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Diagnosis and antenatal management of congenital cytomegalovirus infection

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Congenital cytomegalovirus (CMV) is the most common viral infection, affecting nearly 40,000 infants each year in the United States. Of seronegative women, 1-4% will acquire a primary infection during pregnancy, and the majority of these women will be asymptomatic. Prior maternal exposure to CMV does not preclude neonatal infection. The purpose of this document is to review diagnosis of primary maternal CMV infection, diagnosis of fetal CMV infection, and whether antenatal therapy is warranted. We recommend the following: (1) that women with a diagnosis of primary CMV infection in pregnancy be advised that the risk of congenital infection is 30-50%, on average, and that the severity of infection varies widely (Best Practice); (2) for women suspected of having primary CMV infection in pregnancy, we recommend that diagnosis should be either by IgG seroconversion or with positive CMV IgM, positive IgG, and low IgG avidity (grade 1B); (3) amniocentesis is the best option as a prenatal diagnostic tool to detect fetal congenital CMV infection, performed >21 weeks of gestation and >6 weeks from maternal infection (grade 1C); (4) we do not recommend routine screening of all pregnant women for evidence of primary CMV infection at this time (grade 1B); and (5) we do not recommend antenatal treatment with ganciclovir or valacyclovir; and we recommend that any antenatal therapy, either with antivirals or CMV hyperimmune globulin, should only be offered as part of a research protocol (Best Practice).

Key words: amniocentesis, antiviral agents, cytomegalovirus, cytomegalovirus hyperimmune globulin, cytomegalovirus IgM, congenital cytomegalovirus, fetal infection, primary maternal cytomegalovirus infection, routine screening, seroconversion

Introduction

Cytomegalovirus (CMV) is the most common perinatal viral infection leading to neonatal and childhood sequelae. Diagnosis of primary maternal CMV infection now frequently involves IgG avidity testing, a sensitive marker of primary CMV infection within the last 4 months.

Recently, a European trial was published assessing antenatal CMV hyperimmune globulin (HIG) use to prevent neonatal infection, and the authors found no difference to treatment, and there were a number of adverse events reported in those receiving CMV HIG.[1] The purpose of this document is to review diagnosis of primary maternal CMV infection, diagnosis of fetal CMV infection, and whether antenatal therapy is warranted.

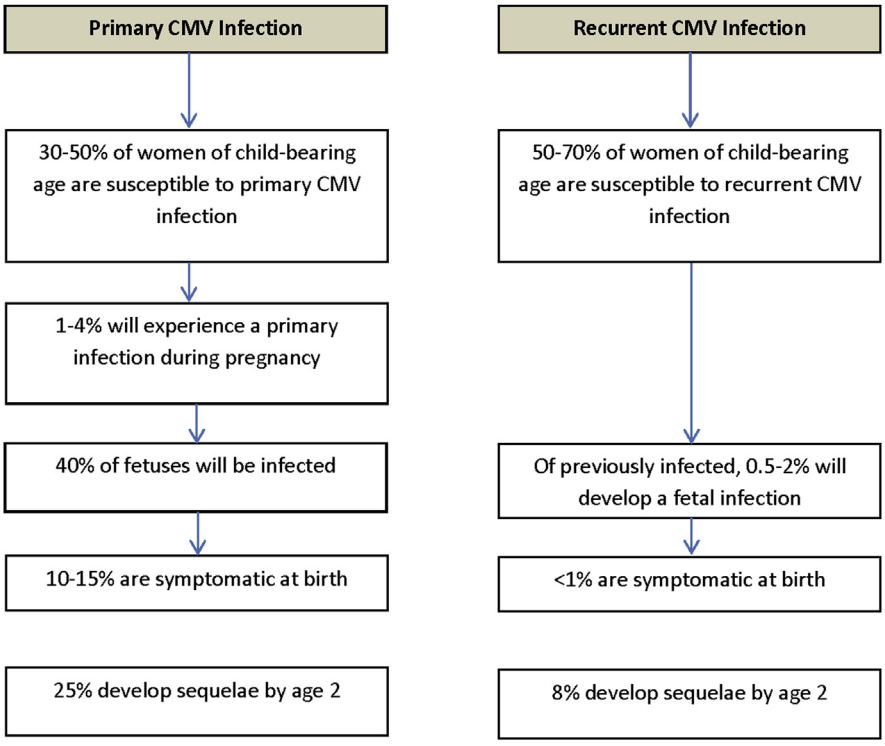
A listing of articles in this series that were published in other journals before #36 appeared in the June 2015 issue of AJOG is available at smfm.org/publications/.

