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CYTOMEGALOVIRUS INFECTION IN PREGNANCY- A REVIEW

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ABSTRACT

Primary and recurrent infections of human cytomegalovirus (HCMV) can occur during pregnancy. Both can result in congenital infection, the leading infectious cause of mental retardation, sensorineural deafness and visual impairment. The intrauterine transmission of HCMV and an adverse outcome are mainly related to a primary maternal infection. However, there is currently increasing evidence that the incidence of symptomatic infections in infants born to immune mothers is higher than previously thought. The option of a pre- natal diagnosis therefore has a crucial role in the management of pregnancies complicated by active HCMV infection. In spite of the potentially devastating consequences of congenital HCMV infection, little information is available concerning antiviral therapy as prophylactic treatment for women at high risk of the transmission of HCMV during pregnancy. Passive immunization for the prevention of vertical transmission of the virus appears promising. Until a HCMV vaccine is available, education is needed regarding the risk involved and the strategies to be adopted for the prevention of HCMV infection during pregnancy.

KEYWORD: human cytomegalovirus, pregnancy, vertical transmission, fetal infection, prena- tal diagnosis, prevention

INTRODUCTION

Human cytomegalovirus (HCMV), or human herpesvirus 5, a large DNA virus, belongs in the subfamily Betaherpesvirus of the family Herpesviridae. It is a widespread opportunistic pathogen and highly host-specific (1). All known strains of HCMV are genetically homologous, but none seem to be genetically identical unless they are obtained from epidemiologically related cases (1). HCMV can cause a lytic and productive infection but, like other herpesviruses, is also capable of latency and reactivation. It establishes life-long latent infection without clinical disease or is asso- ciated with mild symptoms in immunocompetent individuals. However, it may cause severe or even life-threatening illness in the absence of an effective immune response, as in immunological- ly immature and immunocompromised individuals, i.e. in the fetus, in transplant recipients (solid organ or bone marrow transplant patients), and in patients with acquired immune deficiency syn- drome (AIDS). Seropositivity for this virus increases with age, ranging from 40 to 100%, depending upon both geographic location and socioeconomic status (2). Active HCMV infec- tion can occur during pregnancy and, in contrast with other infectious agents such as rubella or toxoplasma, fetal infection can ensue following either primary or recurrent HCMV maternal infection. HCMV is one of the most common causes of birth defects, on a par with Down's syn- drome, fetal alcohol syndrome and spina bifida (2) .

In the present article our understanding of the epidemiology, pathogenesis, diagnosis and management of HCMV infection in pregnancy will be reviewed.

Epidemiology

As HCMV is higly species-specific, humans are believed to be its only reservoir. HCMV infection is endemic and displays no seasonal variation. The sources of HCMV include urine, oropharyn- geal, cervical and vaginal secretions, semen, breast milk, tears, blood products and allografts (2). HCMV is not highly contagious: spreading of the infection appears to require close or intimate contact of either a nonsexual or a sexual nature with a person excreting the virus in the bodily secretions. It can also be transmitted vertically from mother to fetus, via the breast milk, via organ transplants, and rarely via blood transfusion (2). From the standpoint of HCMV persist- ence in the human population, perinatal and breast-milk-associated transmission may be regard- ed as the primary routes of transmission, whereas shedding in the infant urine and transfer of the infectious virus by sexual contact may be viewed as 'back-up' measures that guarantee practically universal infection. The earlier pattern of HCMV transmission has been disturbed by the wide acceptance of the formula-feeding of infants. As a result, 30–50% of women of child-bearing age in the United States are now susceptible to HCMV infection (3). These women may acquire HCMV infection during pregnancy if they

have close contact with the healthy breast-fed infants of HCMV-seropositive mothers or with their own toddlers if they have been infected by expo- sure to healthy infected children (e.g. at day-care establishments). Women may also acquire HCMV infection via sexual contact with a HCMV-seropositive partner who is shedding the virus in the saliva or the semen.

Infection with HCMV can be defined as either primary or recurrent infection (either reacti- vation of endogenous virus or reinfection with a new virus strain). Studies on the age-related prevalence of infection with HCMV suggest that there may be three periods in which there are particularly high rates of acquisition of the virus: early childhood, adolescence and the child- bearing years. The reported prevalence of HCMV infection in the normal population varies widely, between 40% and 98.7%, depending on the race, the gender, the age and the socioeco- nomic status (1). HCMV is more prevalent among people in low socioeconomic brackets living in crowded conditions and in people resident in undeveloped countries (2). In Hungary, the seroprevalence of HCMV at the age of 10 years is 72%, which increases to 96% by the age of 50 (4). Seropositivity to HCMV has been found in 78.7% of 1612 pregnant women with a mean age 26.9 (range, 14-44) years (5).

