23 Congenital Infections

Cristiano Jodicke • Paul Singh • Dev Maulik

Fetal infections account for 2% to 3% of all congenital anomalies.[1] Infections acquired during pregnancy may be associated with significant maternal–fetal morbidity and mortality. Pregnant women are commonly exposed to young children who may be a potential source of infectious disease. Maternal infections may be transmitted to the fetus, leading to poor perinatal and neonatal outcomes. Congenital infections pose many difficult issues for physicians and parents because of the obscure short and potential long-term sequelae that may adversely affect a variety of organ systems. Over the last few decades the prevention, detection, and treatment of congenital infections have improved dramatically. Despite being more common in underdeveloped countries, perinatal infections remain a concern worldwide. Thus, a sound knowledge of congenital infection is important for the clinician involved in maternal–child health. It is estimated that congenital infections account for nearly 20% of fetal and neonatal diseases.

Several organisms, such as cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), *Toxoplasma gondii*, varicella zoster virus (VZV), rubella, and *Treponema pallidum* are known to cause fetal infections. Less commonly considered pathogens include enteroviruses, *Listeria monocytogenes*, *Plasmodium*, and *Mycobacterium tuberculosis*. Efforts such as universal immunizations, preconceptional screening, and good hygienic practices have been instrumental in the reduction of incidence of these diseases.

Concern for exposure to infectious agents during pregnancy should prompt the workup of both the mother and fetus. Sonographic findings may assist in fetal prognostication, aid in patient counseling, and influence perinatal management. Apart from ultrasound, other commonly employed methods for prenatal diagnosis of congenital infection include magnetic resonance imaging (MRI) and amniotic fluid and fetal blood sampling.

Improvement in ultrasound technology has enhanced our understanding of fetal diagnosis and management. However, ultrasound is not a sensitive test for fetal infection and a normal targeted sonogram cannot reliably predict a favorable outcome. Although, most affected fetuses appear sonographically normal, serial imaging may reveal evolving findings. Crino[2] reported that the initial screening ultrasound may not demonstrate any abnormalities; however, the fetus may show signs of undetected clinical infection only during the latter part of pregnancy. Various sonographic abnormalities have been associated with congenital infections, such as ascites, hydrops, ventriculomegaly, intracranial calcifications, hydrocephaly, microcephaly, cardiac anomalies, hepatosplenomegaly, echogenic bowel, and placentomegaly. Multiple organ systems are affected in approximately 50% of cases. Different intrauterine infections may have similar sonographic findings, but certain patterns of images in high-risk patients may lead to a specific diagnosis. Thus, practitioners should understand the limitations of ultrasound for the detection of congenital infection.

Since the central nervous system (CNS) is often affected by infectious exposures, fetal MRI may be utilized as an adjunct to ultrasound to provide further definition of brain injury. MRI will not be emphasized in this chapter, but findings with regard to CNS infection can be found in Chapter 12.2 (Fetal CNS Infection). Sometimes, MRI may also be helpful in evaluation of the gastrointestinal tract and hydropic fetus when the etiology of abnormality is unknown. Discussion of ultrasound and MRI in the evaluation of the GI tract and nonimmune hydrops can be found in Chapters 18.1 and 22.2, respectively.

This chapter reviews the agents most commonly associated with congenital infection and their respective ultrasound findings. In addition, a discussion about pathogenesis and other maternal–fetal diagnostic modalities and management is provided.

VIRAL INFECTIONS

Cytomegalovirus

Definition and Incidence: Cytomegalovirus (CMV) occurs in 0.2% to 2.2% of all live births and is the most common cause of intrauterine infection and the leading infectious cause of sensorineural hearing loss and mental retardation.[3–5]

Pathogenesis: CMV is the largest known member of the human herpes virus family. These viruses are large, enveloped, DNA viruses sharing the biologic properties of latency and reactivation. Endogenous latent virus reactivation may occur regularly. Although CMV is found throughout all geographic locations, it is more widespread in developing countries and in areas of lower-socioeconomic conditions. The seroprevalence increases with age and is due to many other factors such as poor hygiene, underdeveloped infrastructure, and high-risk sexual behavior.[6] Transmission of CMV occurs from person to person and requires intimate contact with infected excretions, such as saliva, urine, breast milk, or other body fluids.[7,8]

Vertical transmission can occur through the placenta from maternal–fetal hematogenous exchange. In addition, fetal infection can also occur as a result of exposure to infected cervical secretions and blood during delivery. The risk for transmission of the virus to the fetus is higher in primary-infected mothers than in those with reactivated disease. Although, primary CMV infections are reported in 1% to 4% of seronegative women during pregnancy, the risk for viral transmission to the fetus is 30% to 40%.[5] Pregnant women who experience recurrent or reactivated CMV infection are much less likely to transmit infection to their fetus. While reactivation of CMV infection during pregnancy is reported to occur in 10% to 30% of seropositive women, the risk of transmitting the virus is only 1% to 3%.

The overall risk of congenital infection is highest when maternal CMV occurs during the third trimester; however, the probability of severe fetal injury is greatest when fetal infection takes place during the first trimester. During early pregnancy, CMV infection may cause disturbances during early brain development. CMV infections acquired during delivery or via breast milk have no effect on future, neurodevelopmental outcome in full-term infants. In contrast, in premature infants (<32 weeks), sepsis-like symptoms have been reported after exposure to contaminated secretions.[6]

Diagnosis: During diagnosis, two important steps must be followed. Initially, maternal infection must be investigated, and

differentiation should be made between maternal primary and secondary infection based on serologic testing. Next, after maternal infection has been demonstrated, congenital infection should be investigated using both noninvasive (ultrasound examination) and invasive (amniocentesis) prenatal testing.

The best method for the diagnosis of asymptomatic maternal primary infection is seroconversion; however, this is clinically problematic due to the lack of universal screening. The detection of IgM antibodies in maternal sera can be helpful, but interpretation is somewhat complicated. Although CMV-IgM antibodies occur in all primary infections, they may also be detected after reactivation or reinfection and remain present for months. Hence, finding CMV-IgM antibodies in a single serum sample is not definitive for the diagnosis of a primary CMV infection and may indicate either remote primary infection acquired before pregnancy or recurrent disease.[5,9]

Apart from seroconversion, the combination of anti-CMV-IgM and low-avidity anti-CMV IgG testing is the best way to diagnose a primary maternal infection. Antibody avidity is an indirect measure of the tightness of antibody binding to its target antigen and increases during the first months after a primary infection. The IgG avidity assay can be a useful tool to assist in distinguishing primary infection from past or recurrent infection as well as to determine when the primary infection occurred. An avidity index $<30\%$ strongly suggests a primary infection of less than 12 weeks.[10,11]

The clinical spectrum of congenital CMV infection is wide, ranging from a complete lack of symptoms to severe disease with multi-organ involvement and postnatal complications. The most sensitive and specific test for diagnosing congenital CMV infection is the identification of CMV in amniotic fluid using virus culture or CMV-DNA analysis by polymerase chain reaction (PCR). CMV-DNA and CMV-IgM antibody activity may also be demonstrable in cord blood. Amniocentesis is generally the procedure of choice because it is safer and has a higher diagnostic sensitivity compared to cordocentesis. The amniotic fluid should be sampled after the 21st week of pregnancy and at least 5 to 6 weeks after the estimated onset of infection.[6]

Approximately 5% to 15% of infants who develop congenital CMV infection as a result of primary maternal infection are symptomatic at birth. The most common clinical manifestations of severe neonatal infection are hepatosplenomegaly, intracranial calcifications, jaundice, growth restriction, microcephaly, chorioretinitis, hearing loss, thrombocytopenia, hyperbilirubinemia, and hepatitis.[6] Approximately 30% of severely infected infants die, and 80% of survivors have major morbidity. Among the 85% to 90% of infants with congenital CMV infection who are asymptomatic at birth, 10% to 15% subsequently develop hearing loss, chorioretinitis, or dental defects within the first 2 years of life.[12,13]

Ultrasound: Ultrasound evaluation is invaluable in providing information about the condition of the fetus. The presence of characteristic ultrasound findings has a high predictive value for fetal infection and also may have prognostic significance. Because routine maternal CMV screening is not recommended, congenital CMV infection is underdiagnosed, and detection during pregnancy is often noted when suspicious sonographic abnormalities are found during routine screening examinations.

The main sonographic findings suggestive of congenital CMV infection are echogenic bowel (Fig. 23.1), ventriculomegaly (Fig. 23.2), microcephaly, periventricular calcifications

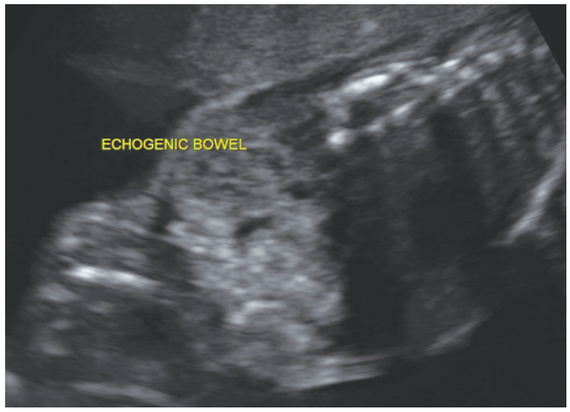

FIGURE 23.1: Sagittal-oblique ultrasound view demonstrating echogenic bowel at 26 gestational weeks in a fetus with known congenital CMV.

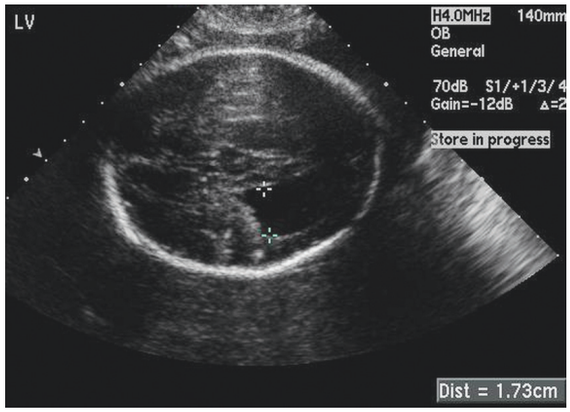

FIGURE 23.2: Axial ultrasound view showing ventriculomegaly in a patient with known congenital CMV at 27 weeks' gestation.

(Fig. 23.3), fetal hydrops, intrauterine growth restriction (IUGR), placentomegaly (Fig. 23.4), and oligohydramnios. Less common findings include supraventricular tachycardia, meconium peritonitis, renal dysplasia, ascites, and pleural effusions.

Ventriculomegaly is frequently diagnosed during fetal life and has multiple etiologies, including CMV infection. Around 5% of all cases of ventriculomegaly are caused by fetal infection. De Vries et al.[14] found periventricular calcifications associated with mild-to-moderate ventriculomegaly in 10 out of 11 children with symptomatic congenital CMV infection. Malinger et al. demonstrated similar findings in five of eight affected fetuses with congenital CMV. In addition, fetuses with ventriculomegaly were identified at a more advanced gestational age (28.6 weeks) and had other associated sonographic findings than those without ventriculomegaly.[15]

Microcephaly is associated with a poor prognosis in cases of congenital CMV, usually due to mental retardation. Noyola et al.[16] reported that microcephaly is the most specific predictor for mental retardation (100%; 95% CI, 84.5–100) and major motor disability (92.3%; 95% CI, 74.8–90) in children with symptomatic congenital CMV infection. Of note, microcephaly may not be apparent during the second-trimester ultrasound examination and generally is not an isolated finding. More common associated findings include intracranial calcifications, increased echogenicity of the lining of the ventricles, and ventriculomegaly.

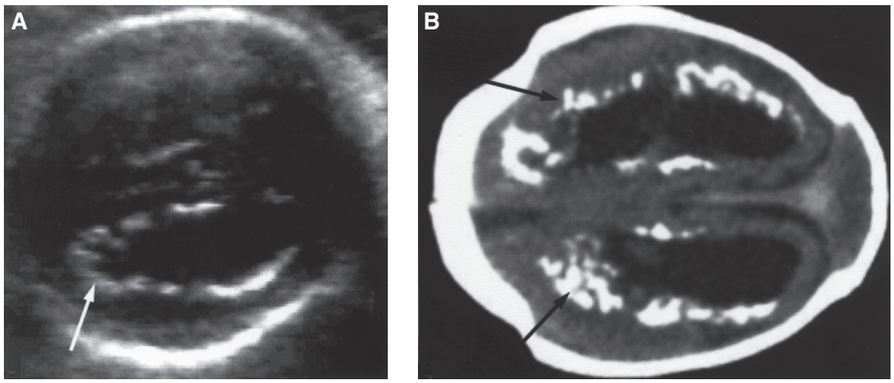

FIGURE 23.3: Cytomegalovirus. **A:** Transverse view of fetal brain shows ventricular dilatation and periventricular echogenic nodules *(arrow)*. **B:** Computed tomography scan (oriented to correspond with ultrasound image) after birth confirms hydrocephalus and marked periventricular calcifications *(arrows)*. (Courtesy of Luis Izquierdo, MD, Miami, FL.)

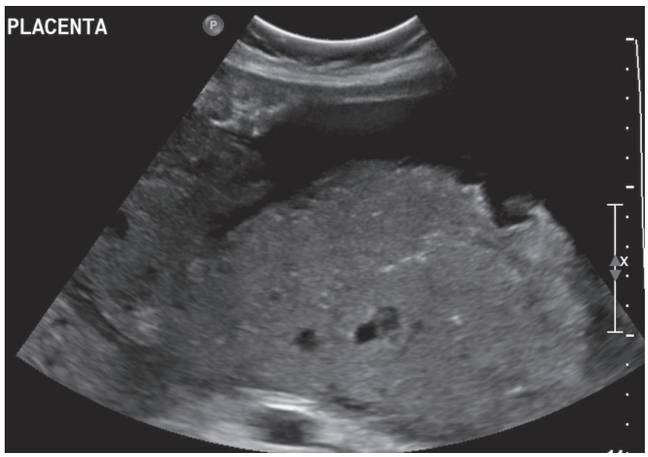

FIGURE 23.4: Thickened placenta in a pregnancy diagnosed with congenital CMV at 30 weeks' gestation.

Ventriculitis, which manifests as an increased echogenicity surrounding the lateral ventricles, is an ultrasound finding that may be present in CMV infection, although it also may be a normal variant. As with ventriculomegaly, it will rarely be an isolated ultrasound finding. Periventricular pseudocysts and intraventricular synechiae (IVS) have also been described in association with CMV infection.

Brain calcifications are considered a strong and common ultrasound marker of intrauterine infections. It is not an exclusive ultrasound finding in CMV infection and has been described in fetuses with other infections such as congenital toxoplasmosis, rubella, herpes simplex, and varicella. The calcifications do not usually have an acoustic shadowing, and although they may be found in any portion of the brain, they have particular predilection for the periventricular zone.

Congenital CMV infection during the late first or early second trimester may interfere with neuronal proliferation and migration, and result in abnormal cortical development, including lissencephaly and schizencephaly. Microcephaly, ventriculomegaly, callosal dysgenesis, and abnormally developed sulci and gyration are the most common initial ultrasound findings in fetuses with congenital CMV infection and malformations of cortical development. A detailed ultrasound, including dedicated neurosonography, and perinatal MRI are indicated when the above-mentioned intracranial ultrasound findings are detected during the initial routine screening examination.

