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# Cytomegalovirus Infection in Pregnancy

**Nicole L. Davis**[*], **Caroline C. King**,
**Athena P. Kourtis**

Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

## Abstract

Cytomegalovirus (CMV) is a DNA herpesvirus that is common worldwide. The two known main sources of primary CMV infection during pregnancy are through sexual activity and contact with young children. Primary infection occurs in approximately 1 to 4% of pregnancies, and is mostly asymptomatic in immunocompetent adults. However, primary infection may manifest as a mild mononucleosis or flu-like syndrome with persistent fever and fatigue. CMV can be transmitted from mother-to-child in utero, intrapartum, or during breastfeeding. Intrauterine transmission can lead to congenital CMV infection, a leading cause of permanent hearing and vision loss and neurological disability among children. Congenital CMV transmission rates are as high as 50% in women who acquire primary CMV infection during pregnancy, and less than 2% in women with nonprimary infection. There is no licensed CMV vaccine. Good hygiene practices and avoiding intimate contact with young children (e.g., kissing on the mouth and sharing utensils) have been suggested as an approach to prevent maternal primary CMV infection during pregnancy, but remains an unproven method of reducing the risk of congenital CMV infection. Approximately 1 in 10 infants who acquire CMV in utero will have clinical signs at birth, and an additional 10 to 15% will go on to develop late-onset sequelae. Antiviral treatment prenatally and postnatally has not proven effective at preventing congenital or postnatal CMV infection, and is not recommended for routine clinical care. However, antiviral treatment when initiated in the first month of life for symptomatic congenital CMV infection is recommended for improved neurodevelopmental and audiologic outcomes.

### Keywords

congenital infection; cytomegalovirus; pregnancy

## Introduction

Cytomegalovirus (CMV) is a DNA herpesvirus that is endemic worldwide. Like all herpesviruses, CMV has biological properties of latency and reactivation, and, therefore,

[*]Correspondence to: Nicole L. Davis, Centers for Disease Control and Prevention, 4770 Buford Highway, MS F-74, Atlanta, GA 30341-3717., dwg4@cdc.gov.

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is a lifelong infection (Alford et al., 1990). The specific mechanisms controlling latency are unclear, but immunosuppressive disease or use of immunosuppressive chemotherapy can induce activation from the latent state. Similarly, conferred CMV immunity does not prevent reinfection with a new CMV strain, and many genetically different strains circulate throughout the world (Alford and Britt, 1990).

In utero transmission to the infant can lead to congenital CMV infection. Congenital CMV infection is the most common intrauterine infection and a leading cause of infectious disability (Kenneson and Cannon, 2007; Revello et al., 2015). Permanent hearing and vision loss and neurological disability are among the most severe sequelae of congenital infection. The burden of congenital CMV disease in children exceeds that caused by other well-known childhood syndromes and diseases, such as fetal alcohol spectrum disorders, Down syndrome, and spina bifida (Cannon and Davis, 2005). This review covers maternal CMV infection during pregnancy and congenital CMV infection, with specific focus on epidemiology, diagnosis, management, and prevention.

## EPIDEMIOLOGY

CMV prevalence varies by population, with an estimated 40 to 100 percent of individuals infected with CMV (Krech et al., 1971; Bate et al., 2010; Cannon et al., 2010). Seroprevalence tends to be highest in lower socio-economic groups, racial and ethnic minority populations, and women of higher parity and advanced maternal age (Gratacap-Cavallier et al., 1998; Mustakangas et al., 2000; Staras et al., 2006; Kenneson and Cannon, 2007). Women with young children in daycare also tend to be at increased risk of primary CMV infection due to high rates of horizontal transmission among young children in group daycare settings (Pass et al., 1986, 1990). As a result of high seroprevalence, a large reservoir of CMV continuously exists in the population.

