33 CME REVIEW ARTICLE

Volume 65, Number 11
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CHIEF EDITOR'S NOTE: This article is part of a series of continuing education activities in this Journal through which a total of 36 *AMA/PRA Category 1 Credits™* can be earned in 2011. Instructions for how CME credits can be earned appear on the last page of the Table of Contents.

Screening, Diagnosis, and Management of Cytomegalovirus Infection in Pregnancy

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Congenital cytomegalovirus (CMV) is the most common intrauterine infection and the leading infectious cause of sensorineural hearing loss and mental retardation. This article reviews the issues that relate to the diagnosis and management of this disease, detailing the points that led to the recent published guidelines by the Society of Obstetricians and Gynaecologists of Canada.

A MEDLINE/Cochrane search of CMV infection, pregnancy, and prenatal diagnosis found 195 studies between 1980 and 2010. Of these, we examined 59 relevant studies. The probability of intrauterine transmission following primary infection is 30% to 40%, but only 1% after secondary infection. About 10% to 15% of congenitally infected infants will have symptoms at birth, and 20% to 30% of them will die, whereas 5% to 15% of the asymptomatic infected neonates will develop sequelae later. Children with congenital CMV infection following first trimester infection are more likely to have central nervous system sequelae, whereas infection acquired in the third trimester has a high rate of intrauterine transmission but a favorable outcome.

The prenatal diagnosis of fetal CMV infection should be based on amniocentesis performed 7 weeks after the presumed time of infection and after 21 weeks of gestation. Sonographic findings often imply poor prognosis, but their absence does not guarantee a normal outcome. The value of quantitative determination of CMV DNA in the amniotic fluid is not yet confirmed. The effectiveness of prenatal therapy for fetal CMV is not yet proven, although CMV-specific hyperimmune globulin may be beneficial. Routine serologic screening of pregnant women or newborns has never been recommended by any public health authority.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this educational activity, the obstetrician/gynecologist should be better able to evaluate the principles of prenatal diagnosis of congenital CMV infection so doctors will be familiar with the tests and procedures needed, in order to reach a diagnosis of congenital CMV; to assess the natural history and outcome of congenital CMV infection enabling obstetricians to counsel prenatally pregnant women with CMV; and to analyze the prognostic markers for fetal CMV, so managing physicians will be able to predict more accurately the outcomes of fetuses infected by CMV.

Unless otherwise noted below, each faculty's and staff's spouse/life partner (if any) has nothing to disclose.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity. Each faculty's and staff's spouse/life partner (if any) has nothing to disclose.

The faculty and staff in a position to control the content of this CME activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

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Cytomegalovirus (CMV) occurs in 0.2% to 2.2% of all live births and is the most common cause of intrauterine infection and the leading infectious cause of sensorineural hearing loss and mental retardation (1,2). CMV is the largest known member of the human herpes virus family. These viruses are large enveloped DNA viruses, sharing the biologic properties of latency and reactivation (3).

Although CMV is found throughout all geographic locations and in all socioeconomic groups, it is more widespread in developing countries and in areas of lower socioeconomic conditions. Factors that have been associated with seropositivity include lower socioeconomic status, maternal age more than 30 years, nonwhite race, lower level of education, and close contact with young children (4). Transmission of CMV occurs from person to person and requires intimate contact with infected excretions, such as saliva, urine, or other body fluids (5,6). Seroprevalence is associated with socioeconomic status, and in the United States and Western Europe, rates in young women of childbearing age range from 40% for women of middle to upper socioeconomic status to 83% for women of lower socioeconomic status (3).

Most healthy individuals who acquire CMV have no symptoms or long-term consequences. A small proportion has mild symptoms of malaise, fever, myalgia, and lymphadenopathy (3).

An important distinction must be made between primary and secondary infection. Primary infection occurs in a seronegative person who has never been infected before. Following primary infection, the virus persists in a latent state. Secondary, or recurrent, infection occurs when an individual with a history of primary infection has a reactivation of the latent virus (5). Secondary infection can also occur due to a second infection with a different strain of the virus. Molecular analysis of viral isolates is required to distinguish between these 2 types of secondary infection (3,7,8).

In 1% to 4% of seronegative pregnancies there is seroconversion, with women of low socioeconomic status or poor personal hygiene experiencing higher rates (9). Immunosuppression during pregnancy may contribute to the increase in the incidence of primary or secondary CMV infections in pregnant women (4).

In April 2010, the Society of Obstetricians and Gynaecologists of Canada published guidelines for prenatal diagnosis and management of the disease in pregnancy (10) (available at: http://www.sogc.org/jogc/abstracts/full/201004_SOGCClinicalPracticeGuidelines_1.pdf). The purpose of this article is to elaborate on the reason for these published guidelines in a review of the diagnostic and prognostic implications of CMV in pregnancy, and an examination of recent developments in treatment and disease prevention.

