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Prevention of Cytomegalovirus Infection in Pregnant Mothers and Neonates

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Abstract
Congenital cytomegalovirus (CMV) is the most common virus spread in utero from mother to fetus, leading to more long-term problems and childhood deaths than other conditions such as Down syndrome, fetal alcohol syndrome, pediatric HIV/AIDS, or neural tube defects. The majority of congenital CMV infections are primary infections in which the mother acquires the infection during pregnancy. Current treatment options for CMV infection are available, but there is limited data on safety and effectiveness in pregnant mothers and neonates. Prevention by screening for CMV is associated with a high cost, and vaccines are currently unavailable. Studies show that education and behavioral modifications are effective ways to lower the risk of CMV infection in neonates, making primary prevention by these methods critical to reducing the transmission of CMV infection.

Overview

Cytomegalovirus is the most common virus spread in utero from mother to fetus within the U.S. Every year, approximately 30,000 infants are born within the U.S. with congenital cytomegalovirus (CMV). Eighty percent of these infants will be asymptomatic, but the remaining infants will likely develop neurologic sequelae, equating to more than 5,000 children each year who are born with or develop permanent disabilities and approximately 400 deaths due to CMV.[1,2] CMV leads to more long-term problems and childhood deaths than other conditions such as Down syndrome, fetal alcohol syndrome, pediatric HIV/AIDS, or neural tube defects. Unfortunately, only 14-22 percent of women are aware of CMV, and fewer than half of obstetricians talk to expectant mothers about the virus.[1,3] A member of the herpes virus family, CMV lives within its host for the duration of the host's lifetime, although its activity is usually dormant.[4]

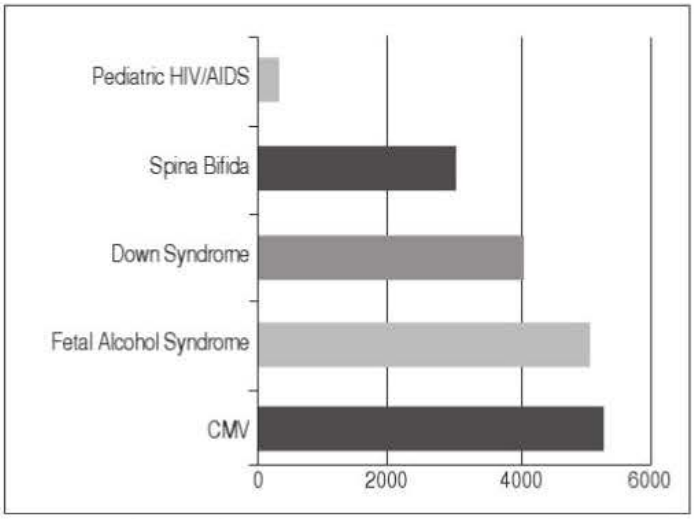

Figure 1. U.S. Children Born with or Developing Long-Term Medical Conditions Each Year[1] (Adapted from CDC.gov)

An estimated 60 percent of women of child-bearing age in the U.S. are infected with CMV.[5] Of the remaining 40 percent of women who have never been infected with CMV, approximately 1-4 percent will acquire a primary infection while pregnant.[1] A mother acquires CMV by coming into contact with urine, saliva or genital secretions of an infected person.[5] Seronegative mothers with a CMV-infected child typically become infected within one year after their child acquires a CMV infection, and up to 70 percent of children in group childcare acquire CMV.[6] CMV infection can occur one of two ways during pregnancy. The mother can either receive a primary infection, in which the mother acquires the virus during pregnancy, or the infection can result from a secondary infection in which a dormant virus reactivates. Primary infections are the cause for the majority of infants who are born with a congenital CMV infection, and secondary infections account for only about 2 percent of congenital CMV infections.[7] Women can infect the fetus during any trimester or perinatally via contact with genital secretions at birth and/or from breast milk.[5]

A majority of children born with congenital CMV never experience any problems or symptoms, but about one in every 750 children born with CMV suffer from permanent problems due to the infection. Short-term effects of congenital CMV infection include premature birth, hepatomegaly, splenomegaly, jaundice, purpura, petechia, pneumonitis and seizures. Permanent outcomes consist of microcephaly, vision loss, hearing loss, learning disabilities, motor disabilities, seizures, cerebral palsy and, in some cases, death.[1,8,9] Almost all adults have been exposed to CMV, but a healthy adult with a normal immune system will likely be asymptomatic. Those at increased risk for infection include babies born to women who have a first-time CMV infection during pregnancy, pregnant women who work with infants and children, and persons with weakened immune systems.[10] Hearing and vision loss may not develop until one to two years after birth, so the Centers for Disease Control and Prevention (CDC, Atlanta, Ga.) recommend that seropositive, asymptomatic children have their hearing and vision monitored regularly. It is estimated that one-third of sensorineural hearing loss in children is due to CMV infection.[9]

