Congenital Cytomegalovirus Infection: An Obstetrician’s Point of View

David E. Soper1,2
1Department of Obstetrics and Gynecology, Division of Infectious Diseases, and 2Department of Medicine, Medical University of South Carolina, Charleston

Maternal cytomegalovirus (CMV) is the cause of the most frequent congenital infection in America; however, pregnant women are not routinely screened. Primary CMV infection is associated with a high maternal-to-child transmission rate (40%); up to 15% of these infected neonates will be symptomatic at birth and develop permanent sequelae that usually involve the central nervous system. New interventions are now available to decrease the rate of primary maternal infection as well as to treat pregnant women with primary infection, thus decreasing the fetal and neonatal morbidity associated with this disease. Based on these data, strategies for maternal screening need to be reconsidered.

Keywords. maternal-to-child transmission; cytomegalovirus; prevention.

The obstetrician is no stranger to the concept of screening for microorganisms that are capable of maternal-to-child transmission and subsequent congenital infection. Currently we routinely use serology to screen for preexisting immunity to rubella and in women with a negative history of varicella zoster virus. We screen for active hepatitis B infection by assessing the gravida’s antigen status. Likewise, we use serology to screen for evidence of infection by Treponema pallidum and human immunodeficiency virus (HIV). Routine prenatal screening for Toxoplasma gondii and Herpes simplex virus is not recommended. The total number of congenital infections from all of these pathogens does not approach the frequency of vertically acquired CMV infection.

Cannon and Davis point out that no single cause of birth defects and developmental disabilities in the United State currently provides greater opportunity for improved outcomes in more children than congenital CMV [1]. Each year in the United States, an estimated 40,000 children are born with congenital CMV infection, causing an estimated 400 deaths and leaving approximately 8000 children with permanent disabilities such as hearing or vision loss or mental retardation. More children are affected by serious CMV-related disabilities than by several better-known childhood maladies, including Down syndrome, fetal alcohol syndrome, and spina bifida.

EPIDEMIOLOGY OF CMV

Primary CMV infection is associated with viral excretion that persists for weeks, months, and even years. Recurrent infection can occur as a result of the reactivation of a latent virus or a reinfection with antigenically diverse strains of CMV. Reinfection is most likely in a high-prevalence population. There are probably thousands of genetically different strains in the general population. Infections are generally subclinical.

Humans are the only reservoir of CMV. It is an endemic infection with no seasonal variation. Its prevalence increases with age. Transmission of the virus requires exposure to body fluids and tissues. Person-to-person transmission requires close or intimate contact, which might be expected in crowded environments, sexual contacts, and exposure to children, particular toddlers [2]. Infected persons continue to expose other susceptible people to CMV. Virus secretion persists for years after congenital, perinatal, and early postnatal infections.
Young children are a particularly significant CMV transmission source for pregnant women. Pass et al showed that 50% of children attending day-care centers excrete CMV [3]. A range was noted, with the lowest rate of excretion in infants aged <1 year at 9% and increasing to a surprising 88% of toddlers excreting virus in their second year of life. Adler et al showed that 50% of CMV-seronegative children in a day-care setting seroconvert [4]. CMV-seronegative parents are at risk for acquiring CMV from their newly infected children attending day care. The risk may approach 45% for parents with a child shedding CMV at age 18 months. The range of CMV shedding among children was noted to vary from 22% to 72% in a survey of 9 day-care centers across the United States and in Sweden. Caretakers working with small children appear to have an elevated risk of CMV infection, with an annual seroconversion rate of 10% when compared with a 2% rate for hospital employees.

MATERNAL-TO-CHILD TRANSMISSION

The public health impact of congenital CMV is significant. The vertical transmission of CMV occurs as a result of maternal viremia and transplacental infection and spread. Perinatal infection can also result from exposure of the neonate to genital tract shedding of CMV and from CMV excretion in breast milk. A diagnosis of perinatal infection is made if congenital infection is ruled out by negative testing for CMV in the first 2 weeks of life. Unlike rubella or toxoplasmosis, in utero infection is not necessarily related only to a primary infection. Recurrent infection by either reactivation of the gravida’s latent viral strain or reinfection by a different CMV strain can cause congenital infection, although the risk is greatly diminished (69% reduction) since the mother is seropositive.

