Congenital cytomegalovirus infection

Karen B. Fowler, DrPH, and Suresh B. Boppana, MD

Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL
Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL
Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL

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.

Disease burden

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. However, cCMV affects significantly more Black infants, 10–12 per 1000 live births, than other racial and ethnic groups in the US. 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.

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. Late onset hearing loss occurs throughout the first several years of life with the median age for late onset...
hearing loss occurring 11 months later (at 44 months of age) in asymptomatic children than in symptomatic children.\textsuperscript{17,18} About 50% of children with SNHL following cCMV will continue to have further deterioration or progression of their loss.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{15,20} 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.\textsuperscript{21} Also, cCMV contributes to childhood mortality, with 75% of cCMV deaths occurring during infancy.\textsuperscript{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\textsuperscript{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\textsuperscript{TM} survey found only 14% of the women in the United States had ever heard of CMV.\textsuperscript{24} Similarly, the 2010 HealthStyles\textsuperscript{TM} survey showed that 13% of women had heard of CMV.\textsuperscript{25} However, the 2015–2016 HealthStyles\textsuperscript{TM} survey found that the percentage of women having heard of CMV had decreased to 9%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{37–39} Congenital CMV is unlike rubella and toxoplasmosis where primary infection during pregnancy accounts for most vertically transmitted infections.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{37} 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.\textsuperscript{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.\textsuperscript{37,46} Recent studies have demonstrated that exposure to a new strain of virus can lead to reactivation of seropositive women, intrauterine transmission, and symptomatic congenital infection.\textsuperscript{57–49} 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.\textsuperscript{50–53} Timing of amniocentesis is critical since the sensitivity for detection of CMV is
higher after 21 weeks of gestation.\textsuperscript{50–57} If amniocentesis is performed earlier in gestation or soon after diagnosis of maternal infection, it is only reliable evidence of fetal infection if positive, and should be repeated later in gestation if negative.

Identification of CMV

Infants with cCMV shed large amounts of virus in saliva and urine, making either specimen useful for the identification of cCMV in infants. However, saliva specimens are easier to collect than urine specimens from newborns and are less prone to contamination. Irrespective of the specimens collected for testing, specimens should be collected from the infant within the first 2–3 weeks of life to distinguish congenital from postnatally acquired CMV infection.

Viral isolation by culture from urine or saliva has long been the gold standard for identifying infants with cCMV.\textsuperscript{54,55} Studies that have investigated the role of urine PCR for the diagnosis of cCMV report sensitivities ranging from 93% to 100%.\textsuperscript{56,57} Recent studies have demonstrated that real-time PCR of newborn saliva and urine specimens has high sensitivity and specificity for screening and diagnosis of infants with cCMV.\textsuperscript{57,58} Additional advantages of PCR assays are that the assays are less expensive, have rapid turnaround times, and do not require maintenance of tissue culture facilities. Furthermore, a DNA extraction step is not required for the real-time PCR assay of saliva specimens.\textsuperscript{58,59} PCR is also unlikely to be affected by storage and transport conditions of the specimens and can be adapted for high-throughput newborn screening.

Newborn CMV screening

Most infants with cCMV have no clinical findings at birth, and therefore, the majority are not identified at birth. Newborn CMV screening is needed to identify infants who have asymptomatic cCMV and who may be at risk for CMV-related SNHL. Additionally, it is well-established that an earlier diagnosis of hearing loss allows for an earlier institution of interventions that will result in better outcomes for children with CMV-related SNHL. Both urine and saliva from newborns have been shown to be reliable specimens for CMV screening.\textsuperscript{56} A prospective multicenter study reported that real-time PCR of saliva had high sensitivity and specificity (>97%) for identifying infants with cCMV.\textsuperscript{59} Although using dried blood spots (DBS) collected at birth for CMV screening has been explored, so far DBS PCR has shown to have low sensitivity for wide scale newborn CMV testing.\textsuperscript{60}

At the present time, universal CMV screening does not routinely occur in the US. Several states and numerous hospitals have proposed targeted CMV screening of newborns who fail hearing screening as a strategy to identify infants with CMV-related SNHL at birth. However, findings from a large multicenter study showed that only 57% of CMV-infected infants with confirmed SNHL during early infancy would be identified by a targeted CMV screening approach.\textsuperscript{61} These findings argue in favor of universal CMV screening of all newborns for early detection and timely interventions. Also, a universal approach would identify the cCMV infants who are at increased risk for late onset SNHL. A recent study has shown that both targeted and universal CMV screenings are cost-effective approaches.\textsuperscript{52}

