Cytomegalovirus Infection in Pregnancy: Should All Women Be Screened?

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Cytomegalovirus (CMV) is the most common cause of congenital infection and complicates approximately 1% of all live births. Primary maternal CMV infection carries a 30% to 40% risk of vertical transmission to the fetus. In cases where maternal CMV infection is suspected, it is important to evaluate the risk to the fetus to provide appropriate counseling and guidance to parents. This article reviews the published literature and summarizes current diagnostic and management recommendations to help answer the question, should all women be screened for CMV infection in pregnancy?
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Cytomegalovirus (CMV) is the most common cause of congenital infection.[1] Moreover, congenital CMV is the most frequently identified viral cause of mental retardation and is the leading nongenetic cause of neurosensory hearing loss.[2,3] In developed countries, congenital CMV infection occurs in 0.3% to 2.4% of all live births.[4] Infection in the newborn can be acquired through close contact (via contaminated blood, urine, and secretions), vertically through transplacental transmission, and postnatally through breast milk.[1] Most symptomatic neonatal CMV infections occur when a woman is newly infected just prior to or during pregnancy.[5,6] Primary maternal CMV infection in

pregnancy carries a 30% to 40% risk of vertical transmission.[1] Of all pregnancies with confirmed vertical transmission, only 10% to 20% of the fetuses will have evidence of clinical infection at birth.[1] As compared with women who are infected in the latter half of pregnancy, women who develop primary CMV infection in the first trimester are more likely to deliver fetuses with sensorineural hearing loss (24% vs 2.5%) or other CNS sequelae, such as mental retardation, cerebral palsy, seizures, or chorioretinitis (32% vs 15%).[7] Mothers who are CMV seropositive prior to pregnancy can also develop a secondary CMV infection either due to reactivation of virus residing at specific sites in the body (primarily the salivary glands) or reinfection with a different viral strain.[6] Such infections tend to be less severe and are usually asymptomatic for both mother and newborn. Infants born to such mothers can also have sequelae of congenital CMV, but this is far less likely (estimated at 0.2% to 2%).[8] In cases where maternal CMV infection is suspected, it is important to evaluate the risk to the fetus of being infected and/or symptomatically affected by CMV to provide appropriate counseling and guidance to parents. We present a case of fetal CMV infection to illustrate and highlight some of the diagnostic and therapeutic issues raised by CMV infection.

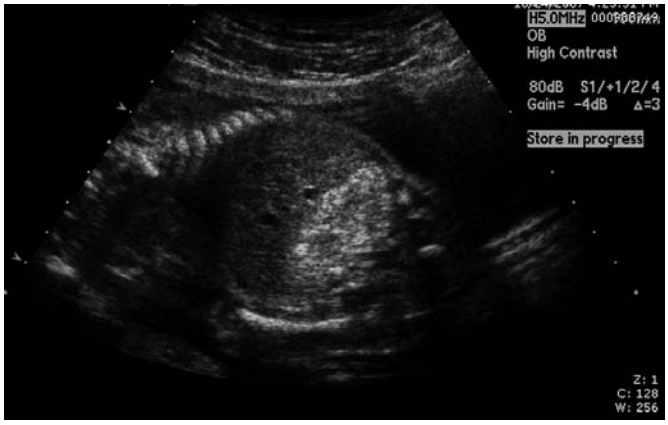
Case Report

A healthy 29-year-old woman (G2, P1) with a well-dated spontaneous conception was seen for routine ultrasound examination at 18-0/7 weeks of gestation. The fetus was noted to have echogenic bowel (Figure 1) and intrauterine growth restriction (IUGR) with an estimated fetal weight in the 9th percentile. Her past obstetric history was remarkable for severe preeclampsia resulting in an induction of labor and vaginal delivery at 34 weeks of gestation 2 years earlier. Maternal serologic tests performed in light of the ultrasound findings revealed elevated CMV IgM and IgG titers. Amniotic fluid was strongly positive for CMV DNA by quantitative real-time polymerase chain reaction (RT-qPCR). After extensive counseling as to the diagnosis of fetal CMV and their options, including pregnancy termination, the couple chose to continue the pregnancy. After consultation with an infectious disease specialist, CMV immune globulin (200 U/kg, for a total dose of 10 g intravenous [IV]) was recommended starting at 25 weeks of gestation with subsequent doses of 5 g IV planned at monthly intervals. Fetal magnetic resonance imaging (MRI) at 25 weeks of gestation showed no evidence of intracranial calcifications or abnormalities.