The two known main sources of primary maternal CMV infection are through sexual activity and contact with young children (Fowler and Pass, 2006). Transmission can occur by direct or indirect person-to-person contact with infectious bodily fluids, including semen, cervical or vaginal secretions, saliva, urine, and blood products (Reynolds et al., 1973; Lang and Kummer, 1975; Bowden, 1991). CMV excretion can last for months or years, and can be continuous or intermittent (Pass et al., 1982, Noyola et al., 2000). History of sexually transmitted diseases, younger sexual debut, and having multiple sex partners have all been associated with CMV seropositivity (Chandler et al., 1985; Coonrod et al., 1998; Staras et al., 2008). Horizontal transmission from child to child or child to adult, particularly in group daycare settings, most likely occurs by transmission of virus through saliva on hands and toys (Faix, 1985; Hutto et al., 1986). CMV transmission through respiratory droplets or aerosolized virus has not been shown.

Primary or nonprimary (recurrent) infection can result in clinical CMV disease, although disease is more severe with primary infection and in immunocompromised hosts. Primary CMV infection occurs in 0.7 to 4.1% of all pregnancies (Nigro, 2009). Higher maternal seroconversion rates have been observed in women of lower socio-economic status compared with women in higher socio-economic groups (Nigro, 2009). Daycare workers and parents of a child shedding CMV are also at increased risk of seroconversion, with up

to 12% of daycare providers and 24% of parents with a child shedding CMV seroconverting annually (Hyde et al., 2010). Healthcare workers, including those caring for infants and children, do not appear to be at increased occupational risk of seroconversion due to routine precautions taken in healthcare settings such as washing hands and wearing gloves when handling secretions (annual seroconversion rate of 2.3%) (Hyde et al., 2010).

Following primary infection, anti-CMV antibodies develop and the virus becomes latent. Periodic reactivation of latent virus with viral shedding is common, and more pronounced in immunocompromised individuals. Viral shedding can occur at variable rates from single or multiple sites after primary or nonprimary infection in both pregnant and nonpregnant women. The prevalence of CMV excretion in urine and saliva is higher in healthy young children (median, 23% for those in daycare, 12% for those not in daycare), than in adults (median, 7%) (Cannon et al., 2011). Young children also shed CMV in their urine and saliva for longer periods of time (6 months or more), and have higher CMV viral loads in their saliva and urine than adults (Cannon et al., 2011).

Congenital CMV transmission rates are as high as 50% in women who acquire primary CMV infection during pregnancy, and less than 2% in women with nonprimary infection (Kenneson and Cannon, 2007). However, due to the high prevalence of preconception CMV infection, two-thirds of congenital CMV cases result from reinfection with a new CMV strain or reactivation of latent virus (Wang et al., 2011). Congenital CMV infection increases in frequency (but decreases in severity of sequelae) with advancing gestation (Bodeus et al., 1999, Pass et al., 2006).

Postnatally, CMV is transmitted to the infant through breast milk, and also by horizontal transmission (Chang et al., 2015). Postnatal CMV infection is generally benign in healthy, full-term infants, although it can be associated with disease and long-term sequelae in premature and immunocompromised infants (Hamele et al., 2010; Lanzieri et al., 2013), and with increased morbidity and decreased growth in infants of HIV-infected mothers in resource-limited settings, even if the infants are HIV-uninfected (Gompels et al., 2012).

## CMV INFECTION DURING PREGNANCY

Primary infection during pregnancy is asymptomatic in approximately 75 to 95% of mothers, but may manifest as a mild mononucleosis or flu-like syndrome with persistent fever and fatigue (Griffiths and Baboonian, 1984; Stagno et al., 1986; Nigro, 2009). Approximately one-third of patients with CMV mononucleosis will also have dermatologic manifestations, including a variety of eruptions (Cohen and Corey, 1985). On occasion, primary CMV infection can lead to severe organ-specific complications resulting in significant morbidity and mortality (Cohen and Corey, 1985, Horwitz et al., 1986).

While there is no evidence that pregnancy increases maternal CMV disease severity, cervical shedding may be more common among pregnant women as gestation advances: < 5% in the first trimester, 6 to 10% in the second trimester and 11 to 28% in the third trimester (Demmler, 1996; Cannon et al., 2011). CMV excretion has occurred more often into breastmilk than into the vagina, urine, or saliva among seropositive postpartum women, with more than 30% of CMV seropositive women intermittently excreting CMV into breastmilk

during the first year of breastfeeding (Dworsky et al., 1983). Reinfection, reactivation, and viral persistence all can occur, but none tends to cause maternal clinical illness (Huang et al., 1980; Nigro et al., 2003).