What is the epidemiology of CMV?

Congenital CMV, a herpesvirus, is the most common viral infection of the fetus and is the leading nongenetic cause of congenital deafness,[2] affecting nearly 40,000 infants each year in the United States. Fetal infection can result in a wide range of outcomes for children, from asymptomatic infection to severe disability and death. Birth prevalence reflects all neonatal infections detected at birth as a result of both primary and recurrent infections. Birth prevalence also varies geographically and is estimated to be 0.48-1.3% in the United States,[3,4] 0.54% in The Netherlands,[5] and 1.08% in Brazil.[6]

The prevalence of prior exposure in women of childbearing age varies by region and income and ranges from 40-83%.[7,8] Of seronegative women, 1-4% will acquire a primary infection during pregnancy,[7] and the majority of these women will be asymptomatic[9] (Figure). Seroconversion varies by socioeconomic status, with 1.6% of women

FIGURE
Maternal and neonatal risks for cytomegalovirus (CMV) infection.[9,14,45]



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from middle- and high-income groups seroconverting during pregnancy, compared to 3.7% of women in low-income groups.[7] Less commonly, women with a prior CMV infection may experience either reinfection with different strains, or reactivation of disease. While congenital infection can occur with reactivation or recurrent infection, it is far more likely to occur in the setting of maternal primary infection.

What are the fetal risks from primary maternal CMV infection in pregnancy?

A primary CMV infection is the first exposure to the virus and it is concerning when it occurs during pregnancy. The likelihood of congenital infection is highest following primary maternal infection and is reported to be approximately 30-50%[1,7,10]; although some series suggest a rate as high as 70% with third-trimester exposure.[11] **Women with primary CMV in pregnancy have a risk of congenital infection of 30-50% and the severity of infection varies widely (Best Practice)**. Recent series of pregnancies with primary infection demonstrate increasing frequency of congenital infection with gestational age, from approximately 30% in the first trimester to 40-70% in the third trimester.[11,12] None of the infants infected during the third trimester in these reports experienced symptomatic disease. There is some variation across gestation, with earlier infection thought to be less frequent but more severe. CMV transmission after preconception primary infection has also been reported. One study found an 8.3% transmission rate when the primary CMV infection occurred 2-18 weeks prior to the last menstrual period.[10] Another study found a similar rate of transmission, 8.8%, after preconception exposure, but importantly, none of those infants showed symptoms at birth.[11] There does not appear to be a seasonal variation to the risk of maternal infections.[13]

Among women with a primary infection, 18% of their infants will be symptomatic at the time of birth.[14] These symptoms include jaundice, petechial rash, hepatosplenomegaly, and death. In a classic article,[14] infants were followed up over time to estimate risks of long-term sequelae. Of those not symptomatic at birth, up to 25% experience sequelae during the first 2 years of life. These sequelae include sensorineural hearing loss, cognitive deficit with an intelligence quotient <70, chorioretinitis, seizures, and death. Among infants followed up to 5 years of age, development of sequelae occurred as late as 72 months. Severe illness appears to be more likely among fetuses whose mothers experience primary infection during the first half of pregnancy.[7,15]

What are the fetal risks from recurrent maternal CMV infection?

Recurrent CMV infection can occur after prior maternal exposure to CMV and does not preclude neonatal infection. Most of the literature surrounding recurrent CMV infection resulting in a symptomatic neonate comes from case reports.[16-19] Of women with recurrent CMV infections, <1% of offspring are symptomatic at birth.[14,16] However, 8% of offspring will develop sequelae including hearing loss, chorioretinitis, or milder neurological sequelae such as microcephaly by age 2 years and 14% by age 5 years.[14] In 1 series, none of the offspring of women with recurrent infection died in the follow-up period.[13]

How is primary maternal CMV infection diagnosed?

