Fetal effects of primary and secondary cytomegalovirus infection in pregnancy

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Abstract

Seroconversion to cytomegalovirus (CMV) occurs in 1–4% of pregnant women. The majority of these women are seropositive prior to pregnancy. In 0.2–2.5% of the newborn infants, there is evidence of intrauterine infection, most of them are born without any clinical findings. The typical clinical symptoms of congenital CMV (symptomatic congenital CMV) that are found in 10–20% of infected neonates include intrauterine growth restriction (IUGR), microcephaly, hepatosplenomegaly, petechiae, jaundice, chorioretinitis, thrombocytopenia, anemia and/or other atypical findings. Of special problem are the different neurodevelopmental sequelae such as mental retardation, motor impairment, sensorineural hearing loss or visual impairment, which 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 in pregnancy. However, since over 60% of the infants infected in utero with CMV are born to mothers with preconceptional immunity who have secondary infection in pregnancy, and more and more studies show severe sequelae in these infants, 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 secondary CMV infection. This also brings in an additional problem, when considering the need for proper immunization against CMV, as immunization is primarily aimed for women without immunity.

Keywords: Cytomegalovirus; Primary infection; Secondary infection; Pregnancy outcome

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Cytomegalovirus (CMV) is found universally throughout all geographic locations and in all socioeconomic groups. In the USA, it infects 50–85% of adults by 40 years of age. In certain populations in Asia and Africa, seroprevalence can be as high as 100% [1–3]. It is the most common intrauterine infection, and a common cause of sensorineural hearing loss and mental retardation [4,5].

CMV is more widespread in developing countries and in areas of lower socioeconomic conditions. In general, factors associated with seropositivity include lower socioeconomic status, maternal age more than 30, nonwhite race, lower level of education and close contact with young children. For most healthy persons who acquire CMV after birth, there are only few or no symptoms and no long-term sequelae. Some experience a mononucleosis-like syndrome with prolonged fever, and a mild hepatitis. 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. The manifestations of acquired CMV infection vary with the age and immunocompetence of the host. In certain high-risk groups, CMV infection may be dangerous, i.e. for pregnant women who may acquire the disease during pregnancy and for immunocompromised persons such as organ transplant recipients, and people infected with human immunodeficiency virus [6–10].

2. The virus

CMV is a member of the herpetoviridae family and is the largest of that group with a diameter of about 200 nm. It has a double stranded DNA core of 200 kilobase pairs enclosed by an icosahedral capsid. It is an intranuclear virus and the core is assembled in the nucleus of the host. It exits from the affected cells by reverse pinocytosis. The DNA genome encodes for over 35 different structural proteins and glyco-proteins. Human and higher primates are apparently the only reservoir for the human CMV [11]. There seem to be several strains of CMV that infect human, hence causing reinfection even in immunocompetent individuals. However, serologic tests do not define different specific serotypes, and all known human strains seem to be genetically homologous. The genomic heterogeneity can, however, be used to characterize individual strains of CMV based on cross neutralization tests or on restriction fragment length polymorphism (RFLP) [12].

3. Epidemiology and transmission of CMV in children and adults

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. Infection requires close intimate contact with persons excreting the virus in their saliva, urine or other body fluids. However, indirect transmission from toys and items that are in close contact with an infected individual is also possible. CMV can be sexually transmitted and can also be transmitted via transplanted organs, and rarely from blood transfusions [12,16].

Day care centers contribute much to the rapid spread of CMV, with infection rates in such centers that may reach 50–70%. Infection is less common among children who are not exposed to other toddlers [12].

The prevalence of CMV antibodies varies widely among different populations depending on socioeconomic status (SES). Most preschool aged children in Africa and Asia are seropositive, while fewer than 20% of young children in the USA and UK are seropositive. The range of congenital CMV infection varies between 0.2–2.5% of live births [6,12,15–17]. Young maternal age, single marital status, and nonwhite race are associated with higher rates of congenital CMV infection [18,19]. Seroprevalence in Israel for CMV IgG is approximately 85% in women of childbearing age [20].

Seroconversion occurs in 1–4% of all pregnancies [21]. It is higher in women of low SES and lower in those of high SES or with good personal hygiene [12].

