Fetal Effects of Primary and Non-primary Cytomegalovirus Infection in Pregnancy: Are we Close to Prevention?

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Abstract

Seroconversion to cytomegalovirus occurs in 1–4% of pregnant women, most of whom are seropositive prior to pregnancy. In 0.2–2.5% of their newborn infants there is evidence of intrauterine infection; most are born without any clinical findings The typical clinical symptoms of symptomatic congenital CMV are observed in 10–20% of infected neonates. They include intrauterine growth restriction, microcephaly, hepatosplenomegaly, petechiae, jaundice, thrombocytopenia, anemia, chorioretinitis, hearing loss and/or other findings. Long-term neurodevelopmental sequelae include mental retardation, motor impairment, sensorineural hearing loss and/or visual impairment. These may occur even in infants who are free of symptoms at birth. Most infants born with severe neonatal symptoms of congenital CMV are born to mothers with primary infection during pregnancy. However, since about half of the infants infected with CMV *in utero*, including those with severe neonatal symptoms, are born to mothers with preconceptional immunity, we have to conclude that congenital CMV may be a significant problem even in children born to mothers with pre-pregnancy immunization. This may justify the use of invasive methods for the detection of possible fetal infection even in cases of non-primary CMV infection. This should also be a consideration when deciding upon population screening or immunization for CMV.

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Cytomegalovirus is found universally – in every geographic location and in all socioeconomic groups. In the United States it infects 50–85% of adults by age 40. In certain populations in Asia and Africa seroprevalence can be as high as 100% [1,2]. It is the most common intrauterine infection and a common cause of hearing impairment and mental retardation [3]. CMV is more widespread in developing countries and in areas of lower socioeconomic conditions. Most healthy persons who acquire CMV after birth do not have symptoms, or only a few, and there are no long-term sequelae. After the primary infection, the virus remains alive but usually dormant within a person's body for life. Therefore, for the majority of people, CMV infection is not a serious problem. However, in certain high risk groups, CMV infection may be dangerous, for example, for the offspring of women who acquire the disease during pregnancy and for immunocompromised persons such as organ transplant recipients and people infected with human immunodeficiency virus [3].

CMV = cytomegalovirus
Ig = immunoglobulin

Epidemiology and CMV transmission in children and adults

Day-care centers contribute much to the rapid spread of CMV, with infection rates in such centers reaching 50–70%. Infection is less common among children who are not exposed to other toddlers [3-5]. Transmission of CMV occurs from person to person. CMV has been isolated in oropharyngeal secretions (saliva), urine, feces, semen, vaginal secretions, breast milk, blood, and tears. Indirect transmission from shared food, toys and items in close contact with an infected individual is also possible.

The prevalence of CMV antibodies varies widely among different populations depending on socioeconomic status. Seroconversion occurs in 1–4% of all pregnancies. It is higher in women with low socioeconomic status and lower in those with high status or with good personal hygiene [3-6]. Seroprevalence for CMV immunoglobulin G in Israel is approximately 85% in women of childbearing age [6].

The virus can also be transmitted to the infant at delivery from contact with genital secretions or later in infancy through breast milk. However, these infections usually result in little or no clinical illness in the infant. This holds true even in premature infants infected by CMV through maternal milk [7].

Primary infection is defined as CMV infection in a seronegative person who was never been infected before, and non-primary (secondary) infection is defined as a rise in IgG or IgM antibody titers in a person who was previously infected. Secondary infection is usually diagnosed if there is either a significant rise in IgG antibodies in a person with previous positive IgG, or positive IgM in a person who was previously IgG positive and IgM negative [3]. It is unknown whether there is any difference in fetal outcome if the mother had CMV reinfection or reactivation; both can apparently lead to symptomatic congenital CMV [3,4,8]. There is always a certain percentage of women with IgG and IgM antibodies in pregnancy in whom it is impossible to determine

if they have primary or secondary infection, and even though IgG avidity may help to differentiate between recent and old infection it is not always performed [3]. IgM antibodies may remain positive for a relatively long period (6–18 months) in both primary and non-primary infections.

Epidemiology of congenital CMV

A variety of studies have found that the prevalence of embryonic and/or fetal infection with CMV, as evidenced postnatally, is 0.2–2.5% [3-5]. Most of these infants were apparently born to mothers who had secondary infection during pregnancy. Petrikovsky et al. [9] studied the prevalence of several viruses (CMV, adenoviruses and enteroviruses) in the amniotic fluid of pregnancy terminations of fetuses with congenital anomalies detected on ultrasound as compared to terminated pregnancies with normal fetuses. The rate of CMV was 2.5% in the congenital anomalies group and zero in the control group of normal fetuses.

Transmission to the embryo and fetus

If the pregnant woman is seronegative at the time of infection, the probability of transmission to the fetus is 30–50% [3,5]. Infection in the first half of pregnancy bears a greater risk of symptomatic fetal involvement in comparison to infection in the second half of pregnancy [3,5]. The degree of fetal damage is also higher in early primary infection than in late infection. CMV can be transmitted from mother to fetus even if the mother had primary infection long before conception, apparently up to 6 months [3,10].