Testing for maternal CMV infection generally occurs after suspicious ultrasound findings. The most common ultrasound findings warranting investigation for CMV infection include echogenic fetal bowel, cerebral ventriculomegaly and calcifications, and fetal growth restriction[20,21] (Table). Hepatic calcifications, microcephaly, and subependymal cysts have also been described.[21] One method for diagnosis of primary infection is seroconversion but this requires serial serology, a strategy unlikely to be feasible for all pregnancies in the United States. Traditional teaching is that the presence of IgM antibody indicates acute infection. However, in the case of CMV serology in pregnancy, <10% of women with positive IgM congenitally infect their infants, compared with 30-50% of those with seroconversion.[10,22,23] This is largely related to the high (up to 90%) false-positive rate for CMV-IgM assays performed by standard enzyme-linked immunoassays, especially those performed in commercial, nonreference laboratories. IgM can be produced during nonprimary infections, which are associated with a much lower risk of congenital infection, as well as in response to other viral infections, such as Epstein-Barr virus. IgM can also persist for months following primary infection, potentially predating pregnancy by a significant time lag. Therefore, the presence of IgM alone should not be used for diagnosis.

The IgG avidity assay is a tool that can be used to more accurately detect a primary infection than IgM alone. Antibodies produced at the time of a primary infection have lower antigen avidity than do those produced during nonprimary response or later in a primary immune response. Over time, the maturation of the antibody response results in higher antibody avidity. Low to moderate avidity antibodies are encountered for 16-18 weeks following primary infection. Therefore, a low avidity IgG result in combination with a positive IgM antibody is indicative of infection within the preceding 3 months, allowing more accurate diagnosis of primary infection occurrence during or shortly prior to pregnancy. Lazzarotto et al[22] published the results of a cohort of 2477 women referred for positive IgM. They performed immunoblot to confirm positivity of IgM and found 55% were not confirmed by immunoblot, and had high avidity until IgG. Of the 514 women found to have confirmed IgM, as well as low to moderate avidity, 25% delivered a congenitally infected infant, a rate similar to the 30% among those with documented seroconversion.

Despite the availability of avidity testing for primary CMV infection, the diagnosis may remain unclear because the significance of intermediate avidity and the appropriate cutoff for low avidity are not well established.[9,22] Alternate methods of diagnosis are also available and include maternal serum or urine virology testing, although this does not correlate well with timing of infection or neonatal outcomes.[22] Newer methodologies include using interferon gamma release assays or intracellular cytokine staining, but these tests are mainly used for diagnosis of immunocompromised patients.[24] **For women suspected of having primary CMV infection in pregnancy, we recommend that diagnosis should be either by IgG seroconversion or with positive CMV IgM, positive IgG, and low IgG avidity (grade 1B).**

How is a diagnosis of fetal CMV infection made?

In the setting of a documented primary maternal infection but without confirmed fetal infection, the risk of severe fetal sequelae is approximately 3% and risk of any adverse outcomes is approximately 8%. Based on serology alone, there is a >90% chance of a good outcome free of sequelae. The sensitivity of prenatal diagnosis techniques varies

TABLE
Ultrasound abnormalities from cases of confirmed congenital cytomegalovirus infection[12,20]

Ultrasound finding	Frequency, %
Cerebral calcifications	0.6–17.4
Microcephaly	14.5
Echogenic bowel	4.5–13
Fetal growth restriction	1.9–13
Subependymal cysts	11.6
Cerebral ventriculomegaly	4.5–11.6
Ascites	8.7
Pericardial effusion	7.2
Hyperechogenic kidneys	4.3
Hepatomegaly	4.3
Placentomegaly or placental calcifications	4.3
Hepatic calcifications	1.4
Hydrops	0.6

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widely depending on the population selected, the gestational age at the time of the technique, as well as the gestational age at the time of fetal infection. The more common method used to diagnose fetal infection is by amniocentesis. The only other diagnostic option, cordocentesis, provides similar sensitivity and specificity to amniotic fluid CMV testing, but with a higher complication rate than amniocentesis.[9,25,26]