Hyperechogenic bowel and ventriculomegaly are the most common abnormal ultrasound findings in CMV infection, although they may also be seen in uninfected fetuses. Guerra et al.[17] reported the following sonographic abnormalities in 23 cases of CMV-infected fetuses/infants: hyperechogenic bowel ($n = 7$), cerebral ventriculomegaly ($n = 7$), IUGR ($n = 3$), hydronephrosis ($n = 1$), hydrops ($n = 1$), cerebral periventricular echogenicity ($n = 1$), and the association of two or more fetal abnormalities (hyperechogenic bowel and cerebral ventriculomegaly, $n = 3$).

Hepatomegaly and hepatic calcifications may be also found in cases of fetal infection. Hydrops and ascites have been documented and may be related to hepatic dysfunction and portal hypertension from liver congestion. Supraventricular tachycardia and pericardial effusion have also been reported in association with CMV infection. During a 6-year study period, Gonce et al.[18] diagnosed 19 fetuses with CMV infection. The main sonographic findings were the following: brain abnormalities ($n = 14$), fetal hydrops ($n = 4$), hyperechogenic bowel ($n = 4$), pericardial effusion ($n = 1$), cardiomegaly ($n = 1$), oligohydramnios ($n = 4$), and placentomegaly ($n = 2$).

Although ultrasound is a valuable tool in evaluating a fetus with CMV infection, its limitations should be discussed when counseling patients. Guerra et al.[17] studied the effectiveness of ultrasound in the antenatal detection of symptomatic congenital CMV infection. Six hundred and fifty ultrasound examinations of fetuses from mothers with primary CMV infection were correlated to fetal or neonatal outcome. Ultrasound abnormalities were found in 51 of 600 mothers with primary infection (8.5%) and 23 of 154 congenitally infected fetuses (14.9%). They concluded that ultrasound abnormalities predict symptomatic congenital infection in only a third of cases. Liesnard et al.[9] reported characteristic sonographic findings in 9 of 55 infected fetuses (16.4%), but the majority of infected newborns were asymptomatic. Another issue is that abnormal sonographic findings may be only detected for the first time during the third trimester after a normal ultrasound examination earlier in the pregnancy. Although repeat ultrasound examination during the

third-trimester scan may lead to a more accurate diagnosis and help with counseling, pregnancy termination would not be an option due to advanced gestational age.

Management: The best prevention for congenital CMV infection is primary prevention with personal hygiene practices, such as hand-washing and avoiding intimate contact with salivary secretions and urine from young children. Vaccination to CMV is currently under investigation and is not available for clinical use yet.

Although there are several methods for the prenatal diagnosis of congenital CMV infection, there is no effective treatment to offer once a diagnosis has been made. The use of CMV-specific hyperimmune globulin for treatment was evaluated by Nigro et al.[19] in 157 pregnant women with primary CMV infection. Forty-five women who had a primary infection longer than 6 weeks and congenital infection confirmed by amniocentesis were enrolled. Thirty-one of these women received intravenous treatment with CMV-specific hyperimmune globulin (200 U per kg of maternal body weight), and only one had an infant with clinical CMV disease at birth. In comparison, of the 14 women who declined treatment, 7 had infants who were symptomatic at delivery (adjusted OR, 0.02, $P < .001$). The maternal administration of valaciclovir and ganciclovir to treat intrauterine CMV infection has also been reported.[20,21] Although these studies were not randomized, they are promising and offer a possible treatment option for congenital CMV infection.

Intrauterine therapy with cytomegalovirus hyperimmunoglobulin has also been attempted. Negishi et al.[22] was the first to report intraperitoneal CMV hyperimmunoglobulin administration in a fetus at 28 and 29 weeks of pregnancy. Since then, other investigators have reported the use of intraperitoneal CMV hyperimmunoglobulin as a possible treatment alternative for congenital CMV.[23–25] In addition, both the intraumbilical and intra-amniotic fluid administration of CMV-specific hyperimmune globulin has been performed.[26]

Parvovirus

Definition and Incidence: Human parvovirus B19 is a small single-stranded DNA virus from the Parvoviridae family that is responsible for erythema infectiosum, also known as fifth disease, and is a common childhood illness. It is a worldwide infection that affects individuals from infancy through adulthood. Infection can occur at any age but most commonly affects children from 6 to 10 years of age. The prevalence of parvovirus IgG antibodies steadily rises throughout life. In children aged from 1 to 5 years and from 6 to 19 years, the prevalence of IgG antibodies is 2% to 15% and 15% to 60%, respectively. In the geriatric population, the prevalence is more than 85%.[27,28]

More than half of reproductive-age women have developed immunity to parvovirus B19. About 35% to 45% of women of childbearing age, however, do not have protective IgG antibodies against parvovirus. During pregnancy, the risk of acquiring parvovirus infection is low. The incidence of acute infection in pregnancy is approximately 1% to 2% during endemic periods.[29] Women at increased risk include mothers of preschool and school-age children, workers at day-care centers, and school teachers. Vertical transmission occurs in about 30% to 50% of mothers infected with parvovirus during pregnancy.[30] Congenital infection can cause severe fetal consequences, such as anemia, nonimmune hydrops fetalis (NIHF), and fetal death. The risk of adverse fetal outcome is increased if maternal infection occurs during the first two trimesters of pregnancy; however, fetal infection can still occur during the third trimester.[31–33] It is highly unlikely that fetal infection will occur if the mother has IgG antibodies, since prior infection with parvovirus B19 confers lifelong immunity.[34]

Pathogenesis: The risk of fetal complications depends upon the gestational age at the time of maternal infection. The incidence of fetal morbidity and mortality decreases with gestational age. The highest risk for fetal loss happens when maternal infection develops during the 9th through the 16th weeks of pregnancy.[35,36] The risk of vertical transmission is maximal at the time IgM antibodies appear. This coincides with maternal peak viral load which occurs generally 7 days after maternal inoculation.[37]

The virus is spread by respiratory droplets, hand-to-mouth contact and by blood products containing factor XIII and IX concentrates.[31–33,38,39] Outbreaks usually occur during the spring every 4 to 5 years and may last up to 6 months. Viremia occurs 4 to 14 days after exposure and may last up to 20 days. Serum and respiratory secretions become positive for parvovirus DNA 5 to 10 days after intranasal inoculation. Symptoms such as erythema infectiosum, mild fever, arthralgias, and headaches start approximately 10 to 14 days after infection; however, many people remain asymptomatic. By the time erythema infectiosum develops, the person is usually no longer infectious.

The fetal liver, the main site of erythrocyte production, is the virus's main target of infection.[31] The fetus is more vulnerable during the second trimester when the liver is the main source of hematopoietic activity, and the half-life of red blood cells is short. Parvovirus is a potent inhibitor of hematopoiesis because it infects erythroid precursor cells such as erythroblasts and megakaryocytes. Resultant severe anemia may occur, leading to congestive heart failure and the development of hydrops fetalis. Parvovirus may infect fetal cardiac myocytes and hepatocytes, resulting in myocarditis and impaired hepatic function, respectively.[40] Subsequent development of fetal high-output cardiac failure, generalized edema, and death may occur.[40] Thus, the development of hydrops may not correlate with the severity of fetal anemia. Placental trophoblastic cells also express the P antigen, the main cellular receptor for the virus, and are thus susceptible to infection by parvovirus. Poor fetal outcomes have been associated with placental villous trophoblast apoptosis in patients with congenital infection.[41] Such observations suggest that parvovirus infection may be associated with placental insufficiency. Stillbirth in nonhydropic fetuses may result from placental damage and occurs in 0.9% to 23% of pregnancies with documented maternal infection.[42,43]

Diagnosis: Serologic examination of maternal blood is the initial and most useful diagnostic tool for parvovirus. Specific IgM and IgG testing should be performed as soon as possible once maternal infection is suspected during pregnancy.[44] IgM antibodies become detectable in maternal serum within 7 to 10 days after infection, sharply peak at 10 to 14 days, and can persist in the circulation for 3 to 4 months or longer.[45] IgG antibodies will rise considerably more slowly and reach a plateau at 4 weeks after infection. Of note, after a recent contact, there will be a serologic window of 7 days, during which both IgG and IgM remain undetectable.[44] Women who are IgG-positive and IgM-negative can be reassured that there is no evidence of recent infection. Patients with IgG- and IgM-negative–specific antibody should be considered susceptible, and further serological testing

should be carried out 4 weeks after the last contact or if signs of the disease develop.[35] IgM-positive patients, irrespective of IgG status, should receive serial fetal evaluation to rule out congenital infection.

Since most infected pregnancies have a favorable outcome, invasive prenatal diagnostic testing should only be used if there are definitive signs of fetal anemia or hydrops fetalis.[35] Ultrasound must be used for diagnosis and surveillance. Fetal infection may be identified by using PCR of parvovirus viral DNA in amniotic fluid or fetal cord blood. Amniocentesis is the preferred method of choice due to less complications and increased availability. Serologic examination of fetal blood samples is highly unreliable since the IgG and IgM response to parvovirus is not produced during intrauterine life. Detection of parvovirus using specific IgM in fetal blood has a sensitivity of 29% compared to almost 100% for PCR.[35,44,46]

Ultrasound: As soon as a recent parvovirus maternal infection is suspected during pregnancy, ultrasound examination should be performed to exclude the presence of fetal anemia and hydrops. The virus infects the liver which is the main site of erythrocyte production in the fetus leading to anemia, most often occurring during the second trimester. Increased cardiac output and decreased viscosity of fetal blood caused by anemia are responsible for the changes in fetal blood during congenital infection. An increase in the middle cerebral artery peak systolic velocity (MCA-PSV) (Fig. 23.5) is a very sensitive measure to identify fetal anemia caused by parvovirus infection.[47] Weekly measurements of MCA-PSV are recommended after maternal infection is documented. Timing of intrauterine transfusion for treatment of fetal anemia and prevention of fetal hydrops can be based on these MCA-PSV measurements. The infection causes anemia and possible myocarditis, leading to high-output cardiac failure and subsequent development of generalized edema. Fetal hydrops, an accumulation of excess fluid in at least two body compartments of the fetus, can be easily seen with ultrasound. The median interval between maternal parvovirus infection and diagnosis of hydrops fetalis is about 3 weeks, but may vary between 1 and 20 weeks.[48] The ultrasonographic findings include fetal ascites, skin edema, pericardial effusion, pleural effusions, and placental edema (Figs. 23.6 to 23.11). Enlargement and thickening of the fetal heart also may be documented during

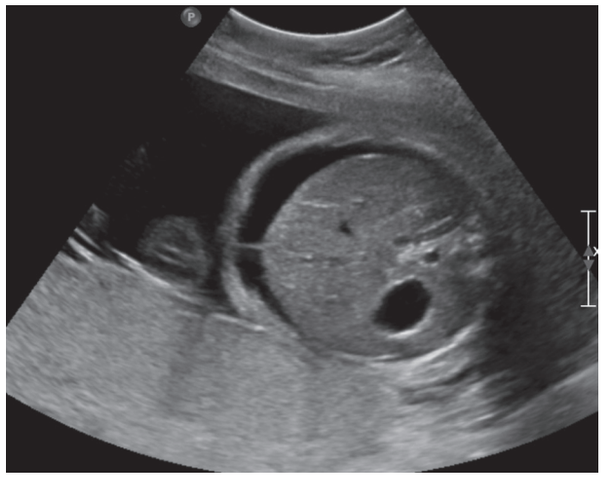

FIGURE 23.6: Cross-sectional ultrasound view of the abdomen showing marked ascites in a fetus with congenital parvovirus.

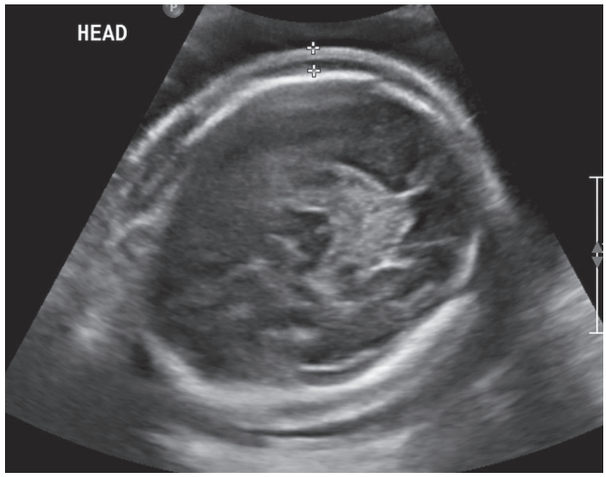

FIGURE 23.7: Axial ultrasound image of the fetal head showing scalp edema in a pregnancy exposed to parvovirus and positive IgM titers.

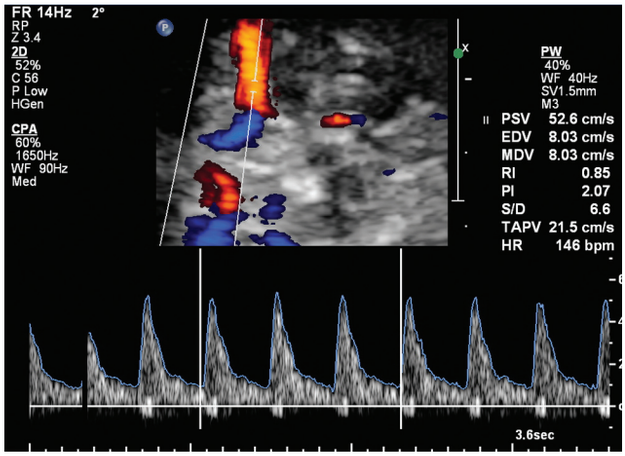

FIGURE 23.5: Duplex Doppler of the middle cerebral artery at 24 gestational weeks demonstrating increased peak systolic velocity in a fetus exposed to parvovirus.

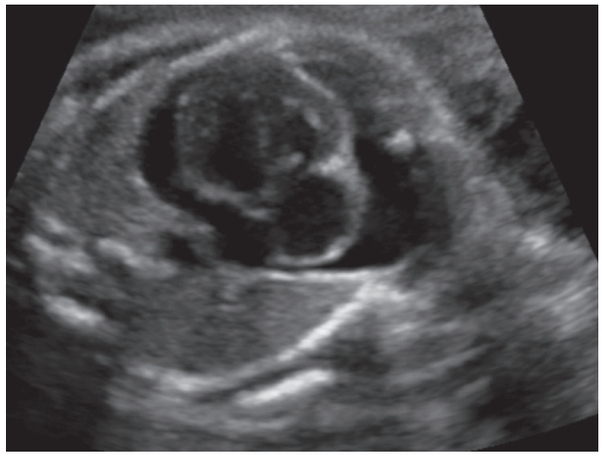

FIGURE 23.8: Cross-sectional ultrasound view of the fetal chest demonstrating marked pericardial effusion in a pregnancy with confirmed parvovirus infection by amniotic fluid PCR.

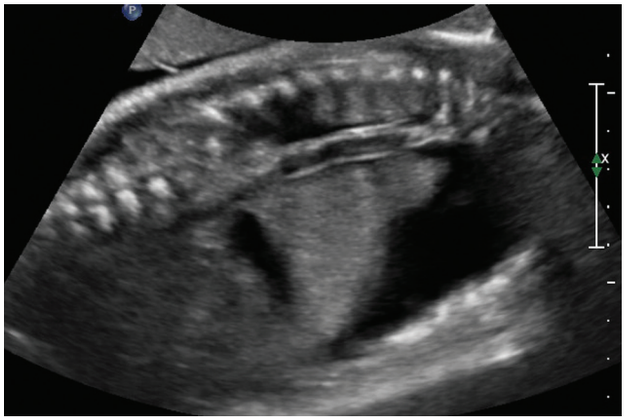

FIGURE 23.9: Sagittal view of chest demonstrating pleural effusion at 20 gestational weeks in a fetus with congenital parvovirus.