At 30 weeks of gestation, following 2 doses of CMV immune globulin, the fetal heart-rate tracing was noted to have absent variability and repetitive late decelerations (category III). A biophysical profile was 2/10 (2 points for amniotic fluid volume only) and umbilical artery Doppler velocimetry showed reversed end-diastolic flow. A viable female infant was delivered by emergent cesarean weighing 920 g with Apgar scores of 2, 7, and 10 at 1, 5, and 10 minutes, respectively. Cord blood analysis showed an arterial pH of 7.16 and base excess of −12.5 and venous of pH 7.29 and base excess of −8.9. The neonate was intubated and admitted to neonatal intensive care. Chest radiography showed ground glass opacities consistent with congenital CMV pneumonia. Hematologic abnormalities included thrombocytopenia, coagulopathy, elevated transaminase levels, and hyperbilirubinemia. CMV antigenemia was present in the infant's blood, and CMV DNA was identified in urine and cerebrospinal fluid. Placental pathology showed diffuse fibrin deposition and villous edema. Specific immunostaining of the placenta was positive for CMV (Figure 2).

The infant was treated with IV ganciclovir (6 mg/kg twice daily) with subsequent resolution of laboratory and imaging abnormalities over a 10-day period. Ultrasound examination

Figure 1. *Representative perinatal ultrasound image showing fetal echogenic bowel. Fetal echogenic bowel refers to increased echogenicity or brightness of the fetal bowel noted on second trimester ultrasound examination. The diagnosis of echogenic bowel should be reserved for fetuses in which the echogenicity of the bowel is equal to or greater than that of adjacent bone. The differential diagnosis of fetal echogenic bowel includes cystic fibrosis, infection with cytomegalovirus or toxoplasmosis, meconium ileus, and chromosomal abnormalities (including Turner syndrome and trisomy 21, 13, or 18).*



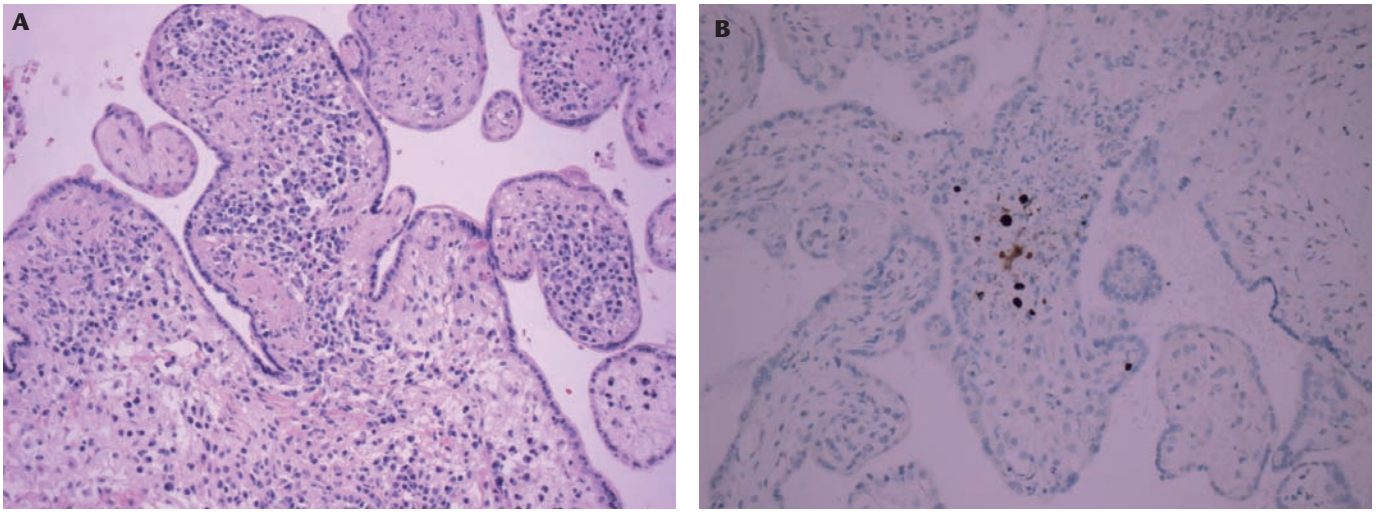


Figure 2. *Representative histologic images of a placenta with cytomegalovirus (CMV) infection.* **(A)** *Placental histology shows moderate villous edema, intervillous fibrin deposition, amnion hyperplasia, and grade I inflammation.* **(B)** *Specific immunostaining confirms the presence of CMV infection.*

of the head and abdomen showed no evidence of calcifications, ventriculomegaly, or hepatosplenomegaly prior to treatment. Ophthalmologic examination showed no evidence of retinitis. However, the infant failed multiple newborn hearing screens and appeared to have profound bilateral deafness. Antiviral therapy was continued for 6 weeks. The infant was discharged home in stable condition on day of life 55.