Transmission of CMV from mother to child (vertical transmission) can occur in utero, intrapartum, or during breastfeeding. Intrauterine transmission is thought to be the result of transplacental crossing of virus, which then replicates in multiple embryonic or fetal tissues (Fisher et al., 2000). Intrapartum and postnatal transmission can occur by ingestion or aspiration of cervicovaginal secretions during delivery, and by breastfeeding or horizontal transmission routes (Reynolds et al., 1973; Fowler et al., 1993). Ascending infection from the maternal genital tract is thought to be rare, but possible, antepartum (Raynor, 1993).

Transmission in utero results in congenital infection and carries the greatest risk of sequelae, compared with intrapartum and postnatal transmission (American College of and Gynecologists, 2015). The risk of in utero transmission is highest when the mother has primary, compared with nonprimary CMV infection during pregnancy (Kenneson and Cannon, 2007). While the severity of sequelae decreases with advancing gestation, the risk of transmission increases from approximately 40% in the first two trimesters to 60% or more in the third trimester of gestation (Bodeus et al., 1999; Pass et al., 2006; Revello et al., 2011; Picone et al., 2013). However, even occurrence of primary CMV infection in the preconception (3 months to 3 weeks before conception) and periconception (3 weeks either side of conception) periods have been associated with increased risk of in utero CMV transmission (5% and 16%, respectively) (Picone et al., 2013). While pre-existing maternal antibody to CMV is the most important protective factor against congenital CMV infection, it does not completely eliminate transmission potential (Fowler et al., 2003). Reactivated latent maternal virus or maternal infection with another virus strain may lead to fetal infection. Furthermore, more than one viral strain can be transmitted to the fetus, either as a single event with co-disseminating strains, or by multiple transmission events of individual viruses, or both (Ross et al., 2011).

## CONGENITAL CMV INFECTION

An estimated 0.6 to 0.7 percent of newborns are congenitally infected with CMV in the United States and other developed countries (Kenneson and Cannon, 2007; Cannon et al., 2014; Goderis et al., 2014). Congenital CMV is the leading cause of nonhereditary sensorineural hearing loss (SNHL), and is a common cause of neurodevelopment disabilities, growth failure, and vision loss (Dollard et al., 2007). It can also result in fetal and neonatal death (estimated at 0.5% of congenital CMV infections) (Hamilton et al., 2014). Approximately 1 in 10 infants who acquire CMV in utero will have clinical signs at birth and be at high risk for severe sequelae (Dollard et al., 2007; Kenneson and Cannon, 2007; Cannon et al., 2014). However, another 10 to 15% of those who are asymptomatic at birth will develop long-term neurological sequelae, primarily hearing loss (Dollard et al., 2007; Boppana et al., 2013; Goderis et al., 2014). The strongest predictor for symptomatic congenital CMV at birth and long-term sequelae is in utero transmission of a primary maternal infection at an earlier gestational age (Enders et al., 2011).

Despite low sensitivity (<25%) and positive predictive value for symptomatic CMV at birth, the earliest signs of congenital CMV infection may be seen on routine fetal anatomy ultrasound at 20 weeks of gestation (Guerra et al., 2008). Echogenic bowel may be the first indication of in utero CMV infection; other indicators include abnormalities of brain development (calcifications and enlarged ventricles), microcephaly, fetal growth restriction, amniotic fluid abnormalities (oligohydramnios or polyhydramnios), placenta enlargement, hepatosplenomegaly or hepatic calcifications, ascites, or hydrops (Guerra et al., 2008; Picone et al., 2014). While fetal blood sampling is very rarely indicated in suspected congenital CMV infection, thrombocytopenia, hemolytic anemia, and elevated liver transaminases may be present in fetal blood and suggestive of disseminated CMV infection. When fetal abnormalities are suggestive of infection and the mother had a documented primary or undefined CMV infection in the first half of her pregnancy, prenatal diagnosis based on amniocentesis is recommended by The Society for Maternal-Fetal Medicine (Hughes and Gyamfi-Bannerman, 2016).