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

4. Epidemiology of congenital CMV

A variety of studies have found that the prevalence of embryonic and/or fetal infection with CMV, as evidenced post-natally, is 0.2–2.5%. The rate of infection seems to be much lower in Europe and Australia, less than 0.5% [11]. The majority of these infants have no long-term clinical sequelae of the infection [12,14,15,27–29]. Most of these infants were apparently born to mothers who had secondary infection during pregnancy. The prevalence of congenital CMV is higher in population of low SES class and in heavily populated areas, where the rate of CMV infection is higher [12,30]. In that context, it is interesting to note that Petrikovsky et al. [31] studied the prevalence of several viruses (CMV, adenoviruses and enteroviruses) in amniotic fluid of pregnancy terminations of fetuses with congenital anomalies detected at ultrasonographic examinations in comparison to pregnancies terminated with normal fetuses. The rate of CMV was 2.5% in the congenital anomalies group and zero in the control group of normal fetuses.

5. Transmission to the embryo and fetus

The fact that the immune system is suppressed during pregnancy contributes to the increase in the incidence of primary or secondary CMV infections in pregnant women, and hence the transfer of the virus to the developing embryo and fetus. Hematogenous spread appears to be the most likely pathway of vertical transmission to the fetus. It has been suggested that placental infection occurs first, followed by replication of the virus and then transfer to the fetus where it seems to replicate in the renal tubular epithelium [26,30]. The typical placental changes are villitis and sometimes the presence of diagnostic viral inclusions in the stromal cells as well as in the endothelial cells [32]. The typical pathological changes are best visualized by immunohistochemistry or by specific localization of the CMV genome [32–34]. By the latter technique, the virus can be localized in the villous stroma, trophoblastic cells and the decidua. CMV spread via ascending infection from maternal genital organs is rare, but possible. In that case, the virus, after entering the amniotic fluid, replicates in the fetal oropharynx [35]. Once fetal infection occurs, the virus continues to replicate in the renal tubular epithelium.

If the pregnant woman is seronegative at the time of infection, the probability of transmission to the fetus is 30–50% [13,17]. Gestational age at infection does not seem to affect the rate of transmission but 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 [15,36]. The degree of fetal damage is also higher in early primary infection than in late infection [11,36]. CMV can be transmitted from mother to fetus even if the mother had primary infection long before conception, apparently up to 6 months [20,37].

The exact risk of symptomatic congenital CMV among the infected fetuses after maternal primary or secondary infection is unknown, but it is estimated to be between 5–15% after primary infection and significantly less (<2%) after secondary infection [6,12,20,23–25,36,37]. Previous maternal immunity therefore, does not provide complete protection against transmission to the fetus.

In a recent study by Fowler et al. [28] conducted in the US, evidence of intratutrine 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 conception. There is no data on the rate of seroconversion in the mothers. These results show that maternal preconceptional immunity against CMV gives relatively good protection to the fetus, but we should still remember 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 60% of the children infected in utero with CMV are born to mothers with preconceptional immunity.

It is generally accepted that most children with congenital CMV born to mothers who had secondary CMV infection are asymptomatic at birth, and less than 10% of them seem to develop postnatal sequelae, mainly sensorineural hearing loss and chorioretinitis [26,36,38]. There is, however, increasing evidence in the last 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 [23,25, 36,39–42]. This is of special concern considering the fact that still approximately 1% of newborn infants are infected with CMV in utero in spite of maternal immunity before pregnancy [28].

We may therefore conclude that most infants with evidence of intrauterine CMV infection, but asymptomatic at birth, are born with secondary infection. Although it is generally accepted that more severe sequelae are seen in children whose mothers had primary infection in pregnancy [28,40], the above described cases of severe sequelae in infants born to mothers with previous immunity somewhat questions that notion. The practical implementation is that even in cases with known secondary maternal CMV infection, one has to attempt to examine if the fetus is infected. If this is proven, it may be important to assess the risk and decide upon the future of the pregnancy, especially if the infection occurred early in gestation.