Discussion

CMV infection is very common in the United States, with 50% to 80% of reproductive-age women showing serological evidence of previous infection.[9] Reproductive-age women of middle and higher socioeconomic status are at higher risk for primary CMV, as approximately half are seronegative for CMV antibodies and are therefore susceptible to infection during pregnancy. In day care centers, approximately 80% of young children will develop CMV within 2 years.[10] Although these children are typically asymptomatic, they will continue to shed virus for years after initial acquisition. Many women with exposure to young children will acquire a CMV infection within 1 year.[1,11] Women with impaired cellular response (eg, patients with HIV/acquired immunodeficiency syndrome [AIDS] or those receiving immunosuppressive therapy) are at higher risk of acquiring CMV infection and, because they are less likely to produce neutralizing antibodies, they are also at higher risk of transmitting the virus to their fetuses.[5]

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How Should the Diagnosis Be Confirmed in the Mother?

Maternal CMV tends to be asymptomatic and patients will rarely be diagnosed by clinical symptoms alone. For most infections, evidence of maternal seroconversion (defined as a conversion from a negative to a positive IgM or a 4-fold increase in IgG antibody titer over a 4- to 6-week period) is sufficient to confirm the diagnosis of a primary infection. However, the accuracy of maternal anti-CMV IgM to predict primary maternal infection is complicated by the fact that IgM antibodies can persist for months or even years after primary infection, and also can be found in the setting of reactivation or reinfection with a different strain of CMV.[12]

Another method of determining the timing of maternal CMV infection is to measure antibody avidity, which refers to the strength of antibody binding to a target antigen. As the immune response to a particular antigen matures over time, avidity increases. Thus, detection of low-avidity anti-CMV IgG early in pregnancy suggests a recent acute infection, and can be used to identify pregnant women at increased risk of having an infected fetus.[4,13] In contrast, the presence of high-avidity antibodies at 12 to 16 weeks of gestation indicates a past infection, likely prior to conception. Improvement in CMV IgM testing has been reported by performing gel electrophoresis Western blotting of CMV viral polypeptides and

may provide the most accurate way to diagnose a primary maternal CMV infection.[12] Although available in Europe, this test is not available in the United States.

How Should the Diagnosis Be Confirmed in the Fetus?

In cases of confirmed maternal CMV infection, it is important to evaluate the risk of fetal infection to provide appropriate counseling and guidance to parents. Perinatal ultrasound can aid in identifying structural or growth abnormalities that may suggest symptomatic fetal infection. These abnormalities include echogenic bowel, IUGR, ventriculomegaly, placental thickening, brain calcifications, evidence of hydrops fetalis, and/or abnormal amniotic fluid volume[14,15] (Table 1). These ultrasound findings are not specific for congenital CMV infection, and there may be other causes for these findings[16] (Table 2). Moreover, only 15% of CMV-infected fetuses will display ultrasound abnormalities.[14] However, the presence of ultrasound abnormalities in a pregnant woman with confirmed primary maternal CMV infection is strongly suggestive of fetal infection.[14]

Table 1
Ultrasound Features of Congenital Cytomegalovirus Infection

- Cerebral ventriculomegaly
- Microcephaly
- Hyperechogenic fetal bowel
- Hepatosplenomegaly
- Cerebral periventricular echogenicity/ intracranial calcifications
- Intrauterine growth restriction
- Abnormal amniotic fluid volume
- Placental enlargement
- Ascites and fetal hydrops

Table 2
Differential Diagnosis of Congenital Cytomegalovirus Infection

- Rubella
- Toxoplasmosis
- Syphilis
- Herpes simplex virus
- Enterovirus

In cases of confirmed maternal CMV infection, it is important to evaluate the risk of fetal infection to provide appropriate counseling and guidance to parents.