Amniotic fluid may be tested for CMV by viral culture or DNA PCR, but the preferred method is CMV PCR performed after 21 weeks of gestation and at least 6 to 7 weeks following maternal infection (Liesnard et al., 2000; Hughes and Gyamfi-Bannerman, 2016). Testing at this time point allows for detection of transmission across the placenta, replication in the fetal kidney, and excretion into the amniotic fluid, and provides high (96–100%) sensitivity and specificity (Liesnard et al., 2000; Benoist et al., 2008). Quantification of CMV viral load in amniotic fluid may help predict risk for symptomatic infection at birth and serious sequelae, with low virus load associated with lower risk (Lazzarotto et al., 2000, 2008; Guerra et al., 2000; Gouarin et al., 2002; Revello and Gerna, 2002). High CMV viral loads ($>10^5$ genome equivalents) have been associated with higher risk of clinical sequelae in some studies (Guerra et al., 2000, Lazzarotto et al., 2000), but not others (Revello et al., 1999 Picone et al., 2004; Goegebuer et al., 2009). To help define prognosis of congenital CMV infection, serial ultrasound examinations should be performed every 2 to 4 weeks to detect and monitor changes in fetal abnormalities. Persistent cerebral abnormalities suggest severe disease and a high risk for neurodevelopmental impairment (Benoist et al., 2008).

Fetal interventions (e.g., paracentesis, in utero transfusions) may be indicated if life-threatening symptoms are present in the fetus, but antiviral treatment during pregnancy is currently not a recommended clinical practice as further study is needed to determine whether it is safe and whether it improves perinatal outcome (American College of and Gynecologists, 2015; Hughes and Gyamfi-Bannerman, 2016). A recent nonrandomized phase II study of valacyclovir (8 g daily) given to 43 pregnant women carrying a symptomatic cytomegalovirus-infected fetus found valacyclovir was well tolerated and increased the proportion of asymptomatic neonates (82%) compared to a historical cohort (43%) (Leruez-Ville et al., 2016). Besides this study, evidence of any benefit of antiviral treatment during pregnancy is currently limited to case reports and a small observational study (20 pregnancies and 21 fetuses) that found maternal valacyclovir significantly decreased fetal CMV viral loads and provided therapeutic concentrations to fetal compartments, however, there was evidence of in utero progression of CMV disease in six of seven cases that later required pregnancy termination, and one in utero death (Puliyanda et al., 2005, Jacquemard et al., 2007).

In contrast, antiviral treatment with intravenous ganciclovir (GCV) or an oral course of its prodrug valganciclovir is recommended for infants with symptomatic congenital CMV infection, with initiation in the first month of life (American Academy of Pediatrics Committee on Infectious Diseases, 2015). Two randomized controlled trials, one of a 6-week course of intravenous GCV (6 mg/kg every 12 hr) (Kimberlin et al., 2003) and another of a 6-month course of oral valganciclovir (16 mg/kg, orally twice daily) (Kimberlin et al., 2015), among infants with symptomatic CMV showed moderate improvement in neurodevelopmental and audiologic outcomes, with greater benefit seen with the longer treatment. Treatment, particularly in the first 6 weeks of life, was associated with substantial incidence of neutropenia: 63% for intravenous GCV and 19% for oral valganciclovir. Therefore, infants receiving GCV or valganciclovir should be carefully monitored for toxicity. Such risks for infant toxicity preclude the use of these antivirals in asymptomatic infants with a low risk of sequelae; moreover, the efficacy of this approach in preventing long-term sequelae in such infants has not been evaluated.

Most congenital CMV infections remain undiagnosed throughout pregnancy and after birth. Infant diagnosis of congenital CMV is currently based on targeted testing within 2 to 3 weeks of birth of symptomatic newborns or newborns who fail the universal newborn hearing test. Therefore, most asymptomatic infants will be undiagnosed, yet an estimated 10 to 15% of them will develop late-onset sequelae (Dollard et al., 2007).