The exact risk of symptomatic congenital CMV among the infected fetuses after maternal primary or non-primary infection is unknown, but it is estimated to be between 5% and 15% after primary infection and less than 2% after secondary infection [3,5,10,11]. Previous maternal immunity, therefore, does not provide complete protection against transmission to the fetus.

In a relatively recent study by Fowler and collaborators [12] conducted in the U.S., evidence of intrauterine CMV infection was found in 3% of infants born to 604 mothers who were seronegative at the beginning of pregnancy and in 1% of the infants born to 2856 mothers who were seropositive prior to pregnancy. These results show that maternal preconceptional immunity against CMV gives relatively good protection to the fetus, but we should keep in mind that 1% of these infants were infected. If this ratio is correct worldwide, then considering that 70–80% of pregnant mothers are seropositive prior to conception, we have to conclude that over half of the children infected with CMV *in utero* are born to mothers with preconceptional immunity.

It is generally accepted that most children with congenital CMV born to such mothers are asymptomatic at birth, and less than 10% of them seem to develop postnatal sequelae, mainly sensorineural hearing loss and chorioretinitis [3,5,11-13]. There is, however, increasing evidence in recent years that secondary maternal CMV may also be a significant cause of severe congenital CMV disease and in some cases may even cause intrauterine fetal death [3,11-13]. This is of special concern considering the fact that approximately 1% of newborn infants are infected with CMV *in utero* despite maternal immunity before pregnancy.

Congenital CMV

In contrast to the classical teratogenic agents that affect the embryo and fetus primarily during organogenesis, many of the teratogenic agents causing intrauterine infections often affect the fetus after major organogenesis is over. CMV is a typical example of such a highly teratogenic virus [3,5]. This explains why the human fetus can be affected by CMV throughout the entire pregnancy. However, the damage is still more severe when infection occurs during the first half of pregnancy, compared to infection in the second half, with reduced morbidity.

Typical clinical findings of congenital CMV include intrauterine growth restriction, microcephaly, hepatosplenomegaly, petechiae, jaundice, thrombocytopenia, anemia, chorioretinitis, hearing impairment, and/or other atypical findings [3,5,10]. Cerebral calcifications, if found in the context of CMV, tend to be periventricular. Often there are additional major congenital anomalies, especially of the cardiovascular system and the brain. The mortality rate among infants with neonatal manifestations of congenital CMV is 10–30% and only about 10% completely recover, while the others will have long-term sequelae. In 10–15% of infants infected during pregnancy, the clinical symptoms develop during the first 1–3 years of life [3-5].

Neurodevelopmental outcome

The major problem of congenital CMV is the neurodevelopmental damage. The two most common handicaps are sensorineural hearing loss that may be progressive due to continuous damage to the cochlea, and visual impairment as a result of progressive chorioretinitis [3,14]. In addition, the neurodevelopmental sequelae range from severe mental retardation to normal cognitive capacity. Inattention, hyperactivity (attention deficit hyperactive disorder) and learning disabilities, which are common features in normal children, may also be found in CMV-infected children with slight mental retardation or with normal intellectual abilities and no other clinical symptoms of congenital CMV. The prevalence of these findings among such children is unknown. A possible association between congenital CMV and autism has also been suggested [15].

It is impossible to accurately predict at birth the extent of the neurodevelopmental impairment. However, most children with congenital CMV and an abnormal CT scan of the brain at birth will develop at least one neurological problem; such problems are significantly less common, with a normal CT study at birth, making a cranial CT scan a good predictor of adverse neurodevelopmental outcome [3,10]. Microcephaly at birth and afterwards seems also to be a predictor of mental retardation. Infants with symptomatic congenital CMV infection at birth are likely to have severe CNS sequelae, including mental retardation, motor impairment, spasticity, microcephaly, sensorineural hearing loss, chorioretinitis and sometimes seizures, with 45% to 90% of these children experiencing these neurological abnormalities.

Antiviral drugs and congenital CMV

Currently there is no approved agent for antiviral therapy for congenital CMV infection. CMV is relatively insensitive to acyclovir, but apparently sensitive to several other drugs [16]. Recent evidence suggests that ganciclovir may have a beneficial effect in neonates with severe congenital CMV infection, such as preventing hearing deterioration, compared to non-treated patients [16]. However, treatment does not seem to induce a significant improvement in the course of disease, or an amelioration of neurodevelopmental sequelae. We conducted a developmental evaluation of five children, aged 2–5 years, born with symptomatic congenital CMV and treated with ganciclovir. Three of them showed significant developmental delay; two also had hearing impairment. However, we were unable to determine whether there was an improvement or deterioration in the clinical findings since they were not evaluated thoroughly prior to treatment.