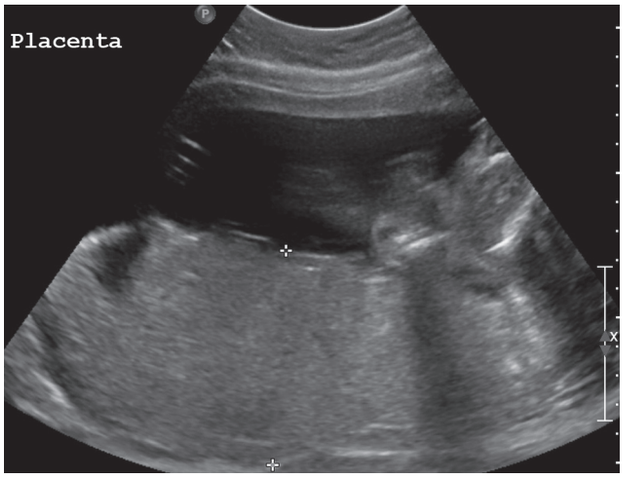

FIGURE 23.10: Placentomegaly demonstrated by ultrasound in a pregnancy complicated by fetal parvovirus infection.

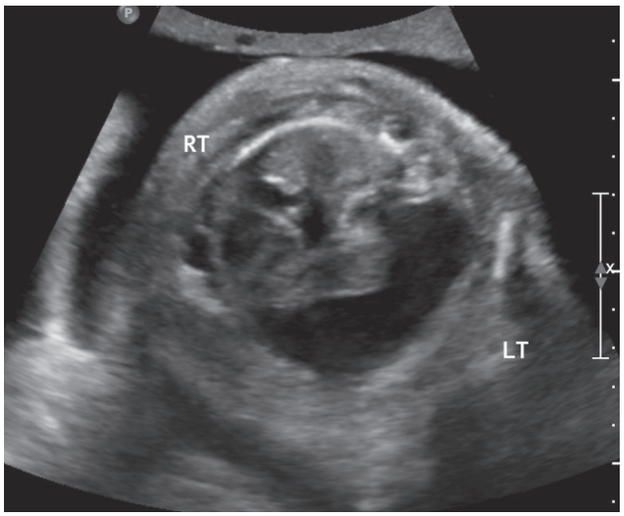

FIGURE 23.11: Cross-sectional view of the chest in a fetus with congenital parvovirus showing bilateral pleural effusions, more prominent in the left hemithorax. The fetal heart is displaced to the right side of the chest.

the examination. Fetal structural anomalies associated with parvovirus are uncommon; however, ultrasound findings such as hydrocephalus, hyperechogenic bowel, meconium peritonitis, fetal liver calcifications, cleft lip and palate, and increased fetal nuchal translucency have been reported.[48–52]

Management: Maternal infection with parvovirus is self-limited and is treated symptomatically. Acute red cell aplasia may rarely occur and requires serial measurements of hemoglobin and possible blood transfusions to prevent maternal complications due to severe anemia. The confirmation of fetal infection is not required for suspected maternal infection.

If serologic evidence suggests possible maternal infection, weekly measurements of fetal MCA-PSV and US assessment for hydrops should be performed. The MCA-PSV may diagnose significant fetal anemia with a sensitivity of as high as 100%.[53] In parvovirus infection, the MCA-PSV was reported to have a sensitivity of 94.1% for the diagnosis of fetal anemia.[47] Percutaneous umbilical blood sampling (PUBS) should be considered once the MCA-PSV reaches 1.5 multiples of the median (MOM) for gestational age. If fetal anemia is confirmed, fetal blood transfusion is indicated. Intrauterine transfusion with packed red blood cells for cases of severe fetal anemia has been shown to reduce perinatal morbidity and mortality. Fetal survival may be as high as 60% to 80% when intrauterine transfusion is attempted, compared to only 15% to 30% with hydrops and no intervention. Fairley et al.[54] compared outcomes of expectant management with intrauterine transfusion in cases of maternal parvovirus infection, and found a greater than 7-fold reduction in fetal death with the use of intrauterine transfusion.

In addition, a targeted fetal ultrasound and echocardiography should be performed, especially in cases complicated by hydrops fetalis. Delivery is recommended at 34 gestational weeks in pregnancies affected with hydrops fetalis. An attempt to correct fetal anemia should be considered before delivery to improve neonatal outcome.

Prognosis: The long-term prognosis for children who received intrauterine transfusion (IUT) for congenital parvovirus infection is controversial. Some studies have shown that children who underwent a successful intrauterine transfusion have good neurodevelopmental outcomes.[36,55] Miller et al.[36] described seven cases of fetal hydrops, two of which received IUT. They were unable to find any long-term developmental problems in the patients who received fetal blood transfusion. Similarly, Dembinski et al.[55] followed up 20 children with parvovirus infection treated with IUT and found no evidence of developmental delay. On the other hand, de Jong et al.[44] described an increased risk of both neurodevelopmental delay and cerebral palsy in children treated with intrauterine transfusions for congenital parvovirus infection. Parvovirus DNA has been detected within white matter multinucleated, reactive microglial cells, suggesting that the virus itself may play a direct role in perivascular changes and white matter damage.[56] Alternatively, severe fetal anemia and hydrops may cause hypoxic-ischemic cerebral injury, thereby, contributing to the increased rate of neurodevelopmental complications. Lindenburg et al.[57] demonstrated similar findings of developmental delay and cerebral palsy in neonates that underwent IUT for severe fetal anemia. However, for a number of reasons, these fetuses are likely to be delivered prematurely, which is itself a significant risk factor for pediatric developmental disorders.

Rubella Virus

Definition and Incidence: Rubella, also known as German measles and "third" disease, is caused by a lipid-enveloped, single-stranded RNA togavirus.[58] Congenital rubella syndrome (CRS) was one of the earliest-described vertically transmitted infections in the newborn infant.[59] The last major epidemic of rubella in the United States occurred between 1964 and 1965, during which time 20,000 cases of infants were born with CRS. Cases of infection during pregnancy have been significantly reduced following vaccine development in 1969. From 1995 to 2000, an average of five cases of CRS has been reported annually in the United States. Newborns affected by CRS are most commonly born in countries where routine rubella vaccination programs are not used.

Pathogenesis: Rubella is an airborne transmitted infection spread by small respiratory droplets which becomes infectious 7 days prior to the appearance of the initial symptoms. Vertical transmission is hypothesized to occur 5 to 7 days following maternal inoculation.[60] The clinical features of rubella are a rash, fever, arthralgias, and lymphadenopathy. The rash generally manifests initially on the face and then gradually migrates toward the trunk and then to the lower extremities.[60] Generally self-limited complications such as encephalitis, thrombocytopenia, neuritis, conjunctivitis, and orchitis have rarely been reported to occur as a result of rubella.[60–62] Importantly, encephalitis from rubella infection has been associated with a 50% mortality. Subclinical infection can occur in up to 50% of patients; however, in these patients, fetal anomalies as a result of congenital infection rarely occur. Reinfection with rubella after prior documented infection or immunization is extremely rare during pregnancy.[63,64] Antibody titers lower than 1/64 has been associated with reinfection.[65] The risk of vertical transmission depends upon gestational age and is 90%, 25%, and 95% during the first, second, and third trimesters, respectively. During the first trimester, CRS is extremely rare if the maternal rash occurs within the first 2 gestational weeks. If the rash appears during the 3rd gestational week, the infection rate is 31%, and nearly 100% afterwards.[66] Congenital heart defects and deafness most commonly occur in infected fetuses during the first trimester, but are rare afterwards.

Laboratory Studies: Serological analysis is based on the detection of IgG, IgM, and also IgG avidity antibodies.[60,67] The enzyme-linked immunosorbent assays (ELISA), hemoagglutination inhibition test (HI), and the immunofluorescent antibody assay (IFA) are the most common methods of antibody detection.[59,60,67–69] Acute rubella infection is characterized by the appearance of rubella IgM about 5 days after the onset of the maternal rash and persists for 6 weeks.[70] The presence of IgM antibodies does not always correspond to an acute infection. A false-positive IgM for rubella can result in patients with parvovirus, mononucleosis, or a positive rheumatoid factor.[71] In addition, IgM antibodies may persist for 1 year or more in a chronic rubella carrier. Thus, in order to properly establish a timeline of infection, it is important to measure the Rubella IgG avidity. A high IgG avidity indicates chronic carrier status, while a lower IgG avidity indicates a more recent infection. The evaluation of IgG, IgM, or the RNA virus in the saliva instead of in the blood has been proposed to diagnose rubella.[72–75] Ramsay et al.[75] found a sensitivity of 98% and a specificity of 100% for IgG, and a specificity of 99% for IgM detected in the saliva.

Amniotic fluid sampling for fetal diagnosis of CRS should be performed 6 to 8 weeks after maternal infection to avoid false-negative results. Samples of amniotic fluid may be sent for viral cultures; however, this method lacks sensitivity and final results may take up to 6 weeks. PCR technology may be used to diagnose CRS, having the advantage of increased detection rates and faster result times.[69] The diagnosis of CRS via chorionic villus sampling has been described.[76]

Ultrasound: Ultrasound has an important role in the prenatal diagnosis of CRS. Migliucci et al.[77] performed a retrospective study on 175 women referred for rubella infection. Sonographic findings of IUGR, polyhydramnios, cardiomegaly, atrial septal defect, hepatosplenomegaly, ascites, echogenic bowel, and placentomegaly were detected. Ugurbas et al.[78] reported an association between microphthalmos and CRS. Ventricular septal defect and pulmonary stenosis have also been reported in cases of CRS.[79] Exencephaly was diagnosed in one case.[80]

Management: Maternal rubella is a self-limited disease requiring only symptomatologic care. Severe complications of rubella infection such as encephalitis, thrombocytopenia, neuritis, conjunctivitis, and orchitis should be aggressively managed. Termination of pregnancy may be offered in cases of maternal infection. The maternal administration of immune globulin in large doses (20 mL in adults) in cases of susceptible women exposed to rubella during gestation has been proposed.[67] This treatment, however, has not produced encouraging results because it does not seem to prevent fetal infection. Post exposure prophylaxis for rubella in early pregnancy is not recommended due to unproven clinical efficacy. The rubella vaccine is contraindicated during pregnancy; therefore, susceptible women should be immunized postpartum.

Prognosis: Up to two-thirds of children with congenital rubella may be asymptomatic at birth, but will develop sequelae within the first 5 years of life.[74] Classic findings associated with neonatal rubella are low birth weight with a cluster of abnormalities, including cataracts, sensorineural deafness, and cardiac defects such as patent ductus arteriosus, pulmonary artery stenosis, and coarctation of aorta. Less common neonatal heart defects that have been reported are aortic stenosis and Ebstein anomaly.[81–84] Purpura (blueberry muffin spots), microphthalmia, corneal opacity, glaucoma, hepatosplenomegaly, thrombocytopenia, and radiolucent bone lesions may also be found.[85] Late manifestations of congenital rubella include hearing loss, pancreatic insufficiency, and behavioral disorders.[74,85] Diagnosis is made by serum detection of rubella IgM before 3 months of age or persistent IgG between 6 and 12 months of age.

Herpes Simplex Virus

Definition and Incidence: Genital HSV type 1 (HSV-1) or HSV type 2 (HSV-2) is a common infection in United States, affecting 16.2% or 1 in 6 people between the ages of 14 and 49 years.[86] Approximately 25% to 65% of pregnant patients in the United States have genital infection with HSV. The frequency of neonatal HSV infection in the United States varies according to the patient population, with the rate of infection ranging from 1 case per 12,500 to 1 case per 1,700 live births. Whitley et al.[87] analyzed the data from 30 U.S. health plans and showed a rate of 60 cases per 100,000 live births. This incidence is higher

than that of congenital syphilis, toxoplasmosis, and congenital rubella.

Pathogenesis: HSV belongs to the family of double-stranded DNA viruses known as Alphaherpesvirinae, a subfamily of the Herpesviridae. HSV type 1 (HSV-1) and type 2 (HSV-2) are differentiated based on the glycoproteins within the lipid envelope. Glycoproteins G1 and G2 are associated with HSV-1 and HSV-2, respectively. The hallmark of herpes infection is the ability to infect epithelial mucosal cells where replication occurs. The virus, then, gains access to sensory neurons and stay latent in the sensory ganglia for years, followed by reactivation.

HSV is transmitted from person to person through direct contact. HSV-1 is usually acquired orally, but may also be sexually transmitted. HSV-2 is primarily a sexually transmitted infection. Most neonatal infections result from exposure to HSV in the genital tract during delivery, although both viruses may also be transmitted vertically during pregnancy. Traditionally, HSV-1 was typically associated with orofacial lesions while HSV-2 was felt to cause genital herpes. Although HSV-2 still predominates as the major etiology for genital herpes, an increasing proportion has been ascribed to HSV-1 recently, especially in younger women. According to the Centers for Disease Control and Prevention (CDC), the rate of HSV-2 seroprevalence in the United States has remained stable since the mid-1990s at 16.2%.[86]

The three categories of genital herpes infections are primary, nonprimary, and recurrent. A primary HSV infection is a newly acquired infection in the absence of preexisting antibodies to either HSV-1 or HSV-2. Primary symptomatic genital herpes have an incubation of a period of 2 to 20 days and cause ulceration of the external genitalia and cervix as well as blistering lesions on the internal thigh, buttocks, and perineal skin. Primary HSV infections can also be associated with a number of systemic symptoms such as fever, malaise, and headache.

Nonprimary episode infection refers to newly acquired antibodies to HSV-1 or 2 in the presence of preexisting antibodies to the other type. Nonprimary infections tend to be less severe than primary HSV infections and to have less systemic symptoms and quicker recovery times. HSV-2 antibodies are highly protective against new HSV-1 infection, thus, nonprimary HSV-1 infections are much less common.

Recurrent genital HSV infections refer to the reactivation of a latent genital HSV. The HSV type obtained from the lesion matches the HSV type obtained from the serum. Recurrent infections are typically less severe, unilateral, and have fewer lesions than either primary or nonprimary infections.[88] As in nonprimary HSV, recurrent genital HSV infections are more common with HSV-2 as opposed to HSV-1. Asymptomatic viral shedding may occur during phases in between clinical outbreaks of genital herpes, where HSV reactivates within the sensory neurons of the genital mucosa. Most sexual transmission of HSV occurs during periods of asymptomatic viral shedding because patients are unaware that they are infectious.[89] Most cases of genital HSV infection in women occur without signs or symptoms of disease and are associated with cervical viral shedding.

Diagnosis: There are a variety of methodologies for the diagnosis of HSV infection, including viral culture, PCR, direct fluorescent antibodies, Tzanck smears, and serologic identification of IgG and IgM. Pregnant women who present with symptoms suggestive of genital herpes should undergo both type-specific assay and viral identification testing. Routine antepartum screening in asymptomatic patients is not recommended.