Amniocentesis may be performed to confirm fetal infection, and is recommended in situations where maternal primary or undefined CMV infection is detected in the first half of pregnancy or in cases where sonographic fetal abnormalities are suggestive of infection. Amniotic fluid should be sent for viral culture and for polymerase chain reaction (PCR) testing for the CMV genome. False-negative results may occur if amniocentesis is performed prior to 21 weeks of gestation because the virus is slow growing and may not be excreted by the fetal kidneys in sufficient quantities for detection in early pregnancy.[4] If viral culture and PCR for CMV are both negative, congenital CMV can be effectively excluded at that time; if positive, this suggests the presence of fetal infection, although the impact on the fetus cannot be determined. Further evaluation by serial ultrasound examinations for signs of fetal brain involvement (intracranial calcifications, ventriculomegaly, microcephaly) or DNA quantification by RT-qPCR may provide additional prognostic information.[17] Fetal thrombocytopenia detected by fetal blood sampling has also been reported to be an independent predictor of poor fetal outcome,[18] but is not generally recommended.

Following birth, CMV infection in the newborn should be confirmed by isolating the virus in the urine and/or saliva in the first 2 to 3 weeks of life. Thereafter, PCR can detect the viral genome in the newborn's blood with equal sensitivity and specificity. CMV IgM antibodies are present in only 70% of infected infants and do not effectively rule out congenital infection.[4] Infants with congenital CMV infection should undergo further testing (including a detailed physical examination and additional radiologic and hematologic tests) to determine whether the infection should be classified as symptomatic.

What Is the Prognosis for the Fetus?

A diagnosis of fetal CMV infection does not equate to an affected fetus, as 80% to 90% of fetuses with congenital CMV infection are asymptomatic at birth. For the 10% to 20% of fetuses who are symptomatic at birth, however, outcomes are generally poor.[1,5,19] Signs and symptoms may include neurologic deficits (eg, seizures, chorioretinitis, hypotonia, hearing loss, microcephaly, and intracranial calcifications) as well as hematologic abnormalities (eg, petechiae, thrombocytopenia, and evidence of liver disease as manifested by jaundice, transaminitis, hyperbilirubinemia, and hepatosplenomegaly). Infants may also show evidence of growth restriction and failure to thrive.

Of CMV-infected children who are asymptomatic at birth, 8% to 15% will develop hearing loss and psychomotor delay later in life.[20]

In vitro and animal studies suggest that CMV hyperimmune globulin (HIG) may be effective in minimizing the damage caused by CMV infection.

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Should CMV Hyperimmune Globulin or Antiviral Agents Be Recommended in Pregnancy?

Because of the poor prognosis associated with primary maternal CMV diagnosed early in pregnancy, elective termination should be discussed as an option. Women who wish to continue the pregnancy may be offered one of several medical therapies; however, these should all still be regarded as investigational.

Ganciclovir has been used extensively in newborns with symptomatic CMV infections. In such newborns, a 6-week course of IV ganciclovir has been shown to significantly reduce the incidence of hearing loss, although some newborns will experience neutropenia.[21] Information on the safety and efficacy of ganciclovir in pregnancy, however, is extremely limited. Animal data have shown an increased risk of fetal malformations when ganciclovir was used in higher than normal doses in pregnancy, although case reports in humans suggest no increased risk of malformations.[5]

In a small pilot study, oral valacyclovir was administered to 21 pregnant women with confirmed CMV-symptomatic fetuses. The medication was well tolerated and a decrease in CMV viral load was noted in the cord blood of the treated fetuses; however, given the small sample size, no clear improvement in perinatal outcome could be demonstrated.[22] Further studies are necessary to determine the safety and efficacy of antiviral agents in the treatment of CMV during pregnancy.

For example, when pregnant guinea pigs were exposed to CMV followed by administration of a neutralizing antisera, fetal survival increased significantly as compared with those animals who did not receive passive immunization, and a similar reduction was noted in fetal infection, placental inflammation, and IUGR.[23,24] CMV HIG consists of enriched CMV-specific immunoglobulins and has been studied extensively in post-transplant patients for CMV prophylaxis.[25,26] It is marketed in the United States as Cytogam® (CSL Behring, King of Prussia, PA).