Approximately half of symptomatic infants with congenital CMV infection present with signs such as petechiae, jaundice, hepatosplenomegaly, and intrauterine growth restriction (Kylat et al., 2006; Boppana et al., 1992, 2013; Dreher et al., 2014). Other common signs are microcephaly and abnormal findings upon brain imaging, both of which indicate central nervous system involvement, along with less common central nervous system signs, such as hypotonia and seizures. Classic sensorineural signs include SNHL, chorioretinitis, and rarely optic atrophy or central vision blindness. Common laboratory abnormalities associated with symptomatic CMV infection include elevated liver transaminases, thrombocytopenia, and elevated direct and indirect serum bilirubin. Approximately a third to a quarter of symptomatic infants with congenital CMV are born prematurely (<37 weeks gestation), and these infants are more likely to present with pneumonitis, sepsis, and thrombocytopenia (Boppana et al., 2013; Turner et al., 2014).

Asymptomatic newborns may have slightly reduced birth weight and earlier gestational age than noninfected newborns, but these subtle findings will rarely lead to CMV diagnosis. Infants with signs consistent with CMV or a failed hearing test should be tested for CMV in urine or saliva using viral culture, rapid shell vial antigen detection, or CMV DNA PCR detection techniques (Harrison, 2015). The sensitivity of these methods for detecting CMV in urine or saliva is 95 to 100% (Ross et al., 2014). Quantification of CMV viral load can help predict risk for long-term sequelae, with low viral load reasonably predicting normal development (Boppana et al., 2005; Lanari et al., 2006; Ross et al., 2009; Cannon et al., 2011). Longitudinal studies that evaluate viremia in asymptomatic newborns as a predictor of long-term sequelae are limited, yet one study among 33 asymptomatic newborns of mothers with primary infection during pregnancy suggested a threshold value ≥12,000 IU/ml

predicts risk of late and progressive CMV-related sequelae, and a threshold of ≥17,000 IU/ml more accurately predicts delayed-onset SNHL (Forner et al., 2015).

Among symptomatic newborns with congenital CMV infection, an estimated 45 to 58% will develop permanent sequelae, including hearing loss (~35%), motor/cognitive deficits (~43%) and vision impairment (~6%) (Dollard et al., 2007; Goderis et al., 2014; Cannon et al., 2014; Bilavsky et al., 2016). In contrast, only approximately 10 to 15% of asymptomatic newborns will have permanent sequelae, predominantly hearing loss (Dollard et al., 2007; Goderis et al., 2014). Premature infants and infants with primary immune disorders of T cells or natural killer cells are at greatest risk for mortality from congenital CMV; cause of death is usually viral-associated hemophagocytic syndrome or severe end-organ disease (Harrison, 2015). A recent systematic review of hearing outcomes among 10 studies using universal newborn screening for congenital CMV and with varied follow-up times found that SNHL occurred in 12.6% of infected infants, comprising a third of symptomatic infants (32.8%) and a tenth of asymptomatic infants (9.9%) (Goderis et al., 2014). Hearing loss may have delayed onset, fluctuate, and be progressive (Foulon et al., 2008; Grosse et al., 2008; Goderis et al., 2014).

Infants with congenital CMV infection have varying degrees of delayed psychomotor and cognitive development that usually remain unrecognized until the first or second year of life. A study of populations of children with congenital CMV infection identified through universal newborn screening estimated that 43% of those symptomatic at birth and 5% of those asymptomatic at birth develop cognitive deficits (Cannon et al., 2014). The prevalence of cognitive disabilities in asymptomatic children is only slightly higher than among the general population (4%), and while lower IQs have been reported in asymptomatic children with congenital CMV infection younger than 6 years, there seems to be no lasting discernible difference in cognitive abilities after the age of 6 years (Temple et al., 2000; Townsend et al., 2013; Cannon et al., 2014). CMV-related vision impairment occurs among approximately 6% of symptomatic infants and 3% of asymptomatic infants, and ranges from blindness that is often present at birth to partial vision loss that is detected later in childhood (Cannon et al., 2014).

Early detection of late-onset or progressive congenital CMV sequelae permits timely intervention and rehabilitation. Therefore, all infants with congenital CMV infection should receive regular audiologic assessments through at least 6 years of age, and infants who were symptomatic at birth should also receive regular neurologic, developmental, and visual assessments (Kadambari et al., 2011).