Ultrasound: Since intrauterine HSV infection is very uncommon, limited experience exists regarding the sonographic prenatal diagnosis. Various fetal malformations have been associated with congenital herpes, including microcephaly, cerebral atrophy, hydranencephaly, intracranial calcifications, ventriculomegaly, microphthalmia, chorioretinitis, cataracts, congenital herpetic keratitis, congenital heart disease, hepatic calcifications, nonimmune hydrops, bullous skin lesions and scars, lower-limb hypoplasia, and abnormal digits. Fetal cerebral malformation, echogenic bowel (Fig. 23.12), and skin lesions seem to be more common ultrasound findings in fetuses with congenital herpes. Brain lesions are considered as secondary to the cytotoxic virus effects, or subsequent ischemia caused by vascular occlusion of cerebral vessels. Lanouette et al.[90] reported a 14-fold increase in α-fetoprotein (AFP) noted during second trimester screening in a patient with multiple fetal congenital anomalies. At 19 weeks' gestation, the patient underwent an amniocentesis and cordocentesis with results consistent with HSV infection.

Jayaram and Wake[91] reported a case with confirmed maternal HSV-2 infection in which a screening ultrasound at 20 weeks did not show any abnormalities. During the third trimester, the patient was admitted with reduced fetal movements. An ultrasound examination then noted absent corpus callosum and gross ventriculomegaly associated with absent end-diastolic flow of umbilical artery Doppler. Interestingly, an irregular heart rate with fluctuating baseline between 60 and 160 beats per minute was also documented.

In a case report by Diguet et al.,[92] during a screening ultrasound at 23 weeks of gestation, IUGR, absence of limb movements, thickened skin, hyperechogenic bowel, placental micronodular alterations, moderate pericardial effusion, and a reverse flow of the ductus venosus were noted. Because of a previous clinical episode of HSV at the beginning of pregnancy, amniocentesis was performed, revealing a positive PCR for HSV-1. On follow-up sonographic examination at 27 weeks of gestation, oligohydramnios associated with fetal abdominal and lower-limb skin irregular thickness, esophageal hyperechogenicity, and persistence of IUGR were found. The pregnancy was terminated, and fetal examination revealed extensive skin ulceration on the trunk and limbs, splenomegaly, and cardiomegaly.

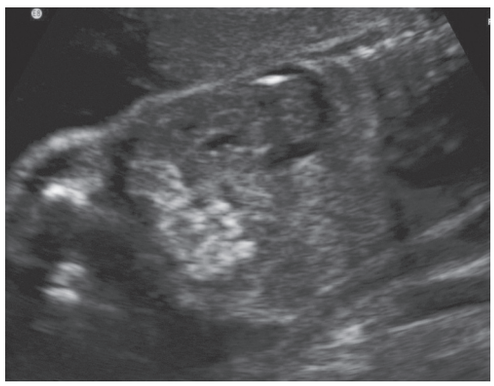

FIGURE 23.12: Sagittal-oblique ultrasound view demonstrating echogenic bowel at 26 gestational weeks in a fetus with congenital herpes simplex virus.

Duin et al.[93] reported a case in a patient with confirmed HSV in which a normal ultrasound at 20 weeks' gestation with symmetric fetal growth was obtained; however, during a third-trimester examination, marked cerebral ventriculomegaly, third ventricle enlargement, frontal thinning of the cerebral cortex, and microcephaly were noted. A follow-up ultrasound demonstrated a slight dissolution of the cortical mantle. Severe parenchymal destruction, particularly in the temporal and parietal lobes, was confirmed by a prenatal MRI. The occipital cerebral cortex was also globally thinned with microgyria. Postmortem examination confirmed the prenatal diagnosis of hydranencephaly. This report suggests that fetal MRI may provide significant additional information in assessing the extensiveness of the fetal HSV infection. Interestingly, fetal malformation caused by congenital herpes infection may be only evident during the late part of pregnancy despite an initial normal screening ultrasound. Thus, third-trimester ultrasound evaluation for an anatomy follow-up and biometry should be considered in pregnancies with known herpes virus infection.

Management: Although considerable effort is made for the viral identification of genital HSV, treatment regiments do not vary by virus type. During a primary outbreak in pregnancy, oral antibiotic therapy is indicated to reduce the duration and severity of symptoms. Viral shedding is also decreased with proper therapy. No data indicates that maternal treatment reduces the risk of neonatal herpes. Acyclovir is not teratogenic and may be administered either orally in pregnant women with a first episode of genital herpes or intravenously in pregnant women with severe genital or disseminated herpetic disease.

Transabdominal invasive procedures, such as chorionic villus sampling, amniocentesis, and percutaneous umbilical sampling, may be performed even when genital lesions are present. Transcervical procedures should not be performed during the presence of active lesions.

Prognosis: Neonatal HSV infection is defined as infection in a newborn within 28 days after birth. There are three categories of neonatal infections: cutaneous disease, CNS disease, and disseminated disease. Cutaneous disease is a HSV disease localized to the skin, eye, and/or mouth. Although cutaneous disease has a low mortality, it may progress to CNS or disseminated disease. CNS disease manifests with neurologic symptoms as well as positive CSF PCR findings and carries a mortality of approximately 15%. Disseminated disease has the worst prognosis with the highest fatality rate. Involvement of multiple organs (e.g., hepatitis, pneumonitis, or disseminated intravascular coagulation) is common and has a mortality rate of 31% and 85%, with and without therapy, respectively.

Human Immunodeficiency Virus

Definition and Incidence: Acquired immune deficiency syndrome (AIDS) is a severe immunological disorder caused by the HIV RNA retrovirus, resulting in a defect in cell-mediated immune response leading to an increased susceptibility to opportunistic infections. Despite aggressive efforts by the health community to reduce vertical transmission, HIV remains a significant perinatal risk globally. Almost 33.3 million people worldwide are infected, with 88% of infected infants born to mothers who did not receive any antiretroviral treatment.[94,95] In the United States, approximately 21% of patients with HIV are unaware of their infection[96]; so the CDC recommends routine preconceptional HIV-testing for all women.[97]

Pathogenesis: HIV attaches to the CD4 molecule on T lymphocytes via the external glycoprotein (gp120) and the transmembrane protein (gp41) located on the HIV envelope.[98] Following release into the cell cytoplasm, the viral RNA is reverse transcribed into DNA by the virus' own reverse transcriptase enzyme. After host-cell synthesis of HIV viral proteins, they are transported in close proximity to the cell membrane for assembly and egress. Destruction of the host's immune system ensues as CD4 T-cells are consumed by the HIV virus. HIV is transmitted primarily by exposure to contaminated body fluids, especially blood and semen. During pregnancy, HIV may be transmitted to the fetus either transplacentally, at the time of vaginal delivery, or through breast milk.

Diagnosis: The enzyme-linked immunosorbent assay performed on a blood sample or the rapid HIV test performed on blood or oral mucosa is the screening test of choice. Any positive HIV-screening test should be followed by a confirmatory western blot assay. Patients with a positive confirmatory testing result are considered to be infected with HIV and should be referred for consultation to an HIV specialist. A thorough laboratory evaluation, including CD4+ T-cell count, and plasma HIV RNA PCR is recommended.

Ultrasound: HIV infection has not been associated with any specific fetal anomalies. Joao et al.[99] followed 995 HIV-infected pregnant patients undergoing antiretroviral therapy (ART). No significant increase in the rate of congenital anomalies was found compared to the overall population. In addition, they found that the prevalence of congenital anomalies was not affected by the timing of ART exposure during pregnancy.[99] However, the increasing complexity of antiretroviral (ARV) regimens used antenatally for HIV treatment may result in potential drug-related adverse events such as low birth weight and preterm birth.[100–103] Late IUGR has been demonstrated in HIV-infected pregnant women.[104] Similarly, in a prospective cohort study, Aaron et al.[105] found an increase in small for gestational age (SGA) births in HIV patients compared to an HIV-negative population. Therefore it is suggested to follow up HIV patients with serial growth ultrasounds. Ultrasound has been used to investigate abnormal placental implantation in HIV-positive women. Savvidou et al. investigated the effect of maternal HIV infection on the degree of placental invasion through pulsatility index measurements of the uterine arteries during the first trimester. No significant differences, however, were found in placental perfusion of HIV patients compared to non-HIV patients.[106]

Management: All women should be tested immediately upon diagnosis of pregnancy. Repeat testing should be done during the third trimester for patients at high risk of acquiring HIV antenatally. Instrumentation and invasive procedures, such as fetal scalp electrodes, forceps, vacuum suction devices, amniocentesis, cordocentesis, and chorionic villus sampling, may increase the risk of vertical transmission and should be avoided. Davies et al.[107] reviewed the risk of fetal infection with amniocentesis in women with HIV. They concluded that in HIV-positive women noninvasive screening tools, such as maternal serum and fetal ultrasound screening, be preferentially performed prior to the consideration of amniocentesis.[107] Furthermore, artificial

rupture of membranes should be avoided in the absence of obstetrical indications.

Plasma viral load prior to delivery is the strongest predictor of vertical transmission and also will determine the mode of delivery. The American College of Obstetricians and Gynecologists recommend a scheduled cesarean delivery at 38 weeks of gestation for HIV-infected women with viral loads >1,000 copies per mL regardless of the ART regimen.[108] The combination of ART antenatally and intrapartum Zidovudine (AZT) has led to a significant decrease in the rate of vertical transmission of HIV. Prior to vaginal delivery, patients should receive a 2 mg per kg intravenous loading dose of AZT over 1 hour, followed by 1 mg per kg of intravenous AZT until cord clamp.[109] For HIV patients undergoing cesarean delivery, AZT should begin 3 hours before the surgery. Aside from AZT, all other ART drugs should be continued intrapartum.[109] Lastly, antibiotic prophylaxis for Pneumocystis and *Mycobacterium avium* complex may be required according to the CD4 count.

Prognosis: Pregnant patients affected with HIV should be counseled that in the absence of ART, the risk of vertical transmission is approximately 25%. With AZT, the risk is reduced to 5% to 8%. When care includes both AZT and scheduled cesarean delivery, the risk is decreased to 2% or less. A similar risk is seen among women with viral loads of less than 1,000 copies per mL despite the mode of delivery. Neonatal administration of ART has been shown to decrease the rate of seroconversion in a newborn of an HIV-infected mother.[110]

Varicella Zoster Virus

Definition and Incidence: Varicella infection, also known as chickenpox, is uncommon during pregnancy though an important cause of maternal and fetal complications. An incidence of 1.6 to 4.6 per 1,000 has been reported among individuals between 15 and 45 years of age in the United States of America (USA).[111,112] Approximately 90% of adults born in the United States and Europe are immune to VZV. The introduction of universal varicella vaccination has reduced the rate of VZV transmission in some countries.

Serious fetal complications have been associated with varicella acquired during pregnancy. Congenital varicella syndrome (CVS) is more common with maternal infection during the first half of pregnancy and may lead to multiple fetal anomalies. Since the first description of CVS in 1947 by Laforet et al.,[113] several other cases have been reported. Primary VZV during pregnancy may result in congenital infection 25% of the time.[114] Fetal outcomes depend on the time when the infection occurs. If maternal infection takes place during the first 20 weeks of gestation, the incidence of CVS is approximately 1% to 2%. The risk for spontaneous abortion is also increased during this period.[115]

Pathogenesis: Varicella zoster virus (VZV) is a DNA virus of the herpes family and is highly contagious. The primary infection, also referred to as chickenpox, is self-limited. It is transmitted from person to person by direct contact, via respiratory droplets or secretions, or via aerosolization of vesicular fluid from skin lesions. The virus enters the host through the upper respiratory tract.[116] The incubation period usually lasts between 14 and 16 days but can vary from as few as 10 or as many as 21 days after contact.[115] Initially, nonspecific prodromal symptoms, such as fever, chills, headache, malaise, and sore throat, occur, followed by pruritus and a maculopapular rash that becomes vesicular. The rash will crust over in approximately 5 days. The period of contagiousness is 1 to 2 days before the onset of the rash and continues until all lesions are crusted.

Intrauterine infection occurs via transplacental transmission following maternal viremia. The vertical transmission rate increases with advancing gestation age. In a large prospective study, Enders et al.[117] demonstrated that IgM was detected in 5%, 10%, and 25% of infants at birth, following maternal varicella infection during the first, second, and third trimester, respectively. The type of fetal infection depends on the gestational age when the disease takes place. Infection during the first half of pregnancy may be complicated by CVS, while maternal disease around the time of delivery results in neonatal varicella.[118,119]

Diagnosis: The diagnosis of varicella generally is based on its classic clinical manifestations, and laboratory testing is unnecessary. Cases in which clinical manifestations are ambiguous but infection is suspected, culture, fluorescent antigen staining, or PCR testing for VZV DNA can be performed on vesicular fluid or scrapings from the lesions. Serologic tests are generally not of use for diagnosis, because specific antibodies only become detectable after the rash has occurred. At present, there are no reliable prenatal markers to predict fetal disease or severity. Serial ultrasound examinations of the fetus may be useful since some anomalies are not detected sonographically during the first examination.[120] PCR testing has been used to detect VZV infection in amniotic fluid with a high sensitivity and specificity.[121,122] Amniocentesis should not be performed until 1 month after maternal infection to avoid false-negative results.[120,123] VZV cultures from amniotic fluid have a poor sensitivity.[124] Disruptions in the fetal skin may cause an elevation of α-fetoprotein (AFP) in maternal blood and amniotic fluid as well as an increase in acetylcholinesterase within the amniotic fluid.[120]

Ultrasound: Targeted ultrasound is recommended for all patients with documented infection to identify fetal anomalies associated with congenital varicella. Possible findings include IUGR, microcephaly, ventriculomegaly, cerebellar dysplasia, polyhydramnios, oligohydramnios, hydrops, and calcifications in the liver (Fig. 23.13), abdomen, and lungs.[120,125,126]

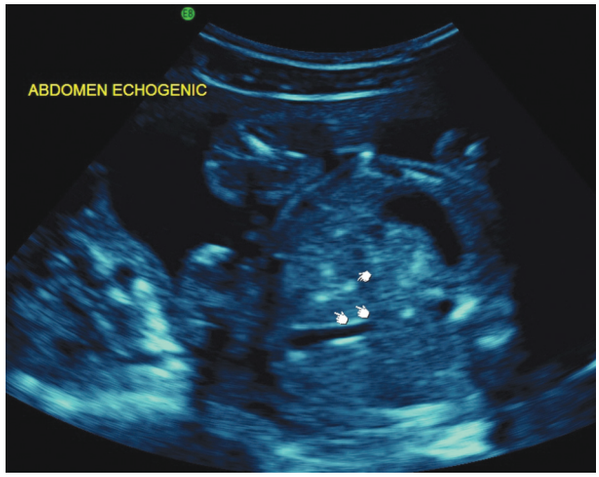

FIGURE 23.13: Liver calcifications seen on cross-sectional ultrasound view of abdomen in a fetus with suspected congenital varicella syndrome.

Limb anomalies, including hypoplasia and contractures, are commonly found in cases of congenital varicella. Free-floating echogenic material and spicular echo reflections surrounding the skin may be indicative of cutaneous lesions.[126] Fetal ocular defects such as cataracts and microphthalmia may be visualized, as well. Interestingly, during a second-trimester ultrasound in a patient with documented varicella infection, a case of congenital pulmonary airway malformation (CPAM) was documented.[127] Multiple bilateral, diffuse hyperechogenic lesions in the lungs as well as multiple sonolucent areas in the liver were the only other noted abnormal images. Of note, sonographic findings associated with varicella fetopathy are nonspecific and may be associated with several other congenital infections, creating a difficulty in obtaining a clear diagnosis.

