Congenital Cytomegalovirus Infection – a Question of Screening

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Routine serologic screening of pregnant women or newborns has never been recommended by any public health authority in any country. As a result of demands by pregnant women and the fear of litigation, most obstetricians in Israel do test pregnant women for cytomegalovirus, and they are confused by the findings.

CMV infection is the most frequent congenital infection, affecting between 0.2% and 2.5% of all live births, and the most common cause of deafness and impairment of intellectual function among infants [1-7]. Each year in the United States, hundreds of children die and thousands develop disabilities such as mental retardation, hearing loss and vision loss due to congenital CMV infection [1-4]. More children are affected by congenital CMV (8000 children per year) than by other childhood disability conditions, such as Down syndrome (4000 children/year), fetal alcohol syndrome (5000 children/year), and spina bifida and congenital rubella syndrome – which have been eliminated and for which screening during pregnancies is still routinely performed [5]. The prevalence of congenital CMV infection in Israel was found to be around 0.7% [6]. Since 15–20% of the annual 145,000 pregnancies in Israel are born to seronegative mothers [7], 21,750–29,000 women are at risk of developing primary CMV infection during pregnancy. With a 1–8% risk of primary infection among seronegative pregnant women and a 40% transmission rate [1-4], 348 to 464 cases of congenital CMV infection resulting from primary infection are expected each year. Since 30% of the infected newborns become symptomatic [1-4], 105 to 139 symptomatic infections are expected each year. Furthermore, 116,000–123,250 women are at risk each year for developing non-primary CMV infection during pregnancy, with a transmission rate of 1% [8].

The percentages of seropositive pregnant women undergoing reactivation during pregnancy and the percentages of symptomatic newborns among those infected are unknown. Boppana et al. [9] and Ahlfors et al. [10] found that among symptomatically infected newborns for whom the immune status of the mothers was defined, almost 50% were born to mothers with non-primary CMV infection. Thus, an additional unknown number of congenital CMV infections resulting from non-primary infection should be added. In the 1990s, the overall disease burden associated with congenital CMV infection was estimated to cost the U.S. healthcare system at least $1.86 billion annually, with a cost per child of more than $300,000 [11].

There are a few potential ways to combat congenital CMV. The development of a vaccine was listed as a top priority by the National Academy of Sciences, following analysis of the cost of disease and its impact on quality-adjusted life-years [12]. Although advances have been made in vaccine development, licensed CMV vaccine remains years away. Furthermore, due to the suggestion in recent reports that non-primary maternal CMV infection can be as dangerous as primary infection, preconception vaccination is no longer considered a solution by some investigators. Universal CMV screening of newborns and/or pregnant women is another preventive approach.

Neonatal screening can be performed by universal hearing screening or by molecular screening tests on newborn blood spots. An estimated 25% of all prelingual hearing deficits, with a prevalence of about 65 per 100,000 children, can be attributed to CMV [13]. Universal postnatal hearing screening of newborns would permit early intervention and diminish intellectual and language disorders. Potential interventions include speech therapy, sound amplification, cochlear implants, and antiviral therapy with gancyclovir which appears to be moderately effective in preventing hearing deterioration among newborns with congenital CMV infection [14]. Oral antiviral drugs like valacyclovir might heighten the need for neonatal screening. However, newborn hearing screening programs may miss a large number of cases of congenital CMV-induced deafness, since the deafness is not yet present in the immediate newborn period when hearing screening is performed. A solution to this problem would be universal newborn screening for CMV infection. Polymerase chain reaction for detecting CMV DNA on neonatal dried blood spots is sensitive, specific, rapid and applicable to large numbers of samples, and was found to be superior to the classic methods of virus isolation from neonatal urine [15]. Although cost-benefit analyses are lacking, there is considerable rationale for implementing neonatal screening.

The issue of whether pregnant women should be routinely tested for CMV immunity is not settled. Most experts believe that this evaluation would be too costly to implement on a wide scale. In Europe and in Israel, serial screening during pregnancy for CMV infection is common, although it is not yet official policy [16]. The most common means of CMV infection among pregnant women is through exposure to toddlers who

CMV = cytomegalovirus

tend to shed large amounts of virus in the saliva and urine for many months after their first infection [1-4]. A possible approach is to serologically screen all pregnant women in early pregnancy. Those women who are seronegative should be aware that young children are likely sources of CMV infection, and they should practice meticulous hygiene with young children, such as frequent hand washing, not kissing the child on the mouth, sterilizing toys, using gloves when changing diapers and avoid sharing food. Adler [17] demonstrated that changing protective behaviors prevents child-to-mother transmission of CMV during pregnancy.