Screening

Currently, there are no systematic screening programs in place to identify patients in at-risk groups so that educational programs can be tailored to patient's specific test results, allowing for appropriate primary, secondary and tertiary prevention methods and behavior modification. A screening program offered at the beginning of pregnancy could identify women who are seronegative and provide an opportunity for primary prevention strategies such as education and behavior modification to prevent seroconversion during pregnancy.[7] Screening at the start of pregnancy uses serological tests of urine, saliva or tissue samples to identify CMV IgG and IgM antibodies. The presence of antibodies indicates CMV infection but cannot identify whether an infection is primary or recurrent. This may cause unnecessary patient anxiety because primary infections are more likely to cause complications than recurrent

infections.[11] If a mother has already seroconverted, additional screenings which use ultrasound can identify fetuses that express cerebral complications, allowing secondary prevention strategies to be implemented with a goal of preventing complications due to infection. Ultrasound screening after mother seroconversion is not very effective because most fetal defects cannot be identified until the last trimester. Screening methods also can be used to target tertiary prevention strategies such as early management of neurological sequelae. One method of tertiary screening is to use serological tests at the beginning and throughout pregnancy to give a prenatal diagnosis of the infant. Another method of screening is to perform a serological test of urine or dried bloodspots upon birth to identify asymptomatic infants. By identifying asymptomatic infants at birth that are seropositive, closer monitoring of neurological development can help manage subsequent sequelae that may not develop until later in infancy. Also, early identification of hearing loss through routine screening at birth may improve the prognosis for children with CMV. Testing of dried bloodspots could easily be incorporated into state newborn screening programs, which are already in place; however, dried blood tests are not as sensitive as urine tests. Limitations of tertiary prevention include minimal benefits for infants with severe neural complications and the lack of programs currently in place for continuing the monitoring of seropositive infants to help identify and manage potential complications. A major drawback to all types of screening is the cost associated with testing all pregnant women and neonates.[7,12]

Treatment

Current treatments for CMV are lacking safety profiles in pregnant women due to severe side effects and have no proven efficacy in preventing transmission to the fetus. Ganciclovir is a treatment option for congenital CMV infection but is limited to only the most severe cases due to its adverse event profile. It is an anti-viral agent that is used in an attempt to prevent hearing loss in infants. In a randomized, controlled trial, patients who received ganciclovir did not have any further hearing deterioration at six months; 41 percent of patients not receiving ganciclovir therapy demonstrated hearing deterioration (adjusted $P < 0.01$). However, the majority of patients who received ganciclovir therapy experienced significant hematological toxicity. Furthermore, its long-term safety has not been established in children.[13]

Another treatment option being explored is intravenous human immunoglobulin (IVIG) administration, but it is not currently approved for use in the treatment of CMV. Limitations in implementing IVIG therapy include a limited supply and cost of treatment.[6,14] Immunoglobulin therapy is still being studied in clinical trials and has emerged as an off-label use for CMV among physicians, but little is known about its toxicity.

Prevention

A vaccine is the most promising way to fight congenital CMV; however, a vaccine is not yet commercially available in the U.S.[5,8] It is estimated that with proper funding, a vaccine could be developed within seven years.[2] A vaccine could be given in childhood or adolescence, and prior immunization could prevent a primary CMV infection in women during pregnancy.[5] By implementing vaccination, it is estimated that approximately $4 billion in health care costs could be saved every year.[2] There currently are several vaccines in development.[5] Novartis and AlphaVax currently are developing a single-cycle particle vaccine that carries RNA encoding three antigens from the CMV virus. The vaccine will target adolescent women.[15] Sanofi Pasteur recently finished phase II trials of a molecule similar to Novartis' and found that the vaccine decreased the incidence of maternal and congenital CMV infection (no P value provided).[16] Vical also is developing a CMV vaccine, CyMVectin™, to prevent seroconversion prior to pregnancy. CyMVectin is set to enter phase I trials with the approval of their Investigational New Drug Application.[17] The biggest limitation in vaccine implementation is that several studies have shown that a previously infected person can become re-infected with a new strain of the virus, thus decreasing the likelihood that a single protein can provide immunity for all strains of the virus.[18]