Fetal MRI may be a valuable adjunct to prenatal ultrasound. Verstraelen et al.[126] reported a case of congenital varicella infection in which additional information was obtained using MRI. During a routine prenatal ultrasound at 26 weeks' gestation, diminished gross fetal body movements, left lower-limb hypoplasia with club-foot deformity, right-kidney pyelectasis, echogenic bowels, and multiple calcifications in the liver and thorax were visualized. CNS lesions including cerebellar hypoplasia, pachygyria, and incomplete opercularization of the Sylvian fissure were missed by ultrasound, but were clearly demonstrated by MRI at 32 weeks. Prenatal MRI may, therefore, contribute to initial sonographic findings which may help enhance patient counseling.[126]

Management: Among adults who do not recall having varicella, the majority of patients are actually immune.[128] A history of varicella or two-dose vaccination is sufficient to reassure a pregnant patient that she is not susceptible to varicella infection. If maternal serology is negative, secondary prevention during pregnancy must be considered. Susceptible pregnant seronegative women exposed to varicella should be offered varicella zoster immunoglobulin (VZIG) to limit maternal disease. Although, optimum protection is obtained when the dose is administered within 96 hours of exposure, some experts suggest that VZIG may be administered with benefit up to 10 days after exposure.[129] VZIG should not be given once active disease has begun.[116] The recommended dose of VZIG is 125 units per 10 kg of body weight, up to a maximum of 625 units. Intravenous immune globulin (IVIG) can be substituted if necessary at a dose of 400 mg per kg if VZIG is not available. If VZIG is not administered within 4 to 10 days of exposure, antiviral therapy may be considered for postexposure prophylaxis; however, some authorities question its safety or efficacy compared to VZIG.

Even though VZIG has been shown to reduce the incidence of symptomatic disease in pregnant women, it does not influence the risk of development of CVS. Since serial ultrasound may lack sensitivity or specificity as a diagnostic tool for fetal varicella syndrome (FVS), invasive prenatal diagnosis to confirm congenital infection should be considered. Although, there is no validated in utero treatment for FVS, a negative amniocentesis result can reassure parents that their child has no risk of FVS or of any long-term impairment.

Prognosis: Maternal infection during the second trimester and early third trimester most often does not result in CVS and is associated with a good prognosis.[130–133] Generally neonates born with CVS have poor outcomes. Isolated cases of more favorable scenarios have been reported.[134,135] Neonatal death usually occurs from intractable gastroesophageal reflux, severe recurrent aspiration pneumonia, or respiratory failure. Structural anomalies are usually not seen with neonatal varicella syndrome. Before VZIG was available, the mortality rate from neonatal varicella syndrome was 31%.[136] Since the introduction of VZIG, the mortality rate has dropped to 7%.[118]

Other Viral Infections

Congenital viral infection with Coxsackie B1 and B5 during the first trimester has been associated with fetal myocarditis resulting in severe heart failure.[79] (pp762–763) Intrauterine infection with enterovirus has been postulated as a possible cause of future development of type 1 diabetes during adolescence.[137]

PARASITIC INFECTIONS

Toxoplasmosis

Definition and Incidence: Toxoplasmosis is a parasitic infection caused by *Toxoplasma gondii*. It is estimated that 400 to 4,000 cases occur in the United States each year.[138–140] Furthermore, recent data suggests that congenital toxoplasmosis occurs in approximately 1 in 10,000 live births.[139] Treatment has been shown to decrease fetal infection rate, thus underscoring the importance of prenatal diagnosis.

Pathogenesis: *T. gondii* undergoes a complex life cycle comprised of three stages known as the tachyzoite, bradyzoite, and sporozoite phases. The tachyzoite phase represents the acute stage of infection where the protozoan invades and replicates within host cells. The bradyzoite phase represents the latent stage of infection where the protozoan exists as a tissue cyst. During the sporozoite phase, the protozoan exists as an environmentally resistant cyst. It is the tachyzoite form of the organism that is responsible for congenital infection. Members of the family Felidae are the definitive reservoir of *T. gondii* while humans are temporary hosts only. During acute infections, cats excrete *T. gondii* oocysts in their feces, and humans are then infected by fecal–oral contact. Other routes of transmission to humans include ingestion of raw or inadequately cooked infected meat or unwashed fruits or vegetables and exposure to contaminated soil from gardening.[141] Sporozoites penetrate the human host's gastrointestinal mucosa and are released in the tachyzoite phase into the systemic circulation. A woman can then transmit the infection to her fetus transplacentally. The incubation period may range from 10 to 23 days after ingestion of undercooked meat, and from 5 to 20 days after ingestion of oocysts from cat feces.[142]

Maternal infection with *T. gondii* prior to conception rarely results in congenital infection.[143] The prevalence of maternal infection is 0.4%, and out of those patients, 40% will develop congenital toxoplasmosis. The risk of congenital infection is directly related to the fetal gestational age. While acute maternal infection occurs between 10% and 25% of the time during the first trimester, it will occur between 60% and 90% of the time during the third trimester.[144,145] The severity of congenital toxoplasmosis, however, is inversely related to fetal gestational age with the most devastating fetal infections occurring during the first half of pregnancy. Significant fetal morbidity and mortality decreases from 75% during the first trimester to almost 0% toward the end of the pregnancy.[79] (763)

Diagnosis: In adults the severity of *T. gondii* infection is correlated with the immune status of the host.[142] Generally, for immunocompetent adults, toxoplasmosis infections result in mild symptoms of lymphadenopathy, fever, fatigue, and malaise that are self-limited and resolve in weeks to months without any specific treatments. In contrast, however, patients who are immunocompromised as a result of AIDS, organ transplants, malignancies, or chronic steroid administration demonstrate severe neurologic manifestations such as meningoencephalitis.

The most common method of diagnosis for acute toxoplasmosis is maternal serum antibody detection; however, individual variation in titers may confound the serologic results. Also, IgM antibodies have been reported to persist for up to 18 months post infection.[146] A negative IgM with a positive IgG result indicates chronic infection. A positive IgM result, on the other hand, may indicate more recent infection or a false-positive reaction. Commercially available test kits for *Toxoplasma* IgG and IgM antibodies have significant variation in sensitivities and specifities.[147] In response to this problem, the FDA in 1997 issued a guide for the interpretation of toxoplasmosis serologic results.[148] Determining when *T. gondii* infection occurred in a pregnant woman is important since infection before conception poses little risk for transmission to the fetus. IgG avidity testing measures the strength with which IgG binds to *T. gondii* and may help to determine when the infection occurred. High IgG avidity indicates that the infection occurred at least 5 months ago; while low IgG avidity reflects a more recent infection.[149] Women with positive serum IgM antibodies should undergo IgG avidity testing by an experienced toxoplasmosis reference laboratory.[149]

After maternal infection is confirmed, congenital toxoplasmosis must be investigated. The identification of *T. gondii* intrauterine infection by amniocentesis using PCR testing has been found to have both high sensitivities and specificities.[150] Foulon et al.[151] reported that a combination of PCR and mouse inoculation of amniotic fluid may improve sensitivities even further. Given the advances in PCR testing of amniotic fluid as well as the risk associated with cordocentesis, amniocentesis is the procedure of choice for the diagnosis of congenital toxoplasmosis infection.

Ultrasound: Ultrasound findings of congenital toxoplasmosis include hydrocephalus, intracranial calcifications, fetal growth restriction, ascites (Fig. 23.14), and hepatosplenomegaly. In a case series published by Hohlfeld et al.,[152] 32 of 89 fetuses with proven congenital toxoplasmosis developed sonographic signs of infection. Ventriculomegaly was found in 25 fetuses, while intracranial calcifications (Fig. 23.15) were found in only 6 fetuses.[152] Furthermore, a number of false negatives were found, with postnatal brain examinations revealing multiple areas of brain necrosis and abscesses in normally reported prenatal studies.[152] With the improvement of ultrasound resolution, the advent of neurosonography, and the addition of fetal MRI, recent studies have been able to better delineate fetal neurologic signs of congenital toxoplasmosis. Malinger et al.[153] in a recent review of eight patients with congenital toxoplasmosis described ventriculomegaly ($n = 7$) and multiple echogenic nodular foci consistent with calcifications in the brain parenchyma ($n = 7$), in the periventricular zone ($n = 3$), and in the caudothalamic zone 9 ($n = 3$). Good correlation has been demonstrated between ultrasound and fetal MRI for diagnosing brain abnormalities in fetal toxoplasmosis.[154,155] Interestingly,

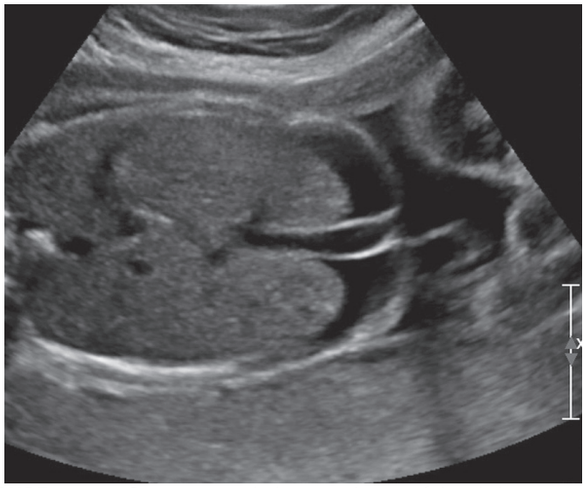

FIGURE 23.14: Cross-sectional ultrasound view of the abdomen at the level of the cord insertion demonstrating ascites in a fetus with congenital toxoplasmosis.

while ultrasound signs of fetal toxoplasmosis are not identified during the routine second trimester ultrasound examination, they may be more commonly detected during the third trimester. It has been speculated that this occurs because of the prolonged time for the fetal insult to develop.[156] Unlike in CMV infection where intracranial echogenic nodules occur most often in the periventricular zone,[157] in toxoplasmosis they may be found dispersed in multiple areas of the fetal brain. Furthermore, periventricular cysts and microcephaly which are characteristic of CMV infections are not common in fetal toxoplasmosis.[153,158] Other non-CNS ultrasound findings such as thickened placenta with hypoechoic areas, liver echogenicities (Fig. 23.16), and hepatomegaly may be visualized, but are not specific for fetal toxoplasmosis.[153]

Management: Since the prevalence of congenital toxoplasmosis is so rare, routine screening during pregnancy for acute toxoplasmosis is not advocated by the American College of Obstetrics and Gynecology[159] and the Royal College of Obstetrics and Gynecology.[160] Routine screening may not be cost effective, but more importantly may result in equivocal or false-positive values, leading to unnecessary treatment and fetal interventions. Interestingly, other countries such as Austria and France have implemented screening programs for toxoplasmosis, demonstrating a decline in the incidence of congenital infection.[161,162] It is difficult to determine whether the proportion of the decline is directly attributable to the program or to the overall general decline in European toxoplasmosis rate.

Treatment for toxoplasmosis infection is available and should be instituted as soon as maternal infection is confirmed. Spiramycin should be started at a maximum dose of 3 g per day in all pregnant women found to have serologic evidence of toxoplasmosis. In the United States, however, spiramycin is not available, but may be obtained from Europe with special approval from the United States Food and Drug Administration. Spiramycin is a macrolide antibiotic that itself does not cross the placenta, but is thought to prevent passage of toxoplasmosis to the fetus.[79] (p165) A combination of pyrimethamine and sulfadiazine has been recommended when congenital infection is confirmed by amniocentesis.[163] Both drugs, however, are contraindicated during the first trimester due to their

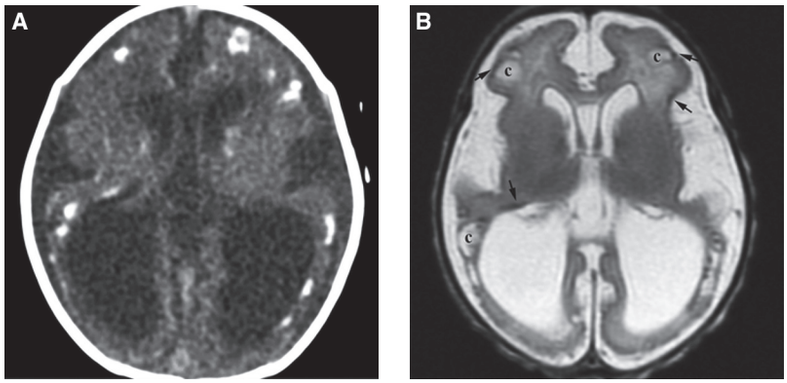

FIGURE 23.15: Congenital toxoplasmosis. **A:** Axial noncontrast CT image in a newborn shows extensive parenchymal calcifications that are predominantly cortical and subcortical in location. Also note moderate ventriculomegaly. Hydrocephalus is more common in toxoplasmosis than in CMV infection. **B:** Axial T2-weighted image shows multiple foci of T2 hypointensity corresponding to CT-confirmed calcification *(black arrows)*. Also note the subcortical cysts (*c*). Ventriculomegaly is moderate. (From Hedlund G, Bale JF, Barkovich AJ. Infections of the developing and mature nervous system. In: Barkovich AJ, Raybaud C, eds. *Pediatric Neuroimaging*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:954–1050.)

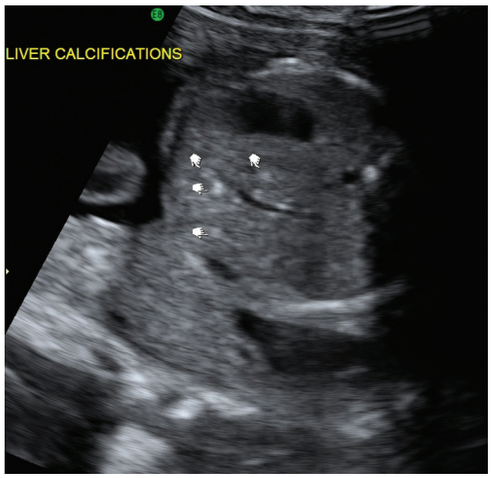

FIGURE 23.16: Axial cross-sectional ultrasound view of multiple nonshadowing hepatic calcifications at 28 weeks' gestation.

teratogenicity. Pyrimethamine is a folic acid antagonist; thus, increasing the risk of neural tube defects if used early in pregnancy. Also, pyrimethamine has been associated with fetal heart and kidney malformations as well as maternal and fetal bone marrow suppression.[164] Sulfadiazine has been associated with an increased incidence of oral clefting. Thus, spiramycin is generally prescribed initially and changed to a pyrimethamine and sulfonamide combination if fetal infection is diagnosed after 15 weeks.[165]

In 2000, the CDC published primary prevention recommendations for pregnant women to avoid toxoplasmosis infection. These guidelines centered around patient and provider education as well as specific hygienic and dietary precautions.[162] Foulon et al.[166] examined the impact of primary prevention on the incidence of toxoplasmosis in pregnancy. Periconceptional education and antenatal education are fundamental in the prevention of maternal and fetal infections. It has been demonstrated that pregnant women who received education sessions were associated with a 63% decrease in toxoplasmosis seroconversion rates compared to women who did not.[166]

Prognosis: The likelihood of long-term sequelae as a result of congenital toxoplasmosis decreases as gestational age increases. Toxoplasmosis acquired during the first trimester may result in a spontaneous abortion while infection incurred during third trimester may be asymptomatic. Although the classic neonatal triad of chorioretinitis, intracranial calcifications, and hydrocephalus is suggestive of congenital toxoplasmosis, up to 90% of neonates affected with congenital toxoplasmosis do not demonstrate obvious signs on routine examination.[152,167] Other findings often seen in congenital toxoplasmosis include lymphadenopathy, hepatosplenomegaly, mental retardation, seizures, encephalitis, malaise, arthralgia, low-grade fever, and occipital and cervical lymphadenopathy. Indeed, disease sequelae may only become apparent when visual impairment, mental and cognitive abnormalities of variable severity, seizures, or learning disabilities present after several months or years.