6. Congenital CMV

6.1. Fetal damage and neonatal presentation

Most infants born with severe neonatal symptoms of congenital CMV are born to mothers with primary infection in pregnancy. The results of embryonic and fetal damage in infants born to such mothers may either be manifested neonatally or appear during the first years of life.

In contrast to teratogenic chemicals and drugs that would generally affect the embryo and fetus mainly during organogenesis, many of the teratogenic infectious agents can also affect the fetus after major organogenesis is over, depending on the time of infection. CMV is an example of a highly teratogenic virus that affects fetal organs after major organogenesis [15,40]. This is why the human fetus can be practically affected by CMV throughout the entire pregnancy. However, the damage is still more severe in infants infection during the second half of pregnancy, while infections in the first half of pregnancy, especially if the infection occurred early in pregnancy, may have an impact on the risk and decide upon the future of the pregnancy, especially if the infection occurred early in pregnancy.

7. 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 [50]. In addition, the neurodevelopmental sequelae range from severe mental retardation to normal cognitive capacity. Slight neurological damage and learning disabilities 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 [51–53]. The prevalence of these findings among such children is unknown. A possible association between congenital CMV and autism was also suggested. Ivarsson et al. described two such children [54] and Yamashita et al. described two additional cases of autism among seven children with congenital CMV [55].

It is impossible to accurately predict at birth the extent of the neurodevelopmental impairment. There are several studies trying to relate abnormalities of imaging techniques (Ultrasound, Computerized Tomography (CT) scans and Magnetic Resonance Imaging (MRI)) of the brain at birth to later outcome. Boppuna et al. [56] performed cranial CT scan on 56 children with symptomatic congenital CMV at birth. Abnormal CT scans were found in 70% of these infants, with intracerebral calcification being the most common finding. Ninety percent of the infants with abnormal CT scans at birth developed at least one sequela of congenital CMV, with 59% suffering from mental retardation. In contrast, only 29% of the infants with normal CT scans at birth had one sequela and only one of them had mental retardation. The authors concluded that “a cranial CT scan is a good predictor of adverse neurodevelopmental outcomes”. Novella et al. [57], while summarizing findings from the Houston Congenital CMV Longitudinal Study Group performed on 41 children, concluded that children with a normal CT scan at birth and without microcephaly have good chances for a normal intellectual function. Recently, De Vries et al. [58] summarized the brain findings on ultrasound of 11 neonates with congenital CMV and the MRI findings in 8 of these infants. Nine of the infants had microcephaly. Typical ultrasonographic findings were periventricular calcifications, mild to moderate ventricular dilatation and/or vasculopathy in the lenticulo-striatal areas. MRI provided additional important information as in some infants, polymicrogyria, hypoplastic lenticula and cerebellar hypoplasia could be detected. They conclude that in neonates with congenital CMV, brain ultrasound examination and MRI can be used to predict the future neurodevelopmental outcome.

Microcephaly at birth and afterwards, in addition to abnormal brain imaging seems to be the most sensitive predictor of mental retardation. Normal development at 12 months of age without microcephaly makes subsequent neurodevelopmental or intellectual impairment unlikely [59]. 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. These sequelae evolve in the early years of life. Follow-up studies report that 45–90% experience these neurologic abnormalities [46,60,61].

The rates of hearing loss in symptomatic and asymptomatic infected infants are approximately 40% and 7%, respectively. In both, the loss may be late in onset, fluctuating and progressive, necessitating follow-up. In a recent study by Barbi et al. [4], the authors studied the rate of prenatal CMV infection in 130 children with sensorineural hearing loss above 40 dB using blood drops from the neonatal period, using the Guthrie cards that contain spots of blood for routine neonatal screening to detect phenylketonuria, hypothyroidism ext. They found that in infants whose sensorineural hearing loss was diagnosed in the first 2 months of life, the rate of CMV infection was 10%, but it increased significantly to 34.2% if the diagnosis was first made at a later age in infancy implying that in most cases hearing loss of congenital CMV is relatively late in onset. In a similar study examining the rate of CMV excretion in the urine of children with severe hearing loss or with mental retardation, Pultrio et al. [5] found that 50% of the deaf children and 17.6% of retarded children excreted CMV. Sensorineural hearing loss is apparently no predictor for other neurologic impairments [59].