## HIV-INFECTED PREGNANT WOMEN

More than 90% of HIV-infected women are CMV seropositive (Quinn et al., 1987; Kovacs et al., 1999). Whether the risk of congenital CMV infection is higher among fetuses of HIV-infected women, compared with fetuses of HIV-uninfected women is unclear. However, there is some evidence that the level of HIV-induced maternal immunosuppression is the main determinant of that risk (Ellington et al., 2016). Increased rates of congenital CMV infection were found among HIV-exposed infants of immunosuppressed mothers compared with their HIV-unexposed counterparts; conversely, maternal antiretroviral therapy may

decrease the risk of congenital CMV infection (Mussi-Pinhata et al., 1998; Bates et al., 2008; Gompels et al., 2012; Mwaanza et al., 2014; Ellington et al., 2016). Assessment of reactivation of disease and management of active maternal CMV disease follow the same recommendations as for nonpregnant HIV-infected adults (Masur et al., 2014). HIV-infected newborns have increased rates of congenital and postnatal CMV infection, compared with HIV-exposed, uninfected neonates (reviewed in Ellington et al., 2016).

## DIAGNOSIS AND MANAGEMENT OF MATERNAL CMV INFECTION

Serologic testing is used to diagnose primary maternal CMV infection. Testing usually occurs after suspicious ultrasound findings, such as intra-uterine growth retardation, echogenic fetal bowel, or brain calcifications (Guerra et al., 2008; Picone et al., 2014; Hughes and Gyamfi-Bannerman, 2016). Recent or prior CMV infection can be diagnosed by measuring the presence of anti-CMV IgM and IgG. Typically, CMV infection induces IgM production first, followed by an IgG response (Verma et al., 2015). IgG avidity measures antibody maturity, which is very low in the first weeks after a primary infection (i.e., antibodies bind weakly to the antigen), and gradually increases with time (i.e., antibodies bind tightly to the antigen). Primary infections can be defined by seroconversion of CMV-specific IgG in paired acute and convalescent sera collected 3 to 4 weeks apart, or a positive IgM combined with a low avidity IgG result (Mace et al., 2004).

While presence of IgM alone traditionally indicates acute infection, IgM can persist for months following primary infection and can be detectable during reactivation or reinfection (Stagno et al., 1985; Hagay et al., 1996). CMV-IgM assays also have a high false-positive rate, with-< 30% of pregnant women with positive IgM having a serologic profile suggestive of true primary infection (Stagno et al., 1985; Guerra et al., 2007; Lazzarotto et al., 2008). Therefore, diagnosis of primary infection cannot be based on the presence of IgM alone. However, low CMV IgG avidity has been shown to be both a sensitive and specific marker of primary CMV infection (Prince and Lape-Nixon, 2014). Nevertheless, CMV-specific IgG is often not detectable until at least two to three weeks after symptom onset, thus limiting the timeliness of serology-based diagnosis (Chou, 1990). Detection of IgM and IgG combined with low IgG avidity suggests a primary infection within the past 2 to 4 months (Lazzarotto et al., 2008; Centers for Disease Control and Prevention,). High IgG avidity suggests that CMV infection occurred more than five months earlier (Prince and Lape-Nixon, 2014). Therefore, a high IgG avidity result during the first trimester of pregnancy suggests that CMV infection occurred before conception; therefore, risk of vertical transmission may be low (Prince and Lape-Nixon, 2014). However, high IgG avidity during the second or third trimester cannot rule out primary infection during pregnancy.

Serologic tests can also be used to determine a patient’s risk for primary CMV acquisition, as only seronegative patients are at risk of primary infection. However, routine screening for CMV during pregnancy is not currently recommended, given the lack of an effective vaccine or other interventions to prevent congenital CMV infection and its sequelae in the neonate, and the limitations of the diagnostic assays in differentiating between primary versus nonprimary infection.

CMV can also be diagnosed by growth of the virus from multiple specimen types using either shell vial or conventional culture (Rabella and Drew, 1990; Razonable et al., 2002). Specimen types include blood, cerebrospinal fluid, urine, pharyngeal washings, bronchoalveolar lavage fluid, and biopsy specimens. CMV grows slowly in conventional cell culture and may take one to six weeks before a diagnosis can be made. Shell vial culture detects CMV early antigen before development of characteristic cytopathic effects, providing results in 1 to 3 days, and is, therefore, preferred in clinical practice. PCR of blood, urine, saliva, cervical secretions, or breastmilk can be used to detect CMV DNA, and CMV antigenemia assays can detect CMV proteins (pp65) in peripheral blood leukocytes (Chang et al., 2015). Antigenemia appears to correlate with viremia in HIV-infected patients and recipients of solid organ transplants (van den Berg et al., 1991; Chevret et al., 1999).