Other Parasitic Infections

Apart from congenital toxoplasmosis, other sources of congenital parasitic infections include malaria, schistosomiasis, and trypanosomiasis. Malaria infection during pregnancy can have a huge impact on both the mother and the fetus, leading to still birth, premature delivery, or fetal growth restriction. Fetal anemia and splenomegaly have also been described in cases of congenital malaria.[168] Considering the poor outcomes associated with congenital malaria,[169,170] fetal ultrasound surveillance in endemic areas to detect and treat cases during pregnancy needs to be actively implemented.

Schistosomiasis mansoni has also been demonstrated to cause placental insufficiency, leading to fetal growth restriction.[171] *Trypanosoma cruzi* can cause congenital Chagas disease. Fetal

organs, including the heart, brain, integumentary and gastrointestinal systems, may be affected, leading to hepatosplenomegaly, anemia, jaundice, and encephalitis.

BACTERIAL INFECTIONS

Syphilis

Definition and Incidence: Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum.* According to World Health Organization (WHO), 12 million people are infected with syphilis each year.[172] In the Unites States, the rate of syphilis among women was 1.1 cases per 100,000 women in 2010, while the rate of congenital syphilis was 8.7 cases per 100,000 live births.[173] In 2008, the WHO reported that approximately 1.9 million pregnant women had active syphilis.[174] The importance of accurate prenatal diagnosis of syphilis was emphasized by Hawkes et al.[175] in a recent meta-analysis, who stated that approximately 70% of pregnant women infected with syphilis will have an adverse pregnancy outcome. Both the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend screening for syphilis at the first prenatal visit and again at 32 to 36 weeks, in high-risk women. Furthermore, CDC recommends screening at delivery.[176]

Pathogenesis: Syphilis is horizontally transmitted via vaginal, anal, or oral sex. Approximately 3 weeks after infection, a round, small, and painless syphilitic chancre may appear on the vulva, vagina, cervix, anus, or rectum indicating primary infection. This lesion may last for 3 to 6 weeks and often goes unrecognized by the host. Eventually *Treponema spirochetes* disseminate systemically, resulting in the cutaneous and mucosal manifestations of secondary infection, lasting for up to a year. During this time the disease can be especially contagious. After primary or secondary syphilis, the infection may enter a latent phase, causing no symptoms to the host. This phase of the disease is divided into early and late depending on the duration of the infection. Initial infection occurring within the previous 12 months and beyond 12 months is characterized as early latent and late latent syphilis respectively. Importantly, during the latent phase, transmission to the fetus may still occur.[177] In approximately one-third of the people who go untreated, tertiary syphilis may develop. Skin, bone, or liver gumma, CNS abnormalities, and cardiovascular disorders are associated with tertiary syphilis. During this stage, individuals are not considered infectious.[178]

Diagnosis: The most specific test for the diagnosis of syphilis when an active chancre or condyloma latum is present is dark field microscopy. In the absence of active lesions, serologic testing for syphilis is performed. Serologic testing includes nontreponemal tests (NTTs) and treponemal tests (TTs). Generally, NTTs are used for screening and monitoring therapy, while TTs are for diagnostic confirmation. The Venereal Disease Research Laboratory (VDRL) test and the rapid plasma reagin (RPR) test are the most commonly used NTTs. Since NTTs detect antibodies to cardiolipin, a compound commonly found in human tissue, false-positive reactions can occur. TTs detect an interaction between serum immunoglobulins and surface antigens of *T. pallidum.* They include the fluorescent treponemal antibody absorption (FTA-ABS) test, the treponemal-specific, microhemagglutination assay for *T. pallidium* (MHA-TP), and

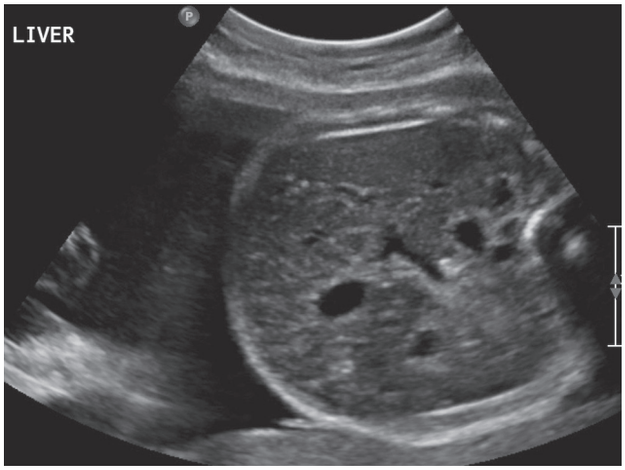

FIGURE 23.17: Axial ultrasound view of the abdomen demonstrating hepatomegaly in a fetus with congenital syphilis.

T. pallidum particle agglutination test (TP-PA). Although far less common than in NTTs, false-positive reactions may still occur in diseases such as Lyme disease and leptospirosis.[177] Unlike NTTs which may become negative, TTs usually remain positive for life.

Ultrasound: In the presence of maternal syphilis, ultrasound findings of fetal hydrops, hepatosplenomegaly (Fig. 23.17), polyhydramnios, and thick placenta strongly suggest congenital syphilis. Other sonographic features include intrahepatic calcifications, ascites, hyperechogenic bowel, and even fetal death. Amniotic fluid dark field testing or PCR may be performed for confirmatory diagnosis. Hematologic sampling for fetal IgM anti-treponemal antibodies has been reported.[179] The degree of fetal hepatomegaly in pregnancies with syphilis has been correlated with amniotic fluid infection.[180] Dilatation of fetal bowel segments has been reported in case of congenital syphilis.[181] Hill and Maloney[182] reported fetal GI tract obstruction involving the stomach and small bowel in a case of congenital syphilis. Treponemal involvement of the intestine causing syphilitic enterocolitis has been described previously in stillbirths.[183] Wendel and Gilstrap[184] reported an association between hyperechogenicity of the vasculature in the basal ganglia and congenital syphilis. It has been demonstrated that congenital infection can result in placental villitis and obliterative arteritis; therefore, resulting in placentomegaly and increased placental vascular resistance.[182] Lucas et al.[185] showed that mean S/D ratios of both the uterine and umbilical arteries were significantly increased in pregnancies affected by syphilis. Interestingly, in a case described by Schulman et al.[186] where decreased fetal movement was the initial complaint, fetal cardiac failure followed by bradycardia was noted. The pathologic examination revealed acute syphilitic funisitis. Using 3D ultrasound, Araujo et al.[187] demonstrated oligodactyly and twisting of the toes in a case of congenital syphilis.

Management: Treatment of maternal infection is effective for both the prevention and the treatment of congenital syphilis. Penicillin G, parenterally administered, is the recommended treatment. In a randomized controlled trial performed by Radcliffe et al.,[188] penicillin G was found to be the most effective treatment for syphilis. The appropriate penicillin regimen

varies according to the stage of infection.[189] A single dose of 2.4 million units of benzathine penicillin G is recommended for the treatment of primary syphilis, secondary syphilis, and early latent syphilis.[189] In cases of late latent syphilis or latent syphilis of unknown duration, the same dosage should be given and repeated twice at weekly intervals.[189] Because penicillin G does not cross the blood–brain barrier, aqueous crystalline penicillin G of 3 to 4 million units parenterally every 4 hours for 10 to 14 days is the treatment of choice for neurosyphilis.[189] Pregnant women who have a history of a penicillin allergy should be desensitized and treated. The titer of NTT antibodies reflects disease activity, with a 4-fold decrease suggesting adequate therapy and a 4-fold increase indicating active disease.

Prognosis: Congenital syphilis is classified as either early congenital syphilis (ECS) or late congenital syphilis (LCS). ECS appears in the first 2 years of life while LCS appears afterwards. Both ECS and LCS affect a variety of organ systems. Findings of ECS include hepatomegaly, splenomegaly, anemia, thrombocytopenia, leukopenia, macular–papular lesions over the hands and feet, ulceration of the nasal mucosa and cartilage (saddle nose deformity), periostitis, osteochondritis, nephrosis, neurosyphilis, and ocular malformations. Findings of LCS include peg-shaped, notched central incisors (Hutchinson teeth), multicuspid first molars (mulberry molars), interstitial keratitis, palsy of cranial nerve 8, rhinitis, impaired maxillary growth, saddle nose deformity, mental retardation, hydrocephalus, seizure disorders, periostitis of the skull, tibia (saber shin), and the clavicle (Higouménakis sign), and symmetric, tender joints (Clutton joints). The prognosis of congenital syphilis is dependent upon a number of factors, including the gestational age when vertical transmission occurred, stage of maternal syphilis, maternal treatment, and immunological response of the fetus.[190]

Other Bacterial Infections

Other bacteria that may cause congenital infections include *Listeria, Chlamydia, Mycoplasma, Mycobacterium,* and *Coxiella*. Q fever infection in pregnancy, caused by *Coxiella burnetii*, is associated with various maternal and neonatal adverse outcomes, including IUGR, stillbirth, preterm delivery, and oligohydramnios.[191,192] Shinar et al.[192] described two pregnancies complicated by Q fever, that resulted in placental infection and abruption remote from term.

Although congenital tuberculosis is rare, a perinatal mortality of nearly 50% has been reported.[193] Clinical presentation of tuberculosis during pregnancy and infancy is often nonspecific, making recognition difficult. Tuberculosis has been associated with increased antenatal admission, premature delivery, IUGR, and maternal–fetal mortality.[194–196] Abramowsky et al.[197] described two cases of placental involvement with *Mycobacterium tuberculosis* causing acute villitis and intervillitis. Principal neonatal sites of involvement include the liver and lungs; however, the bones, kidneys, spleen, GI tract, skin, and lymph nodes may also be affected. Generally, the diagnosis of congenital infection only occurs during the early neonatal period when clinical manifestations present. Common nonspecific clinical symptoms such as fever, respiratory distress, and hepatosplenomegaly most commonly appear within 2 to 3 weeks of delivery.[198] A high index of suspicion by health professionals is paramount in order to detect and manage tuberculosis in pregnancy and the early newborn period.

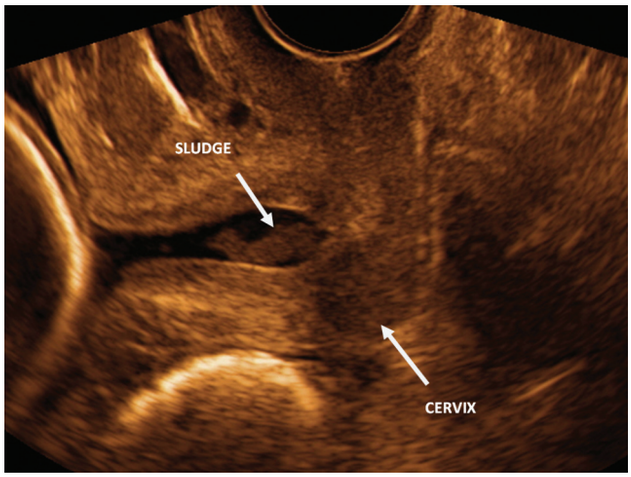

FIGURE 23.18: Transvaginal ultrasound demonstrating intra-amniotic sludge associated with cervical funneling at 24 gestational weeks.

Listeria monocytogenes infection is a rare complication of pregnancy.[199] Intrauterine infection by *L. monocytogenes* has been associated with preterm delivery, meconium-stained amniotic fluid, hydrocephalus, chorioamnionitis, stillbirth, and neonatal death.[200,201] Prompt treatment with antibiotics is paramount in improving maternal and neonatal outcome.[202]

Mycoplasma and ureaplasma have been associated with chorioamnionitis, preterm delivery, and pregnancy loss.[203,204] Intrauterine infection with ureaplasma has also been associated with congenital pneumonia.[205]

Intra-amniotic Sludge

Intra-amniotic sludge is represented by the sonographic appearance of free-floating hyperechoic matter close to the internal cervical os (Fig. 23.18). It has been associated with an increased risk for preterm delivery and other adverse pregnancy outcomes. The precise nature of this material is unclear; however, it has been attributed to bleeding, meconium, vernix, and intrauterine infection.[206–209] For a more comprehensive review, please refer to chapters 7 and 10.

SUMMARY

In summary, the global impact of congenital infections is significant. Although sonography by itself is not a sensitive test for fetal infection, the utilization of ultrasound technology assited by fetal MRI along with other markers for congenital infection may influence clinical management, assist in prognostication, and aid in patient counseling. Indeed, particular findings such as an elevated MCA-PSV in the setting of congenital parvovirus may indicate the need for in utero fetal treatment. As diagnostic fetal imaging continues to advance, sonography will remain an invaluable tool for clinicians involved in the prenatal diagnosis of congenital infections.

REFERENCES

1. Stegmann BJ, Carey JC. TORCH infections: toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), and herpes infections. *Curr Womens Health Rep*. 2002;2(4):253–258.
2. Crino JP. Ultrasound and fetal diagnosis of perinatal infection. *Clin Obstet Gynecol*. 1999;42(1):71–80.