7.1. Diagnosis of intrauterine CMV infection

Since trans-placental 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 find out if the fetus is infected. Diagnosis of fetal infection by studying fetal IgM is not recommended not only because of the risk associated with cordocentesis, but also because of the fact that many fetuses infected by CMV do not develop specific IgM until late in pregnancy [14]. The more effective and less invasive way for diagnosing fetal infection is by isolating the virus from the amniotic fluid and/or by studying viral DNA [14,15,25,45,48]. In the early 1990s, the polymerase chain reaction (PCR) was added to the arsenal of molecular diagnostic assays of infectious agents. This method allowed the amplification of minute amounts of viral DNA present in the amniotic fluid to a detectable level [15,25,45,48] and enhanced the sensitivity by several orders of magnitude. How ever, 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 as the most updated method. Current studies indeed correlate between the “viral load” in the amniotic fluid and the degree of fetal damage, in an attempt to establish the prognostic parameters of this powerful technique.

As it takes 5–7 weeks since fetal infection and replication of the virus in the kidney until a sufficient quantity of the virus is secreted to the amniotic fluid, and the testing is not reliable before the 21st week of pregnancy. PCR should be performed not before the 21st week and in cases of late infection at least 6 weeks after maternal infection [15,45,48]. While it is agreed to perform PCR and virus isolation 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. Due to the description in the literature of several cases of secondary infection with severe fetal sequelae, we suggest to carry out antenatal diagnosis even in cases of proven secondary infections, especially if the infection occurred in the first trimester of pregnancy [15,25]. This is even more advisable if there are any ultrasonographic findings of fetal damage.

7.2. Pathophysiology of congenital disease

CMV infection leads to a characteristic enlargement of cells with intranuclear inclusions, often leading to cell death. These typical pathological changes are found in most infected organs, including the brain, liver and placenta [32,33,62].

7.3. Ultrasonographic diagnosis

Ultrasonographic finding are helpful but not diagnostic as they share common features with other intrauterine infections as well as with other fetal diseases. They are observed in less than half of the infected fetuses [15,63]. Antenatal diagnosis of fetal infection in cases of maternal primary CMV infection should be performed even if there are no ultrasonographic fetal changes. The more common ultrasonographic abnormalities in infected fetuses are: IUGR, ventriculomegaly, oligohydramnios, hyperechoic bowel, polyhydramnios, hydrops fetalis, brain calcifications and pleural effusion [63,64].

7.4. Correlation between quantitative PCR and fetal damage

As the main site of CMV replication in the fetus is the tubular epithelium in the kidney, and the fetal urine is excreted into the amniotic fluid, the viral load in the amniotic fluid would reflect the severity of fetal infection. This can therefore be used for predicting the possible degree of fetal damage. Quantitative determination of CMV DNA in the amniotic fluid (by Real-Time PCR) of at least 1000 genome equivalents gave a 100% certainty of detecting an infected fetus. Higher viral loads with the presence of 100,000 genome equivalents or more predicted the development of a symptomatic infection [65–67]. These results are in line with previous studies on the quantity of CMV particles in the urine of infants infected in utero with CMV, where it was found that infants with high CMV levels are symptomatic, while those with low counts are not [68]. It is, however, unknown why
borns was based on results of examinations by a pediatrician.

The information on the postnatal status of the newborns was based on results of examinations by a pediatrician and/or the evaluation of a developmental pediatrician or child neurologist.