After primary infection, the virus becomes latent, residing in the host throughout life. It is reactivated periodically during episodes of mild immunosuppression caused by intercurrent infection, pregnancy or stress. Recurrent infections are fairly common (2). Intermittent excre- tion of the virus can be anticipated in a significant proportion of seropositive adults. Reinfection by a new strain of HCMV has been documented in immuno compromised individuals, women attending a clinic for sexually transmitted diseases, and healthy children attending day-care cen- ters (6-8).

Increasing numbers of persons are at risk of HCMV infection. The ever greater use of child- care centers is increasing the risk to children and staff. Additionally, the number of people with a weakened immune system is rising because of the increases in frequency of human immunodefi- ciency virus (HIV) infection, organ transplantation and cancer chemotherapy.

HCMV Infection during Pregnancy

Primary HCMV infection in adolescent females (aged 14–20) is mainly acquired by oral/sexual contact with saliva, genital secretions or semen, particularly among those of lower socioeconom- ic groups who change sex partners frequently (9). Women aged 25 years from the middle and upper socioeconomic classes tend to acquire an infection predominantly through close contact with asymptomatic infants and toddlers who excrete HCMV in their saliva and urine (10-11). Once infected, children younger than 2 years of age excrete HCMV both in their saliva and in their urine for an average of 24 months. Fomites may also play a role in the transmission because HCMV has been demonstrated to remain infective for hours on plastic surfaces (12). The above points underline the increased risk of acquiring HCMV infection to seronegative women or women planning pregnancy who are working in a child day-care setting (13). HCMV may also be transmitted and produce a congenital infection if a pregnant woman or her fetus receives a blood product transfusion from a HCMV-seropositive donor.

Recurrent infection is common in pregnant women, as indicated by the rate of congenital infections (2). It occurs most frequently in the late second and third trimesters, when there is a marked transient depression of HCMV-specific cellular immunity, especially in a highly immune population. The most frequent mechanism for recurrent infection during pregnancy seems to be the reactivation of the latent virus. However, the posibility of reinfection by HCMV strains other than the original infecting strain, particularly in women with multiple sexual partners, has been demonstrated by restriction enzyme analysis (14). There is evidence that HCMV-seropositive mothers can be reinfected with a different strain of HCMV (15).

Intrauterine HCMV Transmission

The transmission of HCMV from mother to fetus can occur at any time throughout gestation. Primary infection with HCMV during pregnancy occurs in 0.7–4.1% of pregnancies, with a mean reported transmission rate to the fetus of 40% (range 24–75%) (1). Primary HCMV infec- tion acquired either before or around conception carries the lowest risk of transmission (16). If infection occurs in the 6 months before conception, transmission to the fetus and symptoms at birth will occur at a lower rate (17). Maternal infection acquired during the first and second trimesters of gestation can be transmitted at a relatively constant rate (45%). During the third trimester, however, maternal infection has the highest probability of being transmitted to the fetus (18). The risk of congenital disease is high if the primary infection occurs in the first or sec- ond trimester (19). Infection during the first 16 weeks of pregnancy has been associated with a higher incidence of fetal damage (19-20).

In contrast, the transmission rate is much lower (1–2.2%) during recurrent infection, which accounts for most cases of subclinical congenital infection worldwide (21). Both humoral and cellular immunity to HCMV are important factors in HCMV transmission during pregnancy. Neutralizing titers and IgG avidity to HCMV are both inversely correlated with transmission (22-23). Women with an impaired cellular immune response (e.g. those with AIDS or those receiving immunosuppressive therapy) are more likely to transmit the virus to the fetus.

Primary infection in the mother has a much greater clinical impact on the fetus than does recurrent infection or exogenous reinfection. Since the highest risk of serious consequences for fetal development appears to be associated with primary HCMV infection during gestation, these perturbations in HCMV transmission help to explain the growing importance of congeni- tal HCMV disease in developed countries.

The factors responsible for the transmission and severity of congenital HCMV infection are not well understood. After primary maternal infection, the most likely sequence of events leading to congenital HCMV infection is maternal viremia, followed by placental infection, and hematogenous dissemination to the fetus (24-25). An additional possibility is that the virus may ascend from the vagina via the ruptured membranes, to reach the decidua or amniotic cells (26). Consequently, infected amniotic cells may be ingested by the fetus, after which the virus may replicate in the oropharynx and invade the fetal circulation to reach the target organs. The tubu- lar epithelium within the kidney appears to be a major site of viral replication. By either mecha- nism of infection, the fetus would excrete HCMV via the urine into the amniotic fluid. The amniotic fluid therefore seems a logical choice of body fluid for the prenatal diagnosis of HCMV transmission. In live-born neonates, demonstration of the virus in the urine within the first 3 weeks of life is an indication of congenital infection.