3. Pultoo A, et al. Detection of cytomegalovirus in urine of hearing-impaired and mentally retarded children by PCR and cell culture. *J Commun Dis*. 2000;32(2):101–108.
4. Stagno S, et al. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus, and clinical outcome. *JAMA*. 1986;256(14):1904–1908.
5. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. *Obstet Gynecol Surv*. 2010;65(11):736–743.
6. Malm G, Engman ML. Congenital cytomegalovirus infections. *Semin Fetal Neonatal Med*. 2007;12(3):154–159.
7. Hanshaw JB. Cytomegalovirus infections. *Pediatr Rev*. 1995;16(2):43–48.
8. Stagno S, et al. Maternal cytomegalovirus infection and perinatal transmission. *Clin Obstet Gynecol*. 1982;25(3):563–576.
9. Liesnard C, et al. Prenatal diagnosis of congenital cytomegalovirus infection: prospective study of 237 pregnancies at risk. *Obstet Gynecol*. 2000;95(6, pt 1): 881–888.
10. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. *Semin Perinatol*. 2007;31(1):10–18.
11. Grangeot-Keros L, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. *J Infect Dis*. 1997;175(4):944–946.
12. Boppana SB, et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J*. 1992;11(2):93–99.
13. Jones CA. Congenital cytomegalovirus infection. *Curr Probl Pediatr Adolesc Health Care*. 2003;33(3):70–93.
14. de Vries LS, et al. The spectrum of cranial ultrasound and magnetic resonance imaging abnormalities in congenital cytomegalovirus infection. *Neuropediatrics*. 2004;35(2):113–119.
15. Malinger G, Lev D, Lerman-Sagie T. Imaging of fetal cytomegalovirus infection. *Fetal Diagn Ther*. 2011;29(2):117–126.
16. Noyola DE, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr*. 2001;138(3):325–331.
17. Guerra B, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. *Am J Obstet Gynecol*. 2008;198(4):380.e1–380.e7.
18. Gonce A, et al. Maternal IgM antibody status in confirmed fetal cytomegalovirus infection detected by sonographic signs. *Prenat Diagn*. 2012;32(9):817–821.
19. Nigro G, et al. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med*. 2005;353(13):1350–1362.
20. Jacquemard F, et al. Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection. *BJOG*. 2007;114(9):1113–1121.
21. Puliyanda DP, et al. Successful use of oral ganciclovir for the treatment of intrauterine cytomegalovirus infection in a renal allograft recipient. *Transpl Infect Dis*. 2005;7(2):71–74.
22. Negishi H, et al. Intraperitoneal administration of cytomegalovirus hyperimmunoglobulin to the cytomegalovirus-infected fetus. *J Perinatol*. 1998;18(6, pt 1):466–469.
23. Sato A, et al. Intrauterine therapy with cytomegalovirus hyperimmunoglobulin for a fetus congenitally infected with cytomegalovirus. *J Obstet Gynaecol Res*. 2007;33(5):718–721.
24. Japanese Congenital Cytomegalovirus Infection Immunoglobulin Fetal Therapy Study Group. A trial of immunoglobulin fetal therapy for symptomatic congenital cytomegalovirus infection. *J Reprod Immunol*. 2012;95(1–2):73–79.
25. Matsuda H, Kawakami Y, Furuya K, et al. Intrauterine therapy for a cytomegalovirus-infected symptomatic fetus. *BJOG*. 2004;111(7):756–757.
26. Buxmann H, et al. Use of cytomegalovirus hyperimmunoglobulin for prevention of congenital cytomegalovirus disease: a retrospective analysis. *J Perinat Med*. 2012;40(4):439–446.
27. Brown T, et al. Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet*. 1984;2(8410):1033–1034.
28. Heegaard ED, Brown KE. Human parvovirus B19. *Clin Microbiol Rev*. 2002;15(3):485–505.
29. Dembinski J, et al. Long term follow up of serostatus after maternofetal parvovirus B19 infection. *Arch Dis Child*. 2003;88(3):219–221.
30. Chisaka H, et al. Parvovirus B19 and the pathogenesis of anaemia. *Rev Med Virol*. 2003;13(6):347–359.
31. Nyman M, et al. Detection of human parvovirus B19 infection in first-trimester fetal loss. *Obstet Gynecol*. 2002;99(5, pt 1):795–798.
32. Wattre P, et al. A clinical and epidemiological study of human parvovirus B19 infection in fetal hydrops using PCR Southern blot hybridization and chemiluminescence detection. *J Med Virol*. 1998;54(2):140–144.
33. Yaegashi N, et al. The frequency of human parvovirus B19 infection in nonimmune hydrops fetalis. *J Perinat Med*. 1994;22(2):159–163.
34. Rodis JF. Parvovirus infection. *Clin Obstet Gynecol*. 1999;42(1):107–120.
35. Enders M, et al. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. *Prenat Diagn*. 2004;24(7):513–518.
36. Miller E, et al. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *BJOG*. 1998;105(2):174–178.
37. DeHann T, Oepkes D, Beersma MFC. Aetiology, diagnosis and treatment of hydrops foetalis. *Curr Pediatr Rev*. 2005;1:63–72.
38. Jordan J, et al. Human parvovirus B19: prevalence of viral DNA in volunteer blood donors and clinical outcomes of transfusion recipients. *Vox Sang*. 1998;75(2):97–102.
39. Torok T. Human parvovirus B19. In: Remington JS, Klein JO, eds. *Infectious Disease of the Fetus and Newborn Infant*. 4th ed. Philadelphia, PA: Saunders; 1995:668–702.
40. Rouger P, Gane P, Salmon C. Tissue distribution of H, Lewis and P antigens as shown by a panel of 18 monoclonal antibodies. *Rev Fr Transfus Immunohematol*. 1987;30(5):699–708.
41. Jordan JA, Butchko AR. Apoptotic activity in villous trophoblast cells during B19 infection correlates with clinical outcome: assessment by the caspase-related M30 Cytodeath antibody. *Placenta*. 2002;23(7):547–553.
42. Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on Fifth Disease. *BMJ*. 1990;300(6733):1166–1170.
43. Koch WC, et al. Serologic and virologic evidence for frequent intrauterine transmission of human parvovirus B19 with a primary maternal infection during pregnancy. *Pediatr Infect Dis J*. 1998;17(6):489–494.
44. de Jong EP, et al. Parvovirus B19 infection in pregnancy. *J Clin Virol*. 2006;36(1):1–7.
45. Anderson MJ, et al. Experimental parvoviral infection in humans. *J Infect Dis*. 1985;152(2):257–265.
46. Beersma MF, et al. Parvovirus B19 viral loads in relation to VP1 and VP2 antibody responses in diagnostic blood samples. *J Clin Virol*. 2005;34(1): 71–75.
47. Cosmi E, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia resulting from parvovirus infection. *Am J Obstet Gynecol*. 2002;187(5):1290–1293.
48. Ergaz Z, Ornoy A. Parvovirus B19 in pregnancy. *Reprod Toxicol*. 2006;21(4):421–435.
49. Markenson G, et al. Parvoviral infection associated with increased nuchal translucency: a case report. *J Perinatol*. 2000;20(2):129–131.
50. Simchen MJ, et al. Fetal hepatic calcifications: prenatal diagnosis and outcome. *Am J Obstet Gynecol*. 2002;187(6):1617–1622.
51. Yaron Y, et al. Evaluation of fetal echogenic bowel in the second trimester. *Fetal Diagn Ther*. 1999;14(3):176–180.
52. Zerbini M, et al. Intra-uterine parvovirus B19 infection and meconium peritonitis. *Prenat Diagn*. 1998;18(6):599–606.
53. Mari G, et al; for the Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Engl J Med*. 2000;342(1):9–14.
54. Fairley CK, et al. Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B19 infection. *Lancet*. 1995;346(8986):1335–1337.
55. Dembinski J, et al. Neurodevelopmental outcome after intrauterine red cell transfusion for parvovirus B19-induced fetal hydrops. *BJOG*. 2002;109(11): 1232–1234.
56. Isumi H, et al. Fetal brain infection with human parvovirus B19. *Pediatr Neurol*. 1999;21(3):661–663.
57. Lindenburg IT, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study. *Am J Obstet Gynecol*. 2012;206(2):141.e1–141.e8.
58. Weisse ME. The fourth disease, 1900–2000. *Lancet*. 2001;357(9252):299–301.
59. Zimmerman L, Reef S. Congenital rubella syndrome. In: *VPD Surveillance Manual*. 3rd ed. Washington, DC: Centers for Disease Control and Prevention; 2002.
60. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Disease. Atkinson W, Hamborsky J, Wolfe S, et al, eds. 12th ed. Second printing. Washington DC: Public Health Foundation, 2012
61. Ciofi Degli Atti ML, et al. Pediatric sentinel surveillance of vaccine-preventable diseases in Italy. *Pediatr Infect Dis J*. 2002;21(8):763–768.
62. Gabutti G, et al. Epidemiology of measles, mumps and rubella in Italy. *Epidemiol Infect*. 2002;129(3):543–550.
63. Best JM, Bantavala J. Rubella. In: Pattison JR, ed. *Principles and Practice of Clinical Virology*. 4th ed. New York: John Wiley & Sons; 2000:387–418.
64. Horstmann DM, Liebhaber H, Kohorn EI. Post-partum vaccination of rubella-susceptible women. *Lancet*. 1970;2(7681):1003–1006.
65. Miron D, On A. Congenital rubella syndrome after maternal immunization [in Hebrew]. *Harefuah*. 1992;122(5):291–293.
66. Enders G, et al. Outcome of confirmed periconceptional maternal rubella. *Lancet*. 1988;1(8600):1445–1447.
67. Remington J. *Infectious Diseases of the Fetus and Newborn Infant*. 5th ed. Philadelphia, PA: WB Saunders; 2001.
68. Best JM, et al. Interpretation of rubella serology in pregnancy—pitfalls and problems. *BMJ*. 2002;325(7356):147–148.
69. Bosma TJ, et al. PCR for detection of rubella virus RNA in clinical samples. *J Clin Microbiol*. 1995;33(5):1075–1079.
70. Hudson P, Morgan-Capner P. Evaluation of 15 commercial enzyme immunoassays for the detection of rubella-specific IgM. *J Clin Virol*. 1996;5(1):21–26.
71. Almeida JD, Griffith AH. Viral infections and rheumatic factor. *Lancet*. 1980;2(8208–8209):1361–1362.
72. Akingbade D, Cohen BJ, Brown DW. Detection of low-avidity immunoglobulin G in oral fluid samples: new approach for rubella diagnosis and surveillance. *Clin Diagn Lab Immunol*. 2003;10(1):189–190.
73. Ben Salah A, et al. Validation of a modified commercial assay for the detection of rubella-specific IgG in oral fluid for use in population studies. *J Virol Methods*. 2003;114(2):151–158.
74. World Health Organization. *Report of a Meeting on Preventing Congenital Rubella Syndrome: Immunization Strategies, Surveillance Needs*. Geneva, Switzerland: World Health Organization; 2000:12–14.

75. Ramsay ME, et al. Salivary diagnosis of rubella: a study of notified cases in the United Kingdom, 1991–4. *Epidemiol Infect*. 1998;120(3):315–319.
76. Terry GM, et al. First trimester prenatal diagnosis of congenital rubella: a laboratory investigation. *Br Med J (Clin Res Ed)*. 1986;292(6525):930–933.
77. Migliucci A, et al. Prenatal diagnosis of congenital rubella infection and ultrasonography: a preliminary study. *Minerva Ginecol*. 2011;63(6):485–489.
78. Ugurbas SH, et al. Microphthalmos: clinical and ultrasonographic findings. *Ann Ophthalmol (Skokie)*. 2007;39(2):112–122.
79. Boyle MK, Pretorius DH. Fetal infections. In: Nyberg DA, McGahan JP, Pretorius DH, et al, eds. *Diagnostic Imaging of Fetal Anomalies*. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:756.
80. Andrade J. Congenital Rubella syndrome and fetal exencephaly: a case report. *Ultrasound Obstet Gynecol*. 2000;16(suppl S1):72.
81. Ferreira SM, et al. Semilunar valvar stenosis associated with congenital Rubella syndrome. *Braz J Infect Dis*. 1998;2(5):256–259.
82. Moore JW, Mullins CE. Severe subaortic stenosis associated with congenital rubella syndrome: palliation by percutaneous transcatheter device occlusion of a patent ductus arteriosus. *Pediatr Cardiol*. 1986;7(4):221–223.
83. Varghese PJ, Izukawa T, Rowe RD. Supravalvular aortic stenosis as part of rubella syndrome, with discussion of pathogenesis. *Br Heart J*. 1969;31(1):59–62.
84. Wui ET, Ling LH, Yang H. Severe aortic regurgitation: an exceptional cardiac manifestation of congenital rubella syndrome. *Int J Cardiol*. 2006;113(2):e46–e47.
85. Levy-Bruhl D, Six C, Parent I. Rubella control in France. *Euro Surveill*. 2004;9(4):15–16.
86. Centers for Disease Control and Prevention. Seroprevalence of herpes simplex virus type 2 among persons aged 14–49 years: United States, 2005–2008. *MMWR Morb Mortal Wkly Rep*. 2010;59(15):456–459.
87. Whitley R, Davis EA, Suppapanya N. Incidence of neonatal herpes simplex virus infections in a managed-care population. *Sex Transm Dis*. 2007;34(9):704–708.
88. Clinical manifestations and diagnosis of genital herpes simplex virus infection. *UpToDate*. 2011. http://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-diagnosis-of-genital-herpes-simplex-virus-infection.
89. Dickson N, et al. Risk of herpes simplex virus type 2 acquisition increases over early adulthood: evidence from a cohort study. *Sex Transm Infect*. 2007;83(2):87–90.
90. Lanouette JM, et al. Prenatal diagnosis of fetal herpes simplex infection. *Fetal Diagn Ther*. 1996;11(6):414–416.
91. Jayaram PM, Wake CR. A rare case of absent corpus callosum with severe ventriculomegaly due to congenital herpes simplex infection. *J Obstet Gynaecol*. 2010;30(3):316.
92. Diguet A, et al. Prenatal diagnosis of an exceptional intrauterine herpes simplex type 1 infection. *Prenat Diagn*. 2006;26(2):154–157.
93. Duin LK, et al. Major brain lesions by intrauterine herpes simplex virus infection: MRI contribution. *Prenat Diagn*. 2007;27(1):81–84.
94. World Health Organization. Global summary of the AIDS epidemic: 2009. http://data.unaids.org/pub/report/2009/jc1700_epi_update_2009_en.pdf.
95. World Health Organization. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress Rep. 2010:97. http://whqlibdoc.who.int/publications/2010/9789241500395_eng.pdf.
96. Branson BM, Handsfield HH, Lampe MA, et al; Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55:1–17.
97. Center, N.H.A.C.C., Compendium of State HIV Testing Laws. 2011. www .hivlawandpolicy.org/.../compendium-state-hiv-testing-laws-quick- reference-guide-clinicians-national-hivaids.
98. Ray N, Doms RW. HIV-1 coreceptors and their inhibitors. *Curr Top Microbiol Immunol*. 2006;303:97–120.
99. Joao EC, et al. Maternal antiretroviral use during pregnancy and infant congenital anomalies: the NISDI perinatal study. *J Acquir Immune Defic Syndr*. 2010;53(2):176–185.
100. Cotter AM, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis*. 2006;193(9):1195–1201.
101. Kourtis AP, et al. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS*. 2007;21(5):607–615.
102. Szyld EG, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. *AIDS*. 2006;20(18):2345–2353.
103. Tuomala RE, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr*. 2005;38(4):449–473.
104. Palaii N. Late intrauterine growth restriction in HIV pregnant women in developed countries. *Ultrasound Obstet Gynecol*. 2009;34(S1):151.
105. Aaron E, et al. Small-for-gestational-age births in pregnant women with HIV, due to severity of HIV disease, not antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2012;2012:135030.
106. Savvidou MD, et al. First trimester maternal uterine artery Doppler examination in HIV-positive women. *HIV Med*. 2011;12(10):632–636.
107. Davies G, et al. Amniocentesis and women with hepatitis B, hepatitis C, or human immunodeficiency virus. *J Obstet Gynaecol Can*. 2003;25(2):145–148, 149–152.
108. Opinion AC, Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. *Int J Gynaecol Obstet*. 2001;73:279–281.
109. Davis JA, Yawetz S. Management of HIV in the pregnant woman. *Clin Obstet Gynecol*. 2012;55(2):531–540.
110. Department of Health and Human Services, P.o.A.G.f.A.a.A.,Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2011:1–268. http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines003005.pdf.
111. Enders G, Miller E. Varicella and herpes zoster in pregnancy and the newborn. In: Arvin AM, Gershon AA, editors. *Varicella-Zoster Virus Virology and Clinical Management*. Cambridge, England: Cambridge University Press; 2000:317–347.
112. Lamont RF, et al. Varicella-zoster virus (chickenpox) infection in pregnancy. *BJOG*. 2011;118(10):1155–1162.
113. Laforet EG, Lynch CL Jr. Multiple congenital defects following maternal varicella; report of a case. *N Engl J Med*. 1947;236(15):534–537.
114. Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med*. 1986;314(24):1542–1546.
115. Smith CK, Arvin AM. Varicella in the fetus and newborn. *Semin Fetal Neonatal Med*. 2009;14(4):209–217.
116. Gardella C, Brown ZA. Managing varicella zoster infection in pregnancy. *Cleve Clin J Med*. 2007;74(4):290–296.
117. Enders G, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet*. 1994;343(8912):1548–1551.
118. Miller E, Cradock-Watson JE, Ridehalgh MK. Outcome in newborn babies given anti-varicella-zoster immunoglobulin after perinatal maternal infection with varicella-zoster virus. *Lancet*. 1989;2(8659):371–373.
119. Sauerbrei A, Wutzler P. Neonatal varicella. *J Perinatol*. 2001;21(8):545–549.
120. Mandelbrot L. Fetal varicella: diagnosis, management, and outcome. *Prenat Diagn*. 2012;32(6):511–518.
121. Leung J, et al. Evaluation of laboratory methods for diagnosis of varicella. *Clin Infect Dis*. 2010;51(1):23–32.
122. Mendelson E, et al. Laboratory assessment and diagnosis of congenital viral infections: rubella, cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), parvovirus B19 and human immunodeficiency virus (HIV). *Reprod Toxicol*. 2006;21(4):350–382.
123. Koren G. Congenital varicella syndrome in the third trimester. *Lancet*. 2005;366(9497):1591–1592.
124. Mouly F, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. *Am J Obstet Gynecol*. 1997;177(4):894–898.
125. Tan M, Koren G. Chickenpox in pregnancy: revisited. *Reprod Toxicol*. 2006: 410–420.
126. Verstraelen H, et al. Prenatal ultrasound and magnetic resonance imaging in fetal varicella syndrome: correlation with pathology findings. *Prenat Diagn*. 2003;23:705–709.
127. Fernandez-Aguilar S, et al. Congenital pulmonary airway malformation and congenital varicella infection—a possible association. *Ultrasound Obstet Gynecol*. 2005;26(6):680–682.
128. Watson B, et al. Validity of self-reported varicella disease history in pregnant women attending prenatal clinics. *Public Health Rep*. 2007;122(4):499–506.
129. Salisbury D, Ramsay M, Noakes K. *Immunisation Against Infectious Disease: The Green Book*. 3rd ed. London, England: The Department of Health; 2006:421–442.
130. Balducci J, Rodis JF, Rosengren S, et al. Pregnancy outcome following first-trimester varicella infection. *Obstet Gynecol*. 1992;79:5–6.
131. Siegel M. Congenital malformations following chickenpox, measles, mumps and hepatitis. *JAMA*. 1973;226:1521–1524.
132. Darfour P, de Bievre P, Vinatier N, et al. Varicella and pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1996;66:119–123.
133. Michie CA, Acolet D, Charlton R, et al. Varicella-zoster contracted in the second trimester of pregnancy. *Pediatr Infect Dis J*. 1992;11:1050–1053.
134. Kotchmar GS Jr, Grose C, Brunell PA. Complete spectrum of the varicella congenital defects syndrome in 5-year-old child. *Pediatr Infect Dis*. 1984;3(2):142–145.
135. Schulze A, Dietzsch HJ. The natural history of varicella embryopathy: a 25-year follow-up. *J Pediatr*. 2000;137(6):871–874.
136. Meyers JD. Congenital varicella in term infants: risk reconsidered. *J Infect Dis*. 1974;129(2):215–217.
137. Elfving M, et al. Maternal enterovirus infection during pregnancy as a risk factor in offspring diagnosed with type 1 diabetes between 15 and 30 years of age. *Exp Diabetes Res*. 2008;2008:271958.
138. Alford CA Jr, Stagno S, Reynolds DW. Congenital toxoplasmosis: clinical, laboratory, and therapeutic considerations, with special reference to subclinical disease. *Bull N Y Acad Med*. 1974;50(2):160–181.
139. Guerina NG, et al. Neonatal serologic screening and early treatment for congenital *Toxoplasma gondii* infection. The New England Regional Toxoplasma Working Group. *N Engl J Med*. 1994;330(26):1858–1863.
140. Kimball AC, Kean BH, Fuchs F. Congenital toxoplasmosis: a prospective study of 4,048 obstetric patients. *Am J Obstet Gynecol*. 1971;111(2):211–218.
141. Dubey JP. Toxoplasmosis. *J Am Vet Med Assoc*. 1994;205(11):1593–1598.
142. Jones JL, et al. Congenital toxoplasmosis: a review. *Obstet Gynecol Surv*. 2001;56(5):296–305.
143. Vogel N, et al. Congenital toxoplasmosis transmitted from an immunologically competent mother infected before conception. *Clin Infect Dis*. 1996;23(5):1055–1060.
144. Dunn D, et al. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet*. 1999;353(9167):1829–1833.
145. Foulon W, et al. Treatment of toxoplasmosis during pregnancy: a multicenter study of impact on fetal transmission and children's sequelae at age 1 year. *Am J Obstet Gynecol*. 1999;180(2, pt 1):410–415.
146. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. 2002;185(suppl 1):S73–S82.