Another strategy is to screen pregnant women for primary CMV infection by maternal serology at the beginning of pregnancy and at 20–22 weeks gestation in order to identify those who underwent seroconversion during pregnancy. Screening during the first-trimester screening is recommended, since the time of infection can be determined using immunoglobulin G avidity, and the clinical sequelae of congenital CMV is usually more severe if transmission occurs early in gestation [1-4]. With this screening method prenatal diagnosis could be offered for those with primary infection. This method would prevent the birth of infants with severe disabilities by pregnancy termination. It would also enable early antiviral treatment and fitting with prostheses those suffering from neurosensory defects. Recent years have witnessed several developments concerning CMV infection in pregnancy that make maternal screening attractive. Sensitive and specific methods exist for serologic diagnosis of a primary CMV maternal infection, which includes IgG antibodies with low avidity to CMV [18]. Due to its high sensitivity and specificity, combined viral isolation and PCR from amniotic fluid after the 21st week of pregnancy and after a mean interval of 7 weeks from infection have been established as the reference method for prenatal diagnosis of CMV infection [4,19]. High positive and negative predictive values for clinical disease have been determined for quantitative PCR testing of amniotic fluid [20]. Systematic ultrasound during pregnancy is currently used by almost all obstetricians, enabling detection of major fetal impairment, particularly cerebral defects, that would justify pregnancy termination. However, this method is not sensitive enough [21]. Furthermore, in countries where termination of pregnancy is not available beyond 24 weeks, this strategy has poor efficiency since most CMV complications can be observed only in the last trimester of pregnancy.

Another recent development is CMV hyperimmune globulin which was found to be effective in the treatment and prevention of congenital CMV infection [22]. Although passive immunization of pregnant women has been used to treat a variety of infections with unknown adverse effects in the fetus, the study is limited by low numbers and questionable methodological issues. Screening for infections at the beginning of pregnancy may cause anxiety in the patient, and an excessive number of amniocenteses may increase the risk of spontaneous abortion more than the risk of intrauterine CMV transmission. This would lead to the request for too many unnecessary pregnancy terminations that the obstetricians would not be able to refuse due to the inability of eliminating all possible severe sequelae. Prevention by pregnancy termination raises ethical issues that have to be considered. However, amniocentesis performed only for those indicated, and termination of pregnancies performed only when there is evidence of high DNA copies number will prevent the unnecessary termination of pregnancies. It is also possible to screen seropositive pregnant women for non-primary infection. A population with a high prevalence of IgG antibodies will have more congenital infections caused by non-primary than by primary infections. Furthermore, among symptomatically infected newborns for whom maternal serology was defined, almost 50% were born to mothers with non-primary CMV infection [9,10], leading many obstetricians in Israel to screen for non-primary CMV infection during pregnancy. However, the definition of non-primary infection is not clear. All published studies evaluated non-primary infection from the infected neonates with retrospective evaluation of the mothers' serology. Thus, screening a disease that is ill defined should be avoided.

Finally, it is possible to screen all women of childbearing age who plan pregnancy. Those with primary infection will defer pregnancy for 6 months; IgG-seronegative women will be properly informed, so that whenever they become pregnant they will already be aware of the possible risks and preventive measures, and the IgG-seropositive women will be instructed as mentioned above concerning non-primary infection in pregnancy. However, most young women do not perform routine blood tests before pregnancy, and the time lapse from screening to pregnancy can take years and may no longer be relevant. It is crucial that health professionals with limited knowledge of CMV in pregnancy not inform patients about the infection since they may ultimately affect the choice in the wrong direction, leading to the immediate option of terminating the pregnancy.

In conclusion, in view of the diagnostic achievements of recent years I believe it is now time to consider the introduction of routine antenatal screening for CMV. The implementation of any screening policy for prevention of CMV infection should be based on reliable estimates of prevalence and cost. The frequency of CMV infection in our country, the positive and the negative predictive values of prenatal diagnosis, and the proportion of infants born with hearing impairment and mental retardation are not known. The financial implications of serology, amniocentesis and management of infected fetuses should also be evaluated. It is to be expected that appropriate routine antenatal screening would be cost-effective considering the costs of care and treatment of CMV-damaged infants and of surveying asymptomatic infected newborns for late manifestations.

Ig = immunoglobulin
PCR = polymerase chain reaction

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