Diagnosis of intrauterine CMV infection

Since transplacental transfer of the virus occurs only in about 50% of mothers with primary maternal infection and in a significantly lower percentage in secondary infection, it is important in cases of proven maternal infection to determine if the fetus is infected. The more effective and less invasive way for diagnosing fetal infection is by isolating the virus from the amniotic fluid and/or studying viral DNA by polymerase chain reaction [3,5,17]. However, molecular contaminations may lead to false positive results, creating a dilemma in the interpretation and clinical significance of a positive PCR result not supported by virus isolation. This dilemma and the need to address prognostic issues finally led to the development of quantitative PCR assays, with the highly advanced Real-Time PCR being the most updated. In an attempt to establish the prognostic parameters of this powerful technique, current studies indeed correlate between the "viral load" in the amniotic fluid and the degree of fetal damage.

Since it takes 5–7 weeks from fetal infection and replication of the virus in the kidney until a sufficient quantity of the virus is secreted to the amniotic fluid, and testing is not reliable before the 21st week of pregnancy, PCR should not be performed before the 21st week and in cases of late infection at least 6 weeks after maternal infection [3]. While it is accepted that PCR and virus isolation should be performed in primary maternal infection due to the high risk of fetal damage, there is no agreement whether to perform viral studies in cases of secondary maternal infection, when the risk of fetal damage is relatively low. Since there are cases of severe fetal damage following non-primary infection, it is suggested that antenatal diagnosis be performed, even in cases of non-primary infections, if the infection occurred in the first trimester of pregnancy, and especially if ultrasonography reveals fetal damage [3].

Vaccine

To date, no vaccine for prevention of CMV infection and disease is approved for use. A live attenuated vaccine using the Towne 125 strain has been developed. However, the Towne vaccine was unable to prevent infection in women of childbearing age exposed to young children shedding CMV [3]. There were concerns regarding the ability of the vaccine strain to reactivate and infect the immunized person, the possibility that the vaccine strain may be shed from the cervix and in breast milk, and the possible carcinogenic potential of CMV. A recombinant CMV vaccine based on the envelope glycoprotein gB has been developed and was demonstrated in early trials to be safe and immunogenic. Subunit vaccines eliminate the concerns of viral reactivation and oncogenicity. New CMV vaccines are also being tested. However, in spite of the significant need, an effective vaccine is still not available [18].

Prevention of maternal and fetal infection

General recommendations for pregnant women with regard to CMV infection include practicing good personal hygiene, especially hand-washing with soap and water after contact with diapers or oral secretions, particularly with a child who is in day care as this was associated with a higher risk of maternal infection in pregnancy [4]. Women who develop a mononucleosis-like illness during pregnancy should be evaluated for CMV infection and, if positive, counseled about the possible risks to the fetus. If a woman had primary CMV infection with persistent IgM antibodies and/or virus shedding in the urine, it seems advisable to delay pregnancy for about 6 months since the primary infection.

Screening of pregnant women

This is discussed in length in the Debate section in this journal. Since congenital CMV may pose a serious problem mainly because of the lack of clinical symptoms in the mother even in primary infection, the obvious question is whether all women who are unaware of the CMV antibody status should be screened, despite the difficulty interpreting the results. The screening, if done, should be carried out at the beginning of pregnancy or even prior to a planned pregnancy. If a woman is seronegative, repeated examinations during pregnancy should be performed. As the virus may affect the fetus throughout pregnancy, these examinations should be repeated at least until the time when pregnancy termination is still legally possible. This policy, however, is not practiced in most countries.

It was recently suggested that serial urine studies for CMV by PCR may also be a useful tool to detect primary infection in pregnancy since CMV is secreted in the urine in most such infected women [19]. Another possibility is neonatal screening for CMV, and follow-up, especially for the early identification of hearing loss [20].

PCR = polymerase chain reaction

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Too often we enjoy the comfort of opinion without the discomfort of thought

John F. Kennedy (1917-1963), 35th U.S. president

Of all nature's gifts to the human race, what is sweeter to a man than his children?

Marcus Tullius Cicero (106-43 BCE), Roman statesman, orator, writer, political theorist and philosopher

Capsule

Digesting wood

In the race to replace fossil fuels with biofuels, microbial fermentation may become a key technology. However, microbes can do only so much and balk when their food contains too much lignin. This is not uncommon because the fibrous tangle of lignin and cellulose, called lignocellulose but better known as wood, is ubiquitous. To add to the problem, the enzymatic breakdown of cellulose is not as rapid as the enzymatic breakdown of starches. Jeffries et al. present the genome sequence of the yeast *Pichia stipitis Pignal*, which can digest lignocellulose and can transform xylose, a component of lignocellulose, into ethanol. The yeast sequenced was isolated from insect larvae and is related to yeasts found in the gut of beetles that frequent rotting wood. The 15.4 Mb genome is divided into eight chromosomes and includes 5841 predicted genes, including a group of cellulases and xylanases and a number of genes encoding putative xylose transporters. Further analysis showed which genes in which metabolic pathways respond to changes in xylose, glucose, or oxygen. Unlike *Saccharomyces cerevisiae*, which regulates fermentation according to glucose availability, *P. stipitis* regulates fermentation according to oxygen levels, which is reflected in how the genes respond to oxygen.

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