Primary infection was defined as IgG seroconversion in pregnancy or during 6 months before pregnancy and positive IgM, or positive IgM and IgG with low avidity in pregnancy. Positive IgM in pregnancy with positive IgG and negative IgM before pregnancy were defined as secondary infection. Women who did not meet the above criteria but had a positive IgM in pregnancy were in the undetermined group. Most antibody studies were repeated twice with 1–2 week interval between the first and second examination. Serologic evidence of primary, secondary or undefined infection was found in 88, 36 and 84 women, respectively. In the primary infection group, there were 20 in whom infection occurred within 6 months prior to pregnancy; 58 in whom the infection occurred in the first 20 weeks of pregnancy and 10 women that were infected in the last half of pregnancy. Evidence of vertical transmission was seen in similar percentages in the primary (24/67–35.8%, 3 before pregnancy) and secondary (9/30, 30.0%) infection groups. In the undefined group, the rate of vertical transmission was 15.3% (11/72). Congenital CMV with clinical disease was found in nine cases. It was defined either by CMV isolated from fetal tissues at autopsy (in four cases of pregnancy interruptions) or by clinical and laboratory findings at birth (in four cases). Congenital CMV, symptomatic at birth, was reported in 3/76 (3.9%), 4/34 (11.8%) and 2/80 (2.5%) in the primary, secondary and undefined groups, respectively. In the five live-born infants with symptomatic congenital CMV one was deaf, three had mental retardation and one had mental retardation with hearing impairment at 2 years follow-up. Two of the mentally retarded children were born to mothers with secondary CMV infection in pregnancy. In seven of the nine women whose offspring had congenital CMV, clinical disease (i.e. febrile illness and flu-like symptoms) was present.

Among the fetuses or neonates with evidence of intratropical CMV infection (as evidenced by positive PCR in amniotic fluid cells or positive neonatal urine culture/cord blood IgM), specific ultrasound findings were found in approximately 25% of the cases. There were similar percentages in all three groups: 5/20 (25%) in the primary infections, 2/8 (25%) in the secondary maternal infections and 2/9 (22.2%) in the undefined cases. The ultrasonographic findings included intraterine growth restriction, cerebral and hepatic calcifications, hyperechoic bowel and cardiac hyperechoic focus. We conclude from our cases that secondary CMV infection may be an important cause of severe congenital disease. It therefore appears advisable to offer diagnosis of fetal infection by amniocentesis and PCR not only in cases of primary but also in secondary maternal CMV infection in pregnancy. Moreover, in cases of a fever or a flu-like illness with undefined diagnosis in the first half of the pregnancy, serological testing for CMV is prudent even in women with known CMV infection in the past.

8. Mortality among symptomatic newborns

Neonates with symptomatic congenital CMV infection have a multi-system disease with significant morbidity and mortality. In a study published by Boppana et al. [69], 86% of symptomatic infants had at least two of the manifestations of congenital CMV highly suggestive of congenital infection, with evidence of CNS damage being present in the majority. Twelve percent of these affected infants died by 6 weeks of age. Mortality is rare among infants with congenital CMV born after maternal secondary infection but can occur [42]. Mortality among asymptomatic newborns seems to be rare, as these children have mainly developmental problems or sensory handicap [15,70].

9. The Israeli Teratogen Information Service (TIS) experience with CMV during pregnancy

Maternal primary CMV infection during pregnancy is one of the most common reasons for a high-risk estimate and for pregnancy terminations in our TIS. The number of calls received by the Israeli TIS between 1998 and 2003 in regard to CMV in pregnancy is summarized in Table 1.

We prospectively followed up 208 women counseled by the Israeli TIS or by a large Infectious Disease Clinic in Jerusalem between 1998 and 2001 concerning CMV in pregnancy [25]. The follow-up was done by a telephone interview with the woman, using a detailed questionnaire and receiving the information from the pregnant mother generally approached during the first 2 years after the expected date of delivery or pregnancy termination. Details were verified from documents sent to us either by the women or by the treating physicians. In the Infectious Disease Clinic, details were also verified from the charts of the patients. The information on outcome was based on results of laboratory tests during pregnancy or after delivery. The information on the postnatal status of the newborns was based on results of examinations by a pediatrician.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of annual calls in regard to CMV in pregnancy</th>
<th>Relative annual number (%) of CMV calls of total annual calls</th>
<th>Relative number of calls</th>
<th>Relative annual number (%) of CMV calls of total annual calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>85</td>
<td>1.7 (85/4992)</td>
<td>2.9 (2.9/281)</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>126</td>
<td>2.1 (126/5863)</td>
<td>4.1 (4.1/102)</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>179</td>
<td>2.6 (179/7799)</td>
<td>5.3 (5.3/102)</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>202</td>
<td>2.7 (202/7381)</td>
<td>5.4 (5.4/102)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>242</td>
<td>2.7 (242/9116)</td>
<td>5.0 (5.0/102)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>281</td>
<td>2.9 (281/9664)</td>
<td>5.1 (5.1/102)</td>
<td></td>
</tr>
</tbody>
</table>
10. Treatment

