedi et al., 2016). The risk of perinatal transmission during pregnancy is 1% if pregnant women are compliant with their antiretroviral treatment regimen and have a reduced viral load (Centers for Disease Control and Prevention, 2019a). Mothers in the United States are advised not to breastfeed due to the risk of transmission through breast milk; however, this is a controversial topic in developing countries. More information on these infections and their effect during pregnancy can be found in the provided references.

CONCLUSION

Congenital neurologic infections are major contributors to prenatal, perinatal, and infant morbidity and mortality. Transmission of infection may occur prenatally, perinatally, and postnatally, though the most common risk factors occur during transplacental passage of organisms from contact with blood and vaginal secretions. Evidence of infection may be identified at birth, in infancy, and in some cases, when it occurs many years later. Thus, emphasis is placed on close monitoring of pediatric patients with known maternal exposure of a neurotropic infectious pathogen. A spectrum of early and late manifestations exist, including complications of abnormal growth, structural and developmental abnormalities because of damage to the nervous system, which may lead to seizures and other complications.

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