Nigro and colleagues[27] conducted a multicenter, prospective study of 181 pregnant women with primary CMV infection. Of these women, 79 underwent amniocentesis and 55 were found to have CMV-positive amniotic fluid. Of these, 31 women elected to receive 200 U/kg CMV HIG administered monthly, 14 women elected not to receive HIG, and 10 women elected to terminate the pregnancy. Only 3% (1/31) of fetuses who received HIG were symptomatic at birth as compared with 50% (7/14) of the infants whose mothers declined HIG. In this nonrandomized study, administration of HIG to the mother and the presence of fetal ultrasound abnormalities prior to treatment were important predictors of fetal outcome. In a second study by the same investigators, 3 women with CMV-associated fetal cerebral abnormalities received HIG infusions during pregnancy. In all 3 cases, the fetal ventriculomegaly regressed, other associated abnormalities resolved, and the 3 infants were reportedly developing normally by age 5.[28]

Additional case reports from other investigators have suggested that antenatal administration of CMV HIG may be associated with more favorable outcomes in fetuses suspected of having congenital CMV infection.[29-32] CMV HIG has been given by maternal IV injection, intra-amniotic injection, intraperitoneal injection into the fetus, and by direct IV injection into the umbilical vein. The optimum dosage, route of administration, and indications for its use, along with confirmation of its efficacy in randomized, prospective clinical studies, still need to be identified. However, the use of CMV HIG and/or antiviral agents such as valacyclovir in fetuses with confirmed CMV infection may be an option for women who plan to continue the pregnancy.

Is There a Vaccine Available Against CMV?

In 1999, the Institute of Medicine report entitled, *Vaccines for the 21st Century: A Tool for Decision Making,* stated that development of a CMV vaccine was the highest priority for new vaccines.[33] Recently, a vaccine targeted toward CMV envelope glycoprotein B, an antigen that typically induces a serum antibody response, entered phase 2 clinical trial.[34] This vaccine

Recently, a vaccine targeted toward CMV envelope glycoprotein B, an antigen that typically induces a serum antibody response, entered phase 2 clinical trial. This vaccine has already been shown to be immunogenic with an acceptable risk profile.

has already been shown to be immunogenic with an acceptable risk profile. In this trial, CMV infection occurred in 18 of 225 subjects in the vaccine group (8%) and in 31 of 216 subjects in the placebo group (14%). Four congenital CMV infections occurred as a result of maternal infection during pregnancy. There were 3 congenitally infected infants in the placebo group (1 of which went on to develop severe neurologic sequelae) and 1 congenitally infected infant in the vaccine group (who was asymptomatic).[34] Although these numbers are too small to support any definitive conclusions, they are consistent with our knowledge of decreased CMV transmission in women who carry protective antibodies. Future studies are necessary to demonstrate the safety and efficacy of this vaccine before it can be used for primary prevention of congenital CMV.

Prevention of CMV in Pregnant Women

Given the limited success of vaccine prevention of CMV, attention has been directed at patient education as a means of preventing the acquisition of infection (Table 3). Because 15% to 70% of children in day care acquire CMV infection, attempts at prevention have focused primarily on mothers of small children. It has been shown that CMV-seronegative women have a 5- to 25-fold increased risk of developing CMV if exposed to children in day care.[11] In a study of 166 seronegative women with a young child in day care, women given information concerning handwashing, gloves for diaper changes, and avoiding certain types of intimate contact (sharing utensils, kissing on the lips) were compared with those not given this information.[35] Both groups showed an overall seroconversion rate of 7.8%. However, CMV-seronegative mothers who knew their infant's serostatus and were pregnant had a lower risk of seroconversion (5.8%) as compared with those who were not pregnant (41.6%), suggesting that knowledge of their infant's status and the motivation during pregnancy to avoid becoming infected led to a decrease in acquiring CMV. This also suggests that personal knowledge of a woman's own susceptibility to CMV through screening may be useful when designing and implementing prevention strategies.

Currently, the American College of Obstetricians and Gynecologists (ACOG) recommends that all women be educated about the ways that CMV infection may be acquired in pregnancy.[36] They recommend careful handling of potentially infected articles, such as diapers, and thorough handwashing when around young children or immunocompromised individuals. The Centers for Disease Control and Prevention (CDC) confirms the ACOG recommendations, but also adds that pregnant women with children under the age of 6 should avoid sharing utensils and kissing their children on the lips or cheek.[37] Despite these recommendations, a recent survey study by ACOG of 305 obstetrician-gynecologists reported that only 44% routinely counsel their patients about CMV prevention.[38]

Should All Patients Be Screened for CMV?