Amniocentesis is the best option as a prenatal diagnostic tool to detect fetal congenital CMV infection, performed >21 weeks of gestation and >6 weeks from maternal infection (grade 1C). With the ability to detect CMV-DNA through polymerase chain reaction (PCR) testing, this modality allows for near exclusion of antenatal fetal infection.[9] A negative PCR for CMV by amniocentesis, if performed >21 weeks of gestation or >6-7 weeks from maternal primary infection, has specificity between 97-100%.[25,27,28] Importantly, there may be false-negative findings if the amniocentesis is performed 6 weeks from maternal exposure, but <21 weeks of gestation, such that delaying an amniocentesis until 21 weeks of gestation or repeating an early negative amniocentesis is recommended.[9,28] While the sensitivities vary from 45-80%, the positive predictive value of the test also approaches 100%,[25,27,28] though false-positive CMV by PCR has been reported.[25] Data are conflicting, though, on whether the amount of detectable viral load is related to the severity of infection.[29,30] Fetal blood CMV-DNA assessment via PCR has also been described via cordocentesis.[25] The sensitivity of this method is similar to that of amniotic fluid testing, but the higher complication rate associated with cordocentesis makes amniocentesis the recommended primary method for diagnostic testing.[9,25,31] Women should be counseled that the severity of infection cannot be determined by amniocentesis.

What is the role of imaging in assessing fetal infection?

Ultrasound imaging cannot diagnose a fetal infection. Further, ultrasound imaging suggests fetal infection in <50% of infected fetuses, so when used alone is not appropriate as a diagnostic test for congenital CMV infection.[20,21] In a recent large cohort of 600 women with primary CMV infection, 8.5% of fetuses had ultrasound abnormalities. This number increased to 14.9% after reviewing ultrasounds of neonates with confirmed infections by urine or serum screening. The positive predictive value of ultrasound for predicting fetal or neonatal infection was 35%.[20] The most common ultrasound findings in congenitally infected fetuses include cerebral calcifications, microcephaly, and echogenic bowel (Table). Magnetic resonance imaging has been used in examining fetuses suspected of infection but its use is controversial.[32,33] Normal brain imaging does not necessarily predict normal neurodevelopmental outcome, particularly since hearing loss is frequently progressive in congenital CMV.[34] At this time, the data regarding the addition of magnetic resonance imaging to ultrasound evaluation are insufficient to recommend routine use in evaluation for congenital CMV infection.

Is universal screening for CMV infection recommended?

Routine screening for CMV infection during pregnancy, whether universal or targeted, is not recommended.[9] **We do not recommend routine screening of all pregnant women for evidence of primary CMV infection at this time (grade 1B).** For a screening test to be effective, there needs to be a clearly defined disease process with known prevalence and an "early" intervention that alters the course of the disease.[35] Routine CMV screening does not meet several of the criteria for an effective screening test at this time, thus is not recommended outside of a research setting.[36] Currently, the only available intervention studied in a randomized trial showed no benefit over placebo.[1] Moreover, routine screening can lead to unnecessary intervention, which could, in fact, be harmful. The interventions that are available each have side effects, some for the mother, others for the fetus; are intensive to administer; and are without clear evidence of benefit.

What therapies are recommended for CMV infection?

At this time, there are no proven therapies to prevent or treat congenital CMV infection. The use of CMV HIG for both treatment and prevention has been reported in observational studies. In 2005, Nigro and colleagues[10] first reported the results of an observational cohort study examining the impact of CMV HIG among women with primary infection, some of whom chose to undergo amniocentesis for fetal testing, and another group that did not. The subjects were offered CMV HIG and all patients were followed up, with results being compared between those who did and did not elect to receive HIG.[10] The prevention arm was composed of 102 women who declined amniocentesis. Of these women, 37 elected to receive HIG, and 65 did not, 18 of whom terminated the pregnancy. The HIG regimen was 100 U/kg monthly until delivery. Congenital infection was confirmed in 16% of the women receiving HIG compared to 40% of the women who did not receive HIG ($P = .02$). Of importance, the median gestational age at the time of maternal infection was significantly higher among the women not receiving HIG (20 vs 14 weeks of gestation, $P < .01$). Later gestational age at infection is associated with a higher risk of transmission. Thus, because this was not a randomized trial, it is unknown how much of an impact HIG actually had on transmission. In another report of patients included in the original study, the authors reported regression of cranial and abdominal ultrasound stigmata with the administration of CMV HIG.[37]

The first randomized trial to address the use of CMV HIG (the CHIP study) has subsequently been completed in Italy and did not show a significant reduction in congenital infection.[1] This study enrolled 124 women with primary CMV