Currently, there is no approved agent for antiviral therapy of congenital CMV infection. CMV is relatively insensitive to Acyclovir, but apparently sensitive to intravenous ganciclovir. Recent evidence suggests a limited beneficial role for ganciclovir treatment of neonates with symptomatic congenital CMV infection [71]. In this study, ganciclovir treatment was found to have some beneficial effects on hearing, preventing hearing deterioration, which was observed more frequently in nontreated patients [71]. A similar encouraging result was described by Michaels et al. [72], as on follow-up they found no deterioration in hearing loss in nine treated children with congenital CMV. However, treatment was not associated with a significant improvement in the course of disease, and almost two-thirds of treated infants had significant neutropenia during therapy as well as enlarged liver and spleen. Also, there was no clear-cut evidence of improvement in the neurodevelopmental sequelae. In addition, intravenous ganciclovir treatment in one case of neonatal CMV retinitis has apparently resulted in resolution of the signs of acute ocular infection. However, severe visual impairment was still present at 5 months of age [73]. We have performed developmental evaluation of five children 2–5 years of age born with symptomatic congenital CMV and treated with ganciclovir. In three of them, we found 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 as they were not evaluated thoroughly prior to treatment and we did not examine a comparable untreated control group.

11. 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 [74]. The Towne vaccine was unable to prevent infection in women of child-bearing age exposed to young children shedding CMV [75]. There were concerns in regards to the ability of the vaccine strain to reactivate and infect, 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 appeared to be safe and immunogenic in early trials [76–79]. Subunit vaccines eliminate the concerns of viral reactivation and oncogenicity. New CMV vaccines are also being tested. As of now, however, in spite of the significant need, an effective vaccine is still unavailable.

12. Prevention of maternal and fetal infection

General recommendations for pregnant women in 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). 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. Serologic testing can help to determine if a woman has already had a CMV infection. If a woman had primary CMV infection with persistent IgM antibodies and/or virus shedding in the urine, it seems to be advisable to wait with future pregnancies about 6 months after the primary infection [15,80]. This is, however, in debate since Fowler et al. [81] have shown in a recent study that fetuses may be infected by CMV even years after maternal primary infection.

13. Screening of pregnant women

Since congenital CMV may pose a serious problem mainly because of the lack of clinical symptoms in the mothers even in primary infection, there is an obvious question whether one has to screen all women in whom there is no knowledge on the CMV antibody status. 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, one has to repeat these examinations at least to the time when pregnancy termination is still legally possible. This policy, however, is not practiced in most countries [82–84]. There are several reasons why this is not a practical policy. First, screening is usually done before pregnancy for diseases for which there is a proper immunization, such as Rubella or Varicella, in order to enable effective immunization before pregnancy, thus avoiding possible trans-placental infection. There is as yet no effective and safe immunization against CMV. Secondly, screening for specific antibodies can be done if interpretation of the antibody studies is easy and clear. As CMV IgM antibodies may persist many months and even years after primary infection, the interpretation of positive IgM at the beginning of pregnancy is difficult as it may result either from infection at the beginning of pregnancy or from primary infection even many months before pregnancy [15]. In addition, one has to remember the possibility of cross reactivity with other infections such as Epstein Barr virus, toxoplasmosis, herpes simplex virus and others. Although the test of IgG avidity may be of help, as high avidity may point to an infection that occurred several months before the antibody studies, the avidity test is still in many laboratories not considered to be highly accurate and reliable. Moreover, an additional and apparently most important problem is the fact that there is nothing to offer to a woman who is seronegative for CMV, except repeated antibody studies throughout pregnancy and strict personal hygiene to reduce to minimum the chances for infection. In addition, even demonstration of IgM seroconversion during pregnancy or of a significant increase in IgG, especially in secondary infection, is not widely accepted as an indication.
for considering pregnancy interruption as most infected fe-
tuses will be normal and there is no effective method for the
prediction of fetal outcome [27,80–82]. For these as well as
economical reasons, routine serological examinations are not
recommended in most countries [15,27]. One may conclude
that if there is any reason to recommend routine antibody
testing, it should be done before pregnancy, as it may help
to differentiate between primary and secondary infection in
cases where CMV infection is clinically suspected in preg-
nancy. We should add that in our series [25], the majority of
women who had offspring with congenital CMV had clinical
signs of a flu-like illness. On that basis it may be argued
that women with flu-like symptoms during pregnancy and
no knowledge of previous immunity for CMV, should have
evaluation of their CMV antibody status. Such a recommen-
dation, however, is not clear-cut due to the possible economic
burden and the fact that there are sufficient cases of children
with congenital CMV born to mothers without any evident
disease during pregnancy.
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
infected women [82].