Although ACOG recommends that pregnant women be educated about CMV prevention, they have not endorsed routine screening in pregnancy.[36] The CDC also acknowledges that screening for CMV in pregnant women is not currently recommended. However, they add that, for women planning to become pregnant, routine CMV screening can help them to understand how careful they must be to prevent infection.[37] The reasons given for not recommending routine screening have included the difficulties in accurate diagnosis given the high false-positive rate of commercial IgM testing, the lack of effective treatment of infection during pregnancy, and the possibility of reinfection or virus reactivation in a seropositive woman. In a recent decision-analytic model evaluating options for maternal CMV screening, Cahill and colleagues[39] noted that universal screening was cost effective as long as CMV HIG achieved at least a 47% reduction in neonatal disease. In countries such as Italy where CMV

Table 3
Strategies to Prevent CMV Infection in Women Who Are or Will Become Pregnant

- Educate women with young children or who work with young children that they are at increased risk and that attention to hygiene will help prevent cytomegalovirus (CMV) transmission
- Careful handing of potentially infected articles, such as diapers
- Thorough hand washing when around young children or immunocompromised individuals
- Avoiding sharing utensils
- Avoid kissing children < 6 years on the mouth or cheek

Adapted from American College of Obstetricians and Gynecologists[36] and Centers for Disease Control and Prevention.[37,38]

screening is more widespread, the high incidence of false-positive CMV IgM has been studied. In a series of 1857 pregnant women with a reported positive CMV IgM test, only 26% were thought to represent a true primary CMV infection as confirmed by additional testing with IgG avidity and CMV immunoblot technology, whereas 54% of cases were believed to represent previous infection without active disease, and 20% were thought to be reactivation/secondary infection.[40] Such studies underscore the need for appropriate confirmatory testing to determine the true fetal risk as well as appropriate specialists to provide counseling for the heightened patient anxiety that could result from more widespread screening. However, with improvements in serologic testing (eg, IgG avidity or IgM immunoblot technology) coupled with effective treatments (CMV HIG, antiviral agents, or vaccination), it is hoped that the introduction of more widespread screening of women for CMV serostatus prior to or at the onset of pregnancy will lead to significant improvements in clinical outcome.

Conclusions

CMV is an important cause of congenital infection and can result in significant perinatal morbidity and health care expense. Although existing data suggest a benefit to HIG prophylaxis, additional clinical trials are needed to confirm these observations. Until then, the use of HIG and other antiviral agents for treatment remains experimental. In the absence of proven therapies for congenital CMV infection, prevention is critical. Most importantly, patients, especially those exposed to young children, should be counseled about the importance of careful hand hygiene practices, an intervention that has been proven to decrease the risk of primary CMV infection and subsequent fetal transmission. ■

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Main Points

- Maternal cytomegalovirus (CMV) tends to be asymptomatic and patients will rarely be diagnosed by clinical symptoms alone. For most infections, evidence of maternal seroconversion is sufficient to confirm the diagnosis of a primary infection.
- Perinatal ultrasound can aid in identifying structural or growth abnormalities that may suggest symptomatic fetal infection. Amniocentesis may be performed to confirm fetal infection, and is recommended in situations where maternal primary or undefined CMV infection is detected in the first half of pregnancy or in cases where sonographic fetal abnormalities are suggestive of infection. Following birth, CMV infection in the newborn should be confirmed by isolating the virus in the urine and/or saliva in the first 2 to 3 weeks of life.
- A diagnosis of fetal CMV infection does not equate to an affected fetus, as 80% to 90% of fetuses with congenital CMV infection are asymptomatic at birth. For the 10% to 20% of fetuses who are symptomatic at birth, however, outcomes are generally poor.
- Because of the poor prognosis associated with primary maternal CMV diagnosed early in pregnancy, elective termination should be discussed as an option. Women who wish to continue the pregnancy may be offered one of several medical therapies; however, these should all still be regarded as investigational.
- Given the limited success of vaccine prevention of CMV, attention has been directed at patient education as a means of preventing the acquisition of infection. Currently, the American College of Obstetricians and Gynecologists recommends careful handling of potentially infected articles, such as diapers, and thorough handwashing when around young children or immunocompromised individuals. The Centers for Disease Control and Prevention adds that pregnant women with children under the age of 6 should avoid sharing utensils and kissing their children on the lips or cheek.
- For women planning to become pregnant, routine CMV screening can help them to understand how careful they must be to prevent infection.

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