Because vaccines are currently unavailable and treatment strategies are lacking safety profiles, education on preventing the disease through behavior modification is critical in preventing the transmission of the virus and subsequent infection in neonates.[6]

The American College of Obstetrics and Gynecology recommends counseling about CMV prevention by emphasizing hygienic practices.[8] There are many preventative strategies that can be employed by the patient to reduce the risks of acquiring or transmitting the disease. Both protective and avoidance behaviors need to be taught in the prevention against CMV (Table 1). Protective behaviors include frequent hand-washing after diaper changes, feeding or bathing a child, and handling children's toys as well as using gloves when cleaning surfaces that come in contact with saliva or urine. Avoidance behaviors include eliminating salivary contact by not sharing food, toothbrushes, utensils or pacifiers. Horizontal transmission of CMV is very common in childcare settings due to the high incidence of children under 30 months who actively shed CMV in their urine and saliva. Contact in the day-care setting can increase the risk of acquiring CMV by up to 25 fold.[9] It is estimated that those exposures can cause up to 12,000 cases of newborn infections and neurologic damage.[19]

Table 1: Behavior modifications to prevent transmission of CMV[1,8]

Ways to Reduce CMV Transmission
Wash hands thoroughly with warm soap and water • After diaper changes • After feeding or bathing the child • After wiping a runny nose or drool • After handling children's toys
Clean surfaces that come into contact with the child • Countertops • Toys • Surfaces in contact with urine and saliva
Limit sharing of objects in contact with saliva and/or urine • Cups • Utensils • Food • Plates • Toothbrushes • Towels and washcloths
Do not kiss on or near the mouth
Adults should not put a child's pacifier in their mouth

A study was conducted to test the efficacy of preventative methods in child-to-mother transmission of CMV in pregnant and non-pregnant mothers with children enrolled at 124 day-care centers in Virginia from 1999 to 2001. The women were randomized into three groups: a control group, a partial intervention group and a full intervention group. For all three groups, the women, all children in the home and the fathers had urine and saliva collected every three months for CMV screening for a total of 12 months or until delivery. The control group was only given basic information about CMV, and seroconversion results were not revealed. The partial intervention group was given information about the virus as well as a video presentation that focused on how to prevent transmission. This group was also taught about protective behaviors such as proper handwashing, wearing gloves when changing a diaper, and avoiding salivary contact with children through either sharing food and drink or kissing on the mouth. Latex gloves were given to the mothers to use during diaper changes as well as liquid soap. This group also underwent CMV screening, but only the mother's initial serum status was revealed. The full intervention group was given all of the same educational information, as well as prevention measures, given to the partial intervention group. The full intervention group also received CMV culture screening every three months but were told the initial results of the mother's and the child's screening. If a child was not shedding at enrollment, mothers were educated that there was a high probability their child could begin shedding the virus at any time. An interim analysis showed that half of the children who initially were not shedding began to shed the virus at some point during the study; therefore, all mothers enrolled in the partial intervention group were re-assigned to the full intervention group. The results of this study found that intervention in pregnant women may have lowered the risk of acquiring CMV by as much as 85 percent. Pregnant women were more motivated to incorporate the interventions into their daily lives. The women were more attentive, took notes and asked questions compared to their non-pregnant counterparts who seemed less engaged.[6]

Role of pharmacists

Due to the high financial costs and limitations associated with screenings and the lack of an effective and safe treatment option, the focus of health care providers must be on prevention when educating the patients about CMV. Health care providers can play an important role by raising awareness of CMV and educating the public about CMV, the risks associated with it and prevention of CMV transmission. Pharmacists can have a significant impact in creating awareness about CMV by educating women who are pregnant, planning on becoming pregnant or who have young children. The education can be delivered through materials such as pamphlets and videos, one-on-one counseling in a health care setting, or outreach programs.

Conclusion

CMV is the most commonly transmitted virus in utero and can have significant effects in a neonate. Because only 14-22 percent of women are aware of CMV, it is very important that health care providers become more proactive in educating patients and the general public, especially women of child-bearing age.[1] Pharmacists can play a key role in patient education on congenital CMV infection prevention. Studies have shown that education and behavioral modifications are effective ways to lower the risk of CMV infection in neonates, making primary prevention critical to reducing the transmission of CMV infection.

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