Antiviral therapy

For infants with symptomatic cCMV, 6 months of valganciclovir therapy has been shown to be more beneficial for long-term hearing and neurodevelopmental outcomes than 6 weeks of treatment.\textsuperscript{63} Because of the potential toxicities associated with antiviral therapy, only symptomatic infants with CNS involvement (i.e., the most severely affected infants) who are >32 weeks gestation and less than 1 month of age should be considered for treatment with oral valganciclovir.\textsuperscript{64} For infants who do undergo treatment, regular monitoring for myelosuppression is recommended throughout the 6-month course. There is incomplete agreement regarding whether the presence of isolated SNHL should be considered symptomatic disease. Since antiviral benefit has not been demonstrated in these infants, it is generally not recommended in infants with isolated SNHL.\textsuperscript{64} In addition, there is no evidence of benefit of antiviral therapy for asymptomatic infants without SNHL at this time.

Table – Messages to reduce CMV infection risk for pregnant women.

- Avoid contact with the saliva and urine of young children
  - Do not kiss a young child on or near the mouth. Instead, kiss them on the forehead or the top of the head.
  - Do not put anything in your mouth that has recently been in a child’s mouth. Such as:
    - Food
    - Silverware
    - Cups or bottles
    - Toothbrush
    - Pacifier
  - Do wash hands frequently with soap and water, especially after
    - Wiping a child’s face
    - Feeding a child
    - Changing diapers
Prevention of CMV remains elusive. Although vaccine strategies and activities have been promising, currently there are no CMV vaccines on the market to prevent CMV infection in pregnant women. In addition, results from studies on the prevention or reduction of fetal infection through CMV hyperimmune globulin (HIG) have been mixed. Several observational and non-randomized studies have suggested that CMV hyperimmune globulin (HIG) prevents intrauterine CMV transmission in women with primary CMV infection during pregnancy. However, data from a recent randomized trial of CMV HIG administered to pregnant women with primary CMV infection did not show a significant reduction in fetal infection. A large multicenter randomized trial of CMV HIG is currently underway in the United States and the results from that trial could provide a more definitive answer on the role of HIG in the prevention of cCMV.

Since many women acquire CMV through exposure to children, messaging for reducing women’s risk of CMV infection from children (Table) have been proposed for counseling women about CMV prevention. Adler et al. and Fowler et al. have shown that a brief prenatal behavioral approach in women and found that pregnant women perceived themselves to be at a higher risk than nonpregnant women and were more likely to be amenable to effective behavior changes. Studies in France and Italy have shown that counseling women about their hygiene practices reduced the CMV seroconversion rates in pregnant women. Recent studies in the United States by Hughes et al. and Fowler et al. have shown that a brief prenatal behavioral intervention can reduce CMV risk behaviors in pregnant women. These findings suggest that a screening and brief intervention during pregnancy, focusing on behaviors such as not sharing food or drink with young children, not kissing young children on the mouth, and frequent hand washing could prevent maternal CMV infection thereby protecting their offspring from potentially damaging cCMV.

Future directions

For future vaccine and prevention strategies, understanding of the virologic, immunologic, and other risk characteristics associated with intrauterine transmission in women with non-primary maternal CMV infection is essential. CMV educational programs are necessary to increase awareness and provide accurate CMV information both to mothers and healthcare providers. Also, additional studies to evaluate the effectiveness of brief behavioral interventions during pregnancy in reducing maternal CMV risk behaviors, and thereby cCMV infections, are needed. Clinical trials are currently underway to evaluate whether infants with asymptomatic cCMV or cCMV infants with only isolated SNHL will benefit from antiviral treatment. In addition, assessment of whether antiviral treatment has a sustained effect in prevention of SNHL and/or stopping further deterioration of the hearing loss in treated children is needed. Several states and numerous hospitals have developed targeted CMV screening protocols within newborn hearing screening programs, and the data from these programs will inform the impact of cCMV on hearing loss in children. However without universal CMV screening, most children with cCMV will be missed and it will not be possible to identify the cCMV infants who are at risk for late onset SNHL.

References

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