Congenital Infection

HCMV is the leading cause of congenital infection in developed countries, occurring in 0.2–2.2% of all live births. However, the incidence of congenital infection is variable among dif- ferent populations (2, 27). The prevalence in Hungary is 0.9% (28). It has been reported that more than 10–15% of congenitally infected newborns are symptomatic at birth, and often display visceral organomegaly, microcephaly with intracranial calcification, chorioretinitis and skin mani- festations, including petechiae and purpura (2). This group of findings is characteristic of cytomegalic inclusion disease of the newborn. Virtually all babies with this condition have a pro- found neurodevelopmental handicap, including mental retardation, sensorineural deafness and visual impairment. A majority of congenitally HCMV-infected infants appear normal at birth, but 10–15% of the clinically 'silent' congenital infections lead to neurological sequelae, which may be progressive throughout early childhood (2). This makes HCMV the leading infectious cause of central nervous system damage in children (29-30).

Clinical Presentation

The integrity of the host immune system affects the spectrum of disease due to HCMV. HCMV rarely causes symptoms in an immunocompetent host; and these can be nonspecific symptoms, such as malaise, fever, sweats, aching muscles, atypical lymphocytosis and mild hepatitis during the self-limiting primary infection (31). However, it can give rise to serious disease in immuno- deficient persons, such as those with AIDS or neonates, and especially premature babies (2). Reactivation is asymptomatic, except in immunocompromised individuals.

HCMV infection in both pregnant women and their offspring is usually asymptomatic. Primary HCMV infection in a pregnant women may cause a mild febrile illness or be inapparent. Primary HCMV infections carry the highest risk of symptomatic congenital infection. Congenital infections in infants born to mothers with preconceptual immunity are less likely to be symptomatic at birth (32). However, there is increasing evidence that the incidence of symp- tomatic infection in infants born to immune mothers may be higher than previously thought (33-35). Severe congenital infection can develop and late sequelae can arise, which has led to substantial interest in a prenatal diagnosis.

Testing for HCMV Infection

Maternal HCMV infection is typically diagnosed by serology. The diagnosis of primary HCMV infection is straightforward if seroconversion to HCMV is detected. As women are not routinely screened for HCMV antibodies prior to gestation, the detection of HCMV IgM has been used as a marker of active or recent HCMV infection. The lack of standards for HCMV IgM serology and the high level of discordance among commercial assays for the detection of HCMV-specific IgM limit their diagnostic value. Many false-positive and false-negative results may be reported. In addition, IgM may be detected in the serum of a patient for up to 9 months after a primary infection, and IgM antibody may

reappear during reactivation of a latent infection or reinfection (36). When anti-HCMV IgM antibodies are detected in a pregnant woman, the diagnosis remains open.

IgG avidity assays can help distinguish primary from nonprimary HCMV infection when the presence of HCMV-specific IgM antibody in the serum of a pregnant women can not be directly related to primary infection during pregnancy. The IgG avidity assay is based on the observation that virus-specific IgG of low avidity is produced during the first few months after the onset of infection, whereas subsequently a maturation process occurs via which IgG antibody of increas- ingly higher avidity is generated. Only IgG antibody of high avidity is detected in subjects with remote or recurrent HCMV infection. Avidity levels are reported as avidity indices. Low avidity indices indicate low-avidity IgG antibodies in the serum, due to acute or recent primary HCMV infection. High avidity indices indicate no current or recent primary infection (23, 36). Low avidity indices are encountered 18–20 weeks after the onset of symptoms in immunocompetent subjects. The determination of anti-HCMV IgG avidity before weeks 16–18 of pregnancy identi- fies all women who will have an infected fetus/newborn (sensitivity 100%). The sensitivity is drastically reduced (62.5%) after week 20 of gestation (23, 36).

Immunoblotting is a good standard test with which to confirm the presence of IgM antibod- ies in the serum. The IgM blot has a high sensitivity (100%) and specificity (100%) (36).

The presence of true IgM combined with a low/moderate avidity index has the same diag- nostic value as seroconversion (36).

Virological tests play a secondary role in the diagnosis of primary HCMV infection in preg- nant women. HCMV can be detected in blood by virus isolation and/or the search for viral components by antigenemia tests and polymerase chain reactions (PCRs). The results of these diagnostic tests fail to correlate with either the clinical course of the infection or the risk of intrauterine transmission and the severity of fetal/neonatal injury (36-37). The findings suggest that HCMV may or may not be detected in the blood of pregnant women undergoing primary infection at the time of diagnosis. Positive viral detection is not associated with a greater risk of fetal infection (36).