The consequences of maternal CMV infection are related in Figure 1. Nearly all symptomatic congenital infections are associated with a primary infection either during or just before pregnancy [5]. There appears to be an increasing viral transmission rate as the gestational age advances, but infections that occur earlier in gestation are associated with the worst outcomes.

Figure 1. Consequences of CMV in pregnancy. Abbreviation: CMV, cytomegalovirus.
are less avid (avidity index approaching 20%), while remote infections are more avid (avidity indexes approaching 80%).

Viral cultures, which can be obtained from the cervix, urine, and blood, are not specific for primary infection. In addition, blood viral culture for CMV is not sensitive (only 26%). Viral detection by polymerase chain reaction (PCR) detection of CMV DNA is an improvement over viral culture. Within 1 month of acute CMV infection, the test is 100% sensitive when run on peripheral white blood cells (buffy coat). This drops to 89% in the second month and to 47% in the third month.

Obstetricians will most likely be presented with the possibility of a CMV diagnosis when confronted with an abnormal ultrasound. Suggestive but not diagnostic fetal findings associated with fetal CMV infections include cerebral ventriculomegaly, microcephaly, hyperechogenic fetal bowel, ascites, intracranial calcifications, and fetal growth restriction. Prenatal diagnosis can be made using amniocentesis and cordocentesis. PCR detection in the amniotic fluid approaches 100% sensitivity, obviating the need for cordocentesis. Viral culture of amniotic fluid is only 60% sensitive. A confounding factor in prenatal diagnosis is the gestational age at the time of amniocentesis. After primary maternal infection, it may take weeks to months for transplacental transmission of CMV to occur [7]. Some investigators have suggested an interval of 7 weeks between the maternal onset of infection and the performance of diagnostic tests for fetal infection.

PREVENTION OF CONGENITAL CMV

Preventive interventions include hygienic behavioral changes and the use of CMV hyperimmune globulin (HIG) and vaccines (now in phase 2 trials) [8]. Adler et al showed the value of education and hygienic behavioral changes in decreasing CMV seroconversion in a population of mothers whose children attended day care [9]. Protective behavior included frequent hand washing (eg, after exposure to a child’s bodily fluids and diaper changes, handling dirty laundry, touching the child’s toys and other objects) and wearing protective gloves. Kissing on the mouth, sharing towels and washcloths, and sharing food and beverages were also discouraged. Mothers were informed of their serologic status and as to whether their child was shedding virus. A statistically significant decrease in seroconversion of the pregnant mothers in the intervention group was observed. Nonpregnant women were less likely to comply with the behavioral changes, most likely due to a lack of perceived benefit.

Nigro et al studied the use of passive immunization with HIG in a cohort of 181 nonrandomized women with confirmed primary CMV infection during pregnancy. Of the 31 women undergoing amniocentesis and receiving HIG in the therapy group, only 1 delivered an infant with symptomatic CMV neonatal disease [10]. Of the 14 women not receiving HIG in this group, 50% of neonates showed evidence of symptomatic CMV disease. This difference was highly statistically significant (P < .001). Another cohort, declining amniocentesis, was also randomized to HIG. Of those gravidas receiving HIG, 16% delivered CMV-infected infants; however, none were symptomatic compared with a 40% infection rate among those declining HIG, of which 3 neonates had severe symptomatic infections. The authors concluded that the nonrandomized study suggested that CMV-specific hyperimmune globulin might be effective in the treatment and prevention of congenital CMV infection. A controlled trial was recommended.

In summary, CMV infection should remain a significant concern of providers who care for pregnant patients. The prevalence of disease is substantial, and the sequelae, particularly that associated with primary infection, are significant. With new diagnostic tools to help us define those with primary CMV infection, a reconsideration of screening strategies is important. The advent of new interventions, both preventive and therapeutic, may make identification of the patient at risk for primary infection by CMV a goal for improving prenatal care.

Notes

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