Immunocompetent pregnant women diagnosed with primary CMV infection should be offered supportive care to relieve any symptoms. Timing and route of delivery are determined by standard maternal and fetal indications. While the majority of women with primary CMV infection diagnosed in the first half of pregnancy will deliver an unaffected infant, careful monitoring of fetal development and growth is necessary, and decisions about pregnancy options need to be made after careful consideration of the risks. Antiviral treatment of CMV infection in immunocompetent pregnant women is not recommended, as no antiviral drugs have been shown to reduce transmission to the infant (Roxby et al., 2014).

## PREVENTION OF CMV INFECTION

Good hygiene practices and avoiding intimate contact with young children (e.g., kissing on the mouth and sharing utensils) has been suggested as an approach to prevent maternal primary CMV infection during pregnancy, but remains an unproven method of reducing the risk of congenital CMV infection and may be difficult to implement (American College of and Gynecologists, 2015). Good hygiene practices include frequent hand washing with soap and water after contact with young children’s diapers, toys, high chairs, or other surfaces containing oral or nasal secretions or urine. Female child-care workers in group daycare centers should have access to appropriate hand hygiene measures to minimize occupationally acquired primary CMV infection (American Academy of Pediatrics Committee on Infectious Diseases, 2015).

The role of maternal antibodies in preventing congenital infection may be promising, but is still unclear. In an observational study among 102 women with primary CMV infection and unknown infection status of their fetuses, 37 elected to receive hyperimmune globulin (100 U/kg monthly). Passive immunization with CMV-specific hyperimmune globulin (HIG) of pregnant women with primary CMV infection reduced intrauterine transmission (40% to 16%; $p = 0.02$), and the rate of symptomatic congenital CMV disease (50% to 3%; $p < 0.001$) (Nigro et al., 2005). In a subsequent placebo-controlled, double-blinded, randomized trial of 124 pregnant women with primary CMV infection, there was no significant difference in the rate of congenital infection between the hyperimmune globulin (100 U/kg every 4 weeks) and placebo groups (30% vs. 44%; $p = 0.13$) (Revello et al., 2014). There was also no significant difference in the levels of virus-specific antibodies, T-cell-mediated immune response, or viral DNA in blood and the clinical outcome of congenital infection at

birth was similar between the two groups. In addition, a higher number of obstetric adverse events (preterm delivery, preeclampsia, and fetal growth restriction) was reported in the HIG (13%), compared with the placebo, arm (2%) (Revello et al., 2014). A large, randomized, placebo-controlled trial is currently ongoing in the United States to further investigate the role of HIG in preventing congenital CMV infection (National Institutes of Health,).

Antiviral medications (e.g. GCV, valganciclovir, and foscarnet) are used in the prevention of CMV disease in immunocompromised adults, such as HIV-infected patients with advanced disease or transplant recipients (Bennett et al., 2014), and in neonates with severe congenital disease (American Academy of Pediatrics Committee on Infectious Diseases, 2015). However, antiviral treatment prenatally and postnatally has not proven effective at preventing congenital or postnatal CMV infection (Roxby et al., 2014), and is not recommended as a prevention tool.

Developing a preconception CMV vaccine to prevent congenital infection is a top priority, given the potential health benefits and cost savings. However, no suitable CMV vaccine currently exists (Schleiss, 2008). One major challenge for vaccine development is that reinfections frequently occur in women despite preconception CMV immunity, and reinfections can result in fetal transmission and infant sequelae (Yamamoto et al., 2010). However, maternal immunity modifies the virulence of the fetal infection. Therefore, vaccine--derived preconception immunity may still play a role in reducing the burden of congenital CMV infection.