When a primary HCMV infection is either diagnosed or suspected at the end of the diagnos- tic algorithm, prenatal diagnosis should be offered to pregnant women to verify whether the infection has been transmitted to the fetus (37).

Amniocentesis for PCR to detect HCMV DNA in the amniotic fluid is the preferred diagnos- tic approach for the detection the infection of the fetus (18). Abnormalities on ultrasound exam- ination and a high viral load suggest symptomatic fetal disease.

Prevention of Maternal and Fetal Infection

The probability that preconceptional maternal immunity provides some degree of protection against the most severe sequelae of congenital HCMV infection provides hope for the develop- ment of a HCMV vaccine. A vaccine that could achieve protection similar to that from immuni- ty from naturally acquired infection would be expected to reduce the rate of congenital HCMV infection by at least 70% (38).

Until a HCMV vaccine is available, however, better education regarding the risk of infection during pregnancy is needed. This education is most important for women who come into occu- pational contact with young children. The best way to prevent infection is to practise good per- sonal hygiene, including hand-washing with soap and warm water after diaper changes. Mouth- to-mouth kissing with children attending day-care centers is discouraged (39). Pregnant women should refrain from sharing food or eating and drinking utensils. One study has demonstrated that behavioral intervention can be effective for pregnant women to prevent the transmission of HCMV infection (40). All women in non-monogamous relationships are strongly encouraged to use latex condoms during intercourse.

In order to address primary maternal prevention, the Centers for Disease Control and Preventing Workgroup are developing research and educational projects with a view to promot- ing effective hygiene for the prevention of HCMV infection (41).

Prenatal antibody screening can also be useful. A possible approach is to screen all pregnant women serologically in early pregnancy. Those women who are seronegative should be aware that young children are likely sources of HCMV infection. The finding of preconceptual immu- nity to HCMV cannot provide complete assurance that a baby will be unaffected. Knowing that the patient is HCMV-seronegative may, in some situations, be useful for anticipatory monitoring of the pregnancy (42-43).

The options for monitoring high-risk pregnancies could include the determination of mater- nal IgG avidity maturation, amniocentesis for identification of the HCMV genome and quanti- tative determination of the viral load by PCR (37). If a woman exhibits primary HCMV infec- tion with persistent IgM

antibodies and/or virus shedding in the urine, it is advisable to delay pregnancy for about 6 months after the primary infection (44).

The prevention of congenital HCMV will require the active involvement of health-care pro- fessionals, professional organizations, advocacy groups, policy makers, and the women them- selves (41).

Therapy

Despite advances in the diagnosis of maternal-fetal HCMV infection, effective therapy remains unavailable. Pregnancy termination is often offered as an option when affected or infected fetuses are identified by ultrasonography or amniocentesis, respectively.

Several drugs are now available for the treatment of HCMV disease. Maternal HCMV infec- tions may be treated with one or other of two drugs: ganciclovir or foscarnet. The use of ganci- clovir during pregnancy to prevent or reduce the effects of congenital HCMV infection has been considered. In spite of the potentially devastating consequences of congenital HCMV infections, little information is available concerning antiviral therapy as prophylactic treatment for women at high risk of the transmission of HCMV during pregnancy. Ganciclovir has been shown (in one case report) to have crossed the placenta of a pregnant, HIV-infected woman with HCMV viremia. Although its use during pregnancy did not prevent congenital infection, it was associat- ed with a healthy fetal outcome (45). A recent report documents clearance of the amniotic fluid from HCMV concurrent with the maternal receipt of oral ganciclovir, and delivery of an unin- fected newborn (46). Despite this positive case report in an immunocompromised mother, it is unlikely that human trials of ganciclovir will be initiated during pregnancy because of its terato- genic effect in pregnant animals. Maribavir, a newer antiviral agent with less toxicity, may hold out promise for the future trials (47).

Intrauterine HCMV hyperimmune globulin has also been considered to have potential as treatment whereby to ameliorate the devastating effects of congenital HCMV infection in the fetus (22, 48). Although the results are promising, additional clinical trials are necessary so as to afford a more comprehensive assessment of the true effectiveness of immunotherapy.

Vaccine

The morbidity and mortality associated with congenital HCMV infection underscores the need for a vaccine with which to prevent HCMV infection. Promising advances have been made in vaccine development, and a number of vaccines are currently being tested. The present status of HCMV vaccines has been reported on in several recent reviews (49-50). The vaccines tested in clinical trials fall into two categories: live-attenuated vaccines and subunit vaccines. Vaccines in both categories have been evaluated for safety and immunogenicity. In spite of the significant need, an effective vaccine is not available for use in humans yet.

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