Summary of recommendations

	Recommendations	Grade
1.	Women with primary CMV in pregnancy have a risk of congenital infection of 30-50% and the severity of infection varies widely.	Best Practice
2.	For women suspected of having primary CMV infection in pregnancy, we recommend that diagnosis should be either by IgG seroconversion or with positive CMV IgM, positive IgG, and low IgG avidity.	1B Strong recommendation, moderate-quality evidence
3.	Amniocentesis is the best option as a prenatal diagnostic tool to detect fetal congenital CMV infection, performed >21 weeks of gestation and >6 weeks from maternal infection.	1C Strong recommendation, low-quality evidence
4.	We do not recommend routine screening of all pregnant women for evidence of primary CMV infection at this time.	1B Strong recommendation, moderate-quality evidence
5.	We do not recommend antenatal treatment with ganciclovir or valacyclovir; and we recommend that any antenatal therapy, either with antivirals or CMV hyperimmune globulin, should only be offered as part of a research protocol.	Best Practice

infection and randomly assigned them to CMV HIG or placebo; the risk of infection was 30% among those receiving HIG and 44% among those receiving placebo ($P = .13$). There was no difference in the viral characteristics of the infected fetuses and neonates. The viral load was similar in amniotic fluid and newborn urine between the HIG and placebo groups. The study also reported a number of adverse events in the HIG arm. While not statistically significant ($P = .06$), the risk of significant adverse obstetric events was 13% compared to 2%. These included preterm delivery, preeclampsia, and fetal growth restriction. Given the lack of clear benefit of therapy, it is recommended that use of HIG be reserved for research protocols. Currently, 1 other trial assessing HIG is in progress (Clinicaltrials.gov: NCT01376778).

Antiviral therapy of infected fetuses has been studied in small series and case reports. A small, randomized trial conducted in neonates suggested benefit of ganciclovir for symptomatic infants in the prevention of hearing deterioration.[38] In this study neonates with symptomatic CMV infection were randomized to receive 6 weeks of ganciclovir vs no treatment. The same investigators then assessed whether longer therapy would provide further benefit. When neonates were treated for 6 months instead of 6 weeks, hearing did not improve in the short term but did improve along with other developmental outcomes at 12-24 months.[39] The notion that providing therapy earlier in the course of fetal infection may improve outcomes has prompted some clinicians to consider this therapy in utero. A small observational study done in France suggested that administration of maternal valacyclovir to women with confirmed fetal CMV infections decreased fetal CMV viral loads and provided therapeutic concentrations of drug in the maternal and fetal compartments.[40] In this prospective observational study approximately 50% of fetuses whose mothers agreed to treatment were developing normally at ages 1-5 years. Case report data support clearance of the virus from the amniotic fluid of a patient treated with oral ganciclovir and an infant born without congenital infection.[41] Currently, antenatal treatment with ganciclovir or valacyclovir is not recommended as it has not been proven effective.[42] Based on the available literature, any antenatal therapy, either with antivirals or CMV HIG, should only be offered as part of a research protocol. **We do not recommend antenatal treatment with ganciclovir or valacyclovir; and we recommend that any antenatal therapy, either with antivirals or CMV HIG, should only be offered as part of a research protocol. (Best Practice).**

Is it possible to prevent maternal primary CMV infection?

Education on personal hygiene has been shown in a prospective trial to decrease rates of seroconversion for pregnant seronegative women.[43] Similar findings resulted from a cluster randomized trial where seronegative women with children <36 months of age were randomly assigned to a daycare that included information on hand hygiene and glove use vs one that did not. In the subgroup of women

Guidelines

Recommendations in this document reflect national and international guidelines related to diagnosis and antenatal management of cytomegalovirus infection[42,46-48]

Organization	Title	Publication year
American Congress of Obstetricians and Gynecologists	Practice bulletin no. 151: Cytomegalovirus (CMV), parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy	2015
Society of Obstetricians and Gynaecologists of Canada	Clinical practice guideline: CMV infection in pregnancy	2010
Centers for Disease Control and Prevention	CMV and congenital CMV infection: clinical diagnosis and treatment	2010
Royal College of Obstetricians and Gynaecologists	Review: Primary and secondary CMV in pregnancy	2009

currently pregnant, the seroconversion rate was significantly lower in the intervention group compared with routine daycare: 5.9% vs 41.7% ($P = .008$).[44]

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