## RECENT ADVANCES IN VACCINE DEVELOPMENT

Developing a CMV vaccine was rated the highest priority by the Institute of Medicine in 1999 due to the large number of infants with permanent CMV-associated disabilities and the subsequent substantial economic burden associated with their long-term treatment and care (Arvin et al., 2004). Live-attenuated virus candidates have been investigated for use as a CMV vaccine for over four decades, but none have proven to provide adequate protection. A common problem in live-attenuated clinical vaccine trials is failure to elicit wild-type immunity. Recent efforts have included attempts to elicit a stronger and longer-lasting immune response to CMV by adding an interleukin (IL)-12 adjuvant and creating chimeric viruses encoding portions of the genome found in other nonattenuated strains (Bialas et al., 2015). However, neither approach has been successful at eliciting wild-type immunity (Mitchell et al., 2002; Sabbaj et al., 2011).

CMV subunit vaccines have primarily focused on the surface glycoprotein gB, which is involved in the attachment and entry of CMV into fibroblasts, and is a major target of neutralizing antibodies present in seropositive plasma (Bialas et al., 2015). The only phase 2, randomized, placebo-controlled trial conducted in seronegative women vaccinated over 400 women with a gB/MF59 vaccine or placebo within 1 year of giving birth, when risk of acquiring primary infection is high (Pass et al., 2009). CMV infection occurred in 8% (18/225) of women randomized to receive the vaccine and in 14% (31/216) of women randomized to placebo. An overall vaccine efficacy of 50% (95% CI 7–73%) was estimated. No significant differences in overall rates of adverse events or in serious adverse events occurred between the vaccine and placebo groups. Among the enrolled women who later

became pregnant, only 1 of 81 infants born to vaccinated women had confirmed CMV infection and was nonsymptomatic. In the placebo arm, 3 of 97 infants were congenitally infected and 1 of 3 presented with severe sequelae at birth. All four congenital infections were attributed to primary maternal infection during pregnancy. While the sample size was not sufficient to evaluate the efficacy of preventing congenital CMV infection, the results are promising and encourage a future phase 3 trial (Bialas et al., 2015).

Recent emphasis has been placed on developing a vaccine that elicits neutralizing antibodies to more than one glycoprotein complex to provide broad protection against all CMV isolates, but the studies are in early preclinical evaluation (Ryckman et al., 2008; Bialas et al., 2015). CMV vector and DNA vaccine candidates are also currently being evaluated (Wloch et al., 2008; Bernstein et al., 2009; Kharfan-Dabaja et al., 2012).

Several vaccine strategies have shown promise in guinea pig models, including recombinant live-attenuated CMV vaccines with deletion of the genes responsible for immune evasion, and passive immunization of antibodies specific for glycoprotein B (gB) and the gH/gL complex (Griffith et al., 1982; Bia et al., 1984; Chatterjee et al., 2001; Leviton et al., 2013). However, as previously outlined, human clinical trials with similar immunization approaches have not yielded similar results (Pass et al., 2009; Revello et al., 2014).

## CONCLUSIONS

Even though CMV infection is very common and not associated with increased disease severity during pregnancy, evidence exists of increased rates of reactivation and cervical shedding with advancing gestation. Both primary and nonprimary infection in pregnancy are associated with transmission to the fetus and resulting congenital infection, with sequelae that are more severe with primary maternal infection and infection in the earlier part of pregnancy. Prevention of congenital CMV infection is a very important public health goal, due to the prevalence and potential severity of its sequelae. Despite the intensive research efforts, a vaccine remains elusive. Passive immunization of pregnant women with primary CMV infection may hold promise in preventing transmission of CMV to the fetus; however, the evidence to-date is not conclusive and use of this approach is not recommended.

Female child-care workers in group daycare centers should have access to appropriate hand hygiene measures to minimize occupationally acquired primary CMV infection. However, preventive measures based on pregnant women avoiding close contact with oral secretions and urine of young children shedding CMV (for example, kissing young children in a way that reduces saliva exposures, not putting things in the mouth that had just been in a child’s mouth, and cleaning hands after touching urine or saliva), and limiting the number of new sexual partners during pregnancy, remain unproven methods of reducing the risk of congenital CMV infection.

There continues to be a need for development and testing of behavioral interventions for congenital CMV prevention. Development of newer, less toxic, antiviral agents with activity against CMV may offer opportunities to study their role in decreasing CMV shedding

prenatally and preventing congenital infection. Continuing research on development of active and passive immunization approaches should remain a research priority.

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