14. Breast feeding

CMV can be detected by virus culture in milk of 18–70% of
seropositive mothers [85–90]. In the study published by
Dworsky et al. [87], consumption of CMV-infected breast
milk leads to infection of 69% of the infants. Although there
is some milk secretory immune response to this virus, it did
not prevent viral shedding or viral transmission. All infected
infants chronically shed CMV; however, no infants demon-
strated chronic long-term sequelae. Two preterm infants de-
veloped acute pneumonitis, which resolved. Similar rate of
infected women [82]. The most im-
proved preterm infants with regard to neurologic, speech and
motor and psychosocial development during the first year
of life. Children with low birth weight, not due to prematurity,
and first children, seem to be at a greater risk of acquiring peri-
natal CMV infection and the risk is increased when breast-
feeding duration is longer than 2 months. Perinatal CMV
infection does not seem to influence the general morbidity
of the child [92,93]. A higher incidence of CMV excretion
(85%) into breast milk was detected in CMV seropositive
mothers even in infants born prematurely. The most im-
mature infants had a greater risk to acquire an early and symp-
tomatic CMV infection. Hamprecht et al. [84] found an even
higher rate (96%) of CMV reactivation in seropositive breast-
feeding mothers of preterm infants. The early appearance of
viral DNA and the virus in milk whey were risk factors for
transmission. Approximately, 50% of the infected infants had
no symptoms, but four had sepsis-like illness. Maschmann et
al. [95] found a 38% transmission rate among very low birth
weight (<1500 g) preterm infants to seropositive mothers via
breast milk, 48% of whom presented with symptomatic dis-
ease (i.e. hepatomegaly, neutropenia, thrombocytopenia and
sepsis-like presentation). Yasuda et al. [96] found that 88% of
seropositive mothers to preterm infants had detectable CMV
DNA in breast milk. Most breast milk became positive for
CMV DNA 2 weeks after delivery. Viral DNA copy num-
bers increased until they peaked at 4–6 weeks. Afterwards,
the CMV DNA copy numbers decreased. Infected breast milk
was confirmed in 10% of the infants who were fed CMV positive milk,
but none had clinical symptoms of CMV infection. Human
milk whey is the important fraction for CMV transmission
through breast milk, whereas milk cells are not necessarily
infected in transmitters [97]. Viral load in breast milk cor-
relates with transmission of CMV to preterm neonates [98].
Vollmer et al. [99] studied the long term effects of postnatally
acquired CMV infection via breast milk and did not find sen-
soineural hearing loss in any of the preterm infants. There
was no difference between the group with early infection by
breast feeding and a matched control group of CMV neg-
ative preterm infants with regard to neurologic, speech and
language or motor development.
In Taiwan, duration of breast feeding is a significant risk
factor for the postnatal transmission of asymptomatic CMV
[100]. A higher rate of CMV seropositivity was observed
among breast fed children in urban areas of China [100].
In Italy, the rate of CMV excretion in saliva in children of
middle to low socioeconomic classes was 13% During the
second year of life 100% of the excretors had been breast fed
[101].
In children with vertically acquired HIV infection, breast
feeding increases the risk of combined Pneumocystis carinii
pneumonia and CMV infection, which is associated with se-
vere disease [102].
In conclusion, despite of the possibility for transmission of
CMV virus from the infected mother to the infant, there seems
to be no contraindication for breast feeding in seropositive
mothers, even in infants born prematurely.

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