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Congenital cytomegalovirus infection

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ABSTRACT

Each year, thousands of children are born with or develop permanent disabilities such as hearing loss, vision loss, motor and cognitive deficits from congenital CMV infection (cCMV). However, awareness of cCMV and its associated sequelae is very low in pregnant women and healthcare providers. Both targeted and universal approaches to screen newborns for CMV infection are now achievable due to recent scientific advances including the development of a rapid, high-throughput method for detecting CMV in saliva, the efficacy of antiviral treatment in symptomatic infants, and the demonstration of cost effectiveness of CMV screening. Future studies are needed to address gaps in our understanding on the role of non-primary maternal CMV infections, the evaluation of antiviral treatment in asymptomatic infants, and the implementation of prevention strategies for cCMV.

Congenital CMV infection (cCMV) contributes to thousands of children each year being born with or developing permanent disability such as hearing loss, vision loss, cerebral palsy and/or cognitive impairment worldwide. In the United States (US), Canada, Western Europe, and Australia, cCMV occurs in about 5–7 per 1000 live births overall.[1–5] However, cCMV affects significantly more Black infants, 10–12 per 1000 live births, than other racial and ethnic groups in the US.[1] In other parts of the world, such as Latin America, Africa, and most Asian countries, cCMV rates are higher at approximately 10–30 per live births.[6–13]

Disease burden

Approximately 10% of infants with cCMV have clinical abnormalities at birth (symptomatic infection) including evidence of disseminated disease and/or CNS involvement. The vast majority (≈90%), however, will have no clinical manifestations present during the newborn period (asymptomatic infection).[14] About 40–60% of symptomatic infants will suffer from permanent sequelae, with sensorineural hearing loss (SNHL) being the most common, followed by cognitive impairment, retinitis, and cerebral palsy.[2,15–17] Asymptomatic infants are not without risk of CMV-related disabilities, although a smaller percentage of these infants will have permanent sequelae due to CMV infection. About 10–15% of asymptomatic infants will develop sensorineural hearing loss following infection.[2,16–19] Cognitive impairment and retinitis have been observed in asymptomatic infants but at much lower rates than among symptomatic infants.[2,15]

SNHL is the most common sequela following cCMV and may be present at birth or occur later in the first years of life. Approximately 33–50% of SNHL due to cCMV is late onset loss.[16] Late onset hearing loss occurs throughout the first several years of life with the median age for late onset

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hearing loss occurring 11 months later (at 44 months of age) in asymptomatic children than in symptomatic children.[17,18] About 50% of children with SNHL following cCMV will continue to have further deterioration or progression of their loss.[17,18] The rate of hearing loss progression in cCMV seems to be similar regardless of whether the child had an asymptomatic or a symptomatic infection, although the symptomatic infants have a greater degree of severity and also earlier progression of their hearing loss.[17] Another characteristic of CMV-related hearing loss is fluctuating hearing loss that is not explained by concurrent middle ear infections. Fluctuating hearing loss may occur in only one ear or at only a few frequencies within the ear or occur in both ears if a child has bilateral hearing loss.[17]

CMV-related hearing loss is second only to genetic causes both at birth and during the early years of life as an etiology of permanent childhood hearing loss.[19,20] In addition, cCMV-related disabilities are more common among infants and young children than other more recognized diseases such as Down syndrome, fetal alcohol syndrome, or spina bifida.[21] Also, cCMV contributes to childhood mortality, with 75% of cCMV deaths occurring during infancy.[22]

CMV awareness

Although thousands of children born each year suffer from permanent disability such as hearing loss, vision loss, cerebral palsy, and/or cognitive impairment due to cCMV, most pregnant women have not heard of CMV infection and its associated sequelae. In a 2005 study by Jeon et al[23] only 22% of women had heard of CMV and few knew preventive measures to decrease their risk of CMV infection. Also, the accuracy of their information about cCMV and its sequelae was limited. In the same year, the *HealthStyles*™ survey found only 14% of the women in the United States had ever heard of CMV.[24] Similarly, the 2010 *HealthStyles*™ survey showed that 13% of women had heard of CMV.[25] However, the 2015–2016 *HealthStyles*™ survey found that the percentage of women having heard of CMV had decreased to 9%.[26] These surveys suggest that CMV awareness rates among women in the United States are extremely low and that most women of childbearing age are unaware of the possible CMV risk for their newborn. In contrast, CMV awareness rates (13–60%) are higher in Europe than the reported rates in the United States although CMV knowledge gaps exist.[27–29] In addition, women's healthcare providers are likely to have incomplete information on cCMV and how to prevent CMV infection, and do not routinely provide CMV prevention counseling for women.[30–34] Therefore, future CMV education campaigns should not only include the general population but also a CMV education and prevention component for healthcare providers.

Maternal immunity

An important determinant of cCMV is the prevalence of maternal CMV infection in the population.[35–37] The prevalence of cCMV is directly proportional to the maternal seroprevalence such that higher rates of cCMV are consistently observed in populations with high maternal seroimmunity.[37–39] Congenital CMV is unlike rubella and toxoplasmosis where primary infection during pregnancy accounts for most vertically transmitted infections.[37] Even within a geographic region, CMV seroimmunity varies among women from different racial, ethnic, and socioeconomic backgrounds translating into distinct epidemiologic patterns of congenital infection.

Although it was realized soon after the description of cytomegalic inclusion disease that cCMV can occur in children born to mothers who were CMV-infected prior to pregnancy (non-primary infection), the relative contribution of non-primary maternal infection to cCMV- and CMV-associated hearing loss and other neurologic sequelae was not initially described.[40,41] A systematic review and modeling of the data have suggested that about two-thirds to three-quarters of all cCMV occur in infants born to women with non-primary maternal infections.[36,42] A recent large newborn CMV screening study at two different maternity units in Paris, France found that about half of all CMV-infected babies were born to women with non-primary CMV infection during pregnancy.[43] Therefore, it can be assumed that at least half of the congenitally infected infants in high income countries are likely born to women with preexisting seroimmunity. In populations with high seroprevalence, such as low-income minority women in the United States and women in low- and middle-income countries, the majority of infected infants are likely born to women with non-primary CMV infections.

Acquisition of CMV during pregnancy in seronegative women occurs with increased exposures to CMV through caring for young children or sexual activity.[1,44,45] Similar to primary maternal infections, increased exposure to other individuals excreting CMV increases the risk of non-primary infections in women. While the mechanisms have not been defined, reactivation of endogenous virus or reinfection with a new virus strain have been suggested as possible viral sources leading to intrauterine transmission of CMV in non-primary infections.[37,46] Recent studies have demonstrated that exposure to a new strain of virus can lead to reinfection of seropositive women, intrauterine transmission, and symptomatic congenital infection.[47–49] However, the exact frequency of CMV reinfection in seroimmune women during pregnancy and the rate of intrauterine transmission following reinfection in these women are yet to be defined. The characteristics of antiviral immune responses that provide protection against intrauterine transmission are also not well understood.

Prenatal diagnosis

Testing pregnant women for CMV is only indicated as part of the diagnostic evaluation of a mononucleosis-like illness, when a fetal anomaly suggestive of cCMV is detected on a prenatal ultrasound examination, or if the woman requests the test. Amniocentesis to perform PCR for CMV DNA in the amniotic fluid is the preferred diagnostic approach for identifying an infected fetus.[50–53] Timing of amniocentesis is critical since the sensitivity for detection of CMV is