147. Wilson M, et al. Evaluation of six commercial kits for detection of human immunoglobulin M antibodies to *Toxoplasma gondii*. The FDA Toxoplasmosis Ad Hoc Working Group. *J Clin Microbiol*. 1997;35(12):3112–3115.
148. Administration, FDA public health advisory: limitations of toxoplasmosis IgM commercial test kits. 1997. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062411.htm.
149. Montoya JG, et al. VIDAS test for avidity of *Toxoplasma*-specific immunoglobulin G for confirmatory testing of pregnant women. *J Clin Microbiol*. 2002;40(7):2504–2508.
150. Hohlfeld P, et al. Prenatal diagnosis of congenital toxoplasmosis with a polymerase-chain-reaction test on amniotic fluid. *N Engl J Med*. 1994;331(11):695–699.
151. Foulon W, et al. Prenatal diagnosis of congenital toxoplasmosis: a multicenter evaluation of different diagnostic parameters. *Am J Obstet Gynecol*. 1999;181(4):843–847.
152. Hohlfeld P, et al. Fetal toxoplasmosis: ultrasonographic signs. *Ultrasound Obstet Gynecol*. 1991;1(4):241–244.
153. Malinger G, et al. Prenatal brain imaging in congenital toxoplasmosis. *Prenat Diagn*. 2011;31(9):881–886.
154. Cuillier F. Case of the week #168. TheFetus.net. 2006-02-27. http://sonoworld.com/fetus/case.aspx?id=1696.
155. Garel C. MRI ot the fetal brain. In: *Normal Development and Cerebral Pathologies*. Springer: Berlin; 2004.
156. Gay-Andrieu F, et al. Fetal toxoplasmosis and negative amniocentesis: necessity of an ultrasound follow-up. *Prenat Diagn*. 2003;23(7):558–560.
157. Becker LE. Infections of the developing brain. *AJNR Am J Neuroradiol*. 1992;13(2):537–549.
158. Baron J, et al. The incidence of cytomegalovirus, herpes simplex, rubella, and toxoplasma antibodies in microcephalic, mentally retarded, and normocephalic children. *Pediatrics*. 1969;44(6):932–939.
159. ACOG Practice Bulletin. Perinatal viral and parasitic infections. Number 20, September 2000. (Replaces educational bulletin number 177, February 1993). American College of Obstetrics and Gynecologists.
160. Newton LH, Hall SM. Survey of local policies for prevention of congenital toxoplasmosis. *Commun Dis Rep CDR Rev*. 1994;4(10):R121–R124.
161. Aspock H, Pollak A. Prevention of prenatal toxoplasmosis by serological screening of pregnant women in Austria. *Scand J Infect Dis Suppl*. 1992;84:32–37.
162. Lopez A, et al. Preventing congenital toxoplasmosis. *MMWR Recomm Rep*. 2000;49(RR-2):59–68.
163. Dorangeon PH, et al. The risks of pyrimethamine-sulfadoxine combination in the prenatal treatment of toxoplasmosis. *J Gynecol Obstet Biol Reprod (Paris)*. 1992;21(5):549–556.
164. Remington J. Toxoplasmosis. In: Remington JS, Klein J, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 5th ed. Philadelphia, PA: WB Saunders; 2001:205–346.
165. Gilbert R, Gras L. Effect of timing and type of treatment on the risk of mother to child transmission of *Toxoplasma gondii*. *BJOG*. 2003;110(2):112–120.
166. Foulon W, et al. Impact of primary prevention on the incidence of toxoplasmosis during pregnancy. *Obstet Gynecol*. 1988;72(3, pt 1):363–366.
167. Wilson CB, et al. Development of adverse sequelae in children born with subclinical congenital *Toxoplasma* infection. *Pediatrics*. 1980;66(5):767–774.
168. Chigozie JU. Impact of placental *Plasmodium falciparum* malaria on pregnancy and perinatal outcome in Sub-Saharan Africa. *Yale J Biol Med*. 2007;80(3):95–103.
169. Desai M, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. 2007;7(2):93–104.
170. Poespoprodjo JR, et al. Vivax malaria: a major cause of morbidity in early infancy. *Clin Infect Dis*. 2009;48(12):1704–1712.
171. Bittencourt AL, et al. Placental involvement in schistosomiasis mansoni: report of four cases. *Am J Trop Med Hyg*. 1980;29(4):571–575.
172. World Health Organization. The global elimination of congenital syphilis: rationale and strategy for action. 2007. http://www.who.int/reproductivehealth/publications/rtis/9789241595858/en/.
173. Centers for Disease Control and Prevention. Sexually transmitted diseases surveillance. 2010. http://www.cdc.gov/STD/stats10/default.htm.
174. World Health Organization. Towards eliminating congenital syphilis. 2011. http://www.who.int/reproductivehealth/topics/rtis/cs_regional_updates/en/.
175. Hawkes S, et al. Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. *Lancet Infect Dis*. 2011;11(9):684–691.
176. Centers for Disease Control and Prevention. Syphilis. CDC Fact Sheet. 2012.
177. Ingall D. Syphilis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 5th ed. Philadelphia, PA: WB Saunders; 2001:643–681.
178. Kent ME, Romanelli F. Reexamining syphilis: an update on epidemiology, clinical manifestations, and management. *Ann Pharmacother*. 2008;42(2):226–236.
179. Hallak M, et al. Nonimmune hydrops fetalis and fetal congenital syphilis: a case report. *J Reprod Med*. 1992;37(2):173–176.
180. Nathan L, et al. Fetal syphilis: correlation of sonographic findings and rabbit infectivity testing of amniotic fluid. *J Ultrasound Med*. 1993;12(2):97–101.
181. Satin AJ, Twickler DM, Wendel GD Jr. Congenital syphilis associated with dilation of fetal small bowel: a case report. *J Ultrasound Med*. 1992;11(1):49–52.
182. Hill LM, Maloney JB. An unusual constellation of sonographic findings associated with congenital syphilis. *Obstet Gynecol*. 1991;78(5, pt 2):895–897.
183. D'Aunoy R, Pearson B. Intestinal lesions in congenital syphilis. *Arch Pathol*. 1939;27:239–248.
184. Wendel G, Gilstrap LC. Syphilis during pregnancy. In: Gillstrap LC, Faro S, eds. *Infections in Pregnancy*. New York: Alan R. Liss; 1990:115–125.
185. Lucas MJ, Theriot SK, Wendel GD Jr. Doppler systolic-diastolic ratios in pregnancies complicated by syphilis. *Obstet Gynecol*. 1991;77(2):217–222.
186. Schulman H, Miller JN, Dolisi F. The pathophysiology of acute syphilitic funisitis. *Ultrasound Obstet Gynecol*. 1991;1:353–356.
187. Araujo Júnior E, et al. Prenatal diagnosis of congenital syphilis using two- and three-dimensional ultrasonography: case report. *Case Rep Infect Dis*. 2012;2012:478436.
188. Radcliffe M. et al. Single-dose benzathine penicillin in infants at risk of congenital syphilis—results of a randomised study. *S Afr Med J*. 1997;87(1):62–65.
189. Workowski K. Sexually transmitted diseases treatment guidelines. *MMWR Morb Mortal Wkly Rep*. 2010;59(RR-12):1–113.
190. Saloojee H. The prevention and management of congenital syphilis: an overview and recommendations. *Bull World Health Organ*. 2004;82(6):424–430.
191. Jover-Diaz F, et al. Q fever during pregnancy: an emerging cause of prematurity and abortion. *Infect Dis Obstet Gynecol*. 2001;9(1):47–49.
192. Shinar S, Skornick-Rapaport A, Rimon E. Placental abruption remote from term associated with Q fever infection. *Obstet Gynecol*. 2012;120(2, pt 2):503–505.
193. Peker E, Bozdogan E, Dogan M. A rare tuberculosis form: congenital tuberculosis. *Tuberk Toraks*. 2010;58(1):93–96.
194. Carter EJ, Mates S. Tuberculosis during pregnancy: the Rhode Island experience, 1987 to 1991. *Chest*. 1994;106(5):1466–1470.
195. Hamadeh MA, Glassroth J. Tuberculosis and pregnancy. *Chest*. 1992;101(4):1114–1120.
196. Llewelyn M, et al. Tuberculosis diagnosed during pregnancy: a prospective study from London. *Thorax*. 2000;55(2):129–132.
197. Abramowsky CR, Gutman J, Hilinski JA. *Mycobacterium tuberculosis* infection of the placenta: a study of the early (innate) inflammatory response in two cases. *Pediatr Dev Pathol*. 2012;15(2):132–136.
198. Peng W, Yang J, Liu E. Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009. *Pediatr Pulmonol*. 2011;46(12):1215–1224.
199. Rivera-Alsina ME, et al. Listeria monocytogenes: an important pathogen in premature labor and intrauterine fetal sepsis. *J Reprod Med*. 1983;28(3):212–214.
200. Cheng BR, Kuo DM, Hsieh TT. Perinatal listeriosis: a case report. *Chang Gung Med J*. 1990;13(2):152–156.
201. Valkenburg MH, Essed GG, Potters HV. Perinatal listeriosis underdiagnosed as a cause of pre-term labour? *Eur J Obstet Gynecol Reprod Biol*. 1988;27(4):283–288.
202. Nolla-Salas J, et al. Perinatal listeriosis: a population-based multicenter study in Barcelona, Spain (1990–1996). *Am J Perinatol*. 1998;15(8):461–467.
203. Cassell G. Mycoplasmal infections. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 5th ed. Philadelphia, PA: WB Saunders; 2001:733–767.
204. Cassell GH, et al. Ureaplasma urealyticum intrauterine infection: role in prematurity and disease in newborns. *Clin Microbiol Rev*. 1993;6(1):69–87.
205. Cassell GH, et al. Isolation of *Mycoplasma hominis* and *Ureaplasma urealyticum* from amniotic fluid at 16–20 weeks of gestation: potential effect on outcome of pregnancy. *Sex Transm Dis*. 1983;10(4 suppl):294–302.
206. Benacerraf BR, Gatter MA, Ginsburgh F. Ultrasound diagnosis of meconium-stained amniotic fluid. *Am J Obstet Gynecol*. 1984;149(5):570–572.
207. DeVore GR, Platt LD. Ultrasound appearance of particulate matter in amniotic cavity: vernix or meconium? *J Clin Ultrasound*. 1986;14(3):229–230.
208. Romero R, et al. What is amniotic fluid "sludge"? *Ultrasound Obstet Gynecol*. 2007;30(5):793–798.
209. Sherer DM, et al. Sonographically homogeneous echogenic amniotic fluid in detecting meconium-stained amniotic fluid. *Obstet Gynecol*. 1991;78(5, pt 1):819–822.