METHODS

We performed a systematic review of the literature regarding prenatal diagnosis, outcomes, and treatment of congenital CMV infection. Studies were identified by electronic searches of the MEDLINE database and the Cochrane Library for the time period of 1980 to 2010. The keywords used were congenital CMV infection, pregnancy, and prenatal diagnosis. The reference lists of relevant articles retrieved by the searches were also reviewed. Reports included in our review were limited to those written in English. Studies were eligible if the diagnosis of congenital CMV infection was based on CMV culture or polymerase chain reaction (PCR) of the amniotic fluid and confirmed by neonatal urine culture for CMV after birth. The literature search yielded 195 articles with potential relevance. After screening these articles on the basis of title and abstract, 59 articles were identified and used for our review.

Fetal CMV Infection and Postnatal Outcome

Primary Infection

Maternal viremia, placental infection, and hematogenous dissemination to the fetus is the most likely sequence of events leading to congenital CMV infection after primary maternal infection (11). Transmission can occur after either primary or secondary infection, but the likelihood is much greater after primary infection, with a probability of 30% to 40% (1,12).

The burden of disease for congenitally infected infants is high, with 10% to15% having symptoms at birth, including intrauterine growth restriction, microcephaly, hepatosplenomegaly, petechiae, jaundice, chorioretinitis, thrombocytopenia, and anemia. Of infants who are symptomatic at birth, 20% to 30% will die, and 90% of the symptomatic survivors will have late complications (12–14). Despite 85% to 90% of congenitally infected infants showing no signs or symptoms at birth, late sequelae appear in 5% to 15%. These include sensorineural hearing loss, delay of psychomotor development, and visual impairment (15,16) (Fig. 1).

Data regarding transmission rates according to gestational age are not consistent. While primary CMV infection acquired either before or around conception carries the lowest risk of transmission (17), CMV

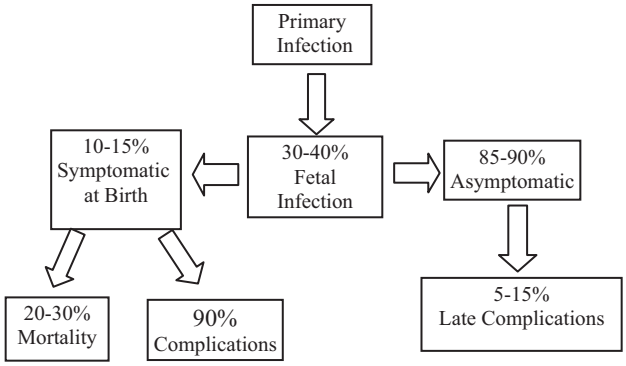

Fig. 1. Fetal outcome after primary CMV infection.

transmission rates appear to increase with advancing stages of pregnancy. Daiminger et al demonstrated transmission rates of 30%, 39%, and 58% following primary infection at gestational weeks 6 to 20, 18 to 22, and 20 to 38, respectively (18). Revello and Gerna reported transmission rates of 45.4%, 45.6%, and 78.6% following primary infection in the first, second, and third trimesters, respectively (11). Bodeus et al have recently reported that the rate of transmission increases gradually during gestation, based on 524 seroconversions. The transmission rate was 34.5% during the first trimester, 44.1% during the second trimester, and 73.3% when seroconversion occurred during the third trimester (19).

Despite the higher transmission rate with maternal infection occurring later in pregnancy, the rate of sequelae in infected offspring appears to be lower. Liesnard et al studied 55 cases of congenital CMV infection and found 10/38 (26%) cases infected before 20 weeks of gestation had severe disease, compared with only 1/16 (6.2%) case infected after 20 weeks (20). Pass et al found sensorineural hearing loss in 8/34 (24%) of first trimester cases compared with 1/40 (2.5%) in the later infection group (21), and Daiminger's series included 18 cases of infection occurring after 20 weeks' gestation, of which none had evidence of congenital disease (18). Gindes et al have recently reported on 28 women with primary CMV infection acquired after 25 weeks of gestation, of whom 21 (75%) had evidence of fetal infection but none of the live infected newborns had congenital CMV disease (22).

In summary, the research shows that children with congenital CMV infection following first trimester maternal infection are more likely to have central nervous system sequelae, whereas CMV infection acquired during the third trimester is associated with a high rate of intrauterine transmission but a more favorable outcome for the infant.

Secondary Infection

As noted above, fetal infection may occur following both primary and recurrent maternal infection, but the difference in the incidence of transmission is remarkable. During recurrent infection, virus replication occurs in the presence of both humoral and cell-mediated immune responses. As a result, viremia occurs as a rule only in primary infection and, therefore, the transmission rate is about 40% following primary infection and only about 1% in cases of recurrent maternal infection (11). Fowler et al found evidence of intrauterine CMV infection in 3% of infants born to 604 mothers who were seronegative at the beginning of pregnancy, and in 1% of the infants born to 2857 mothers who were seropositive before pregnancy (23). These results show that maternal preconceptional immunity against CMV gives relatively good protection to the fetus, but a small proportion may still become infected. Yamamoto et al have recently shown that maternal reinfection by new strains of CMV is a major source of congenital infection in CMV seroimmune women. Seroconversion to new CMV strains during pregnancy was observed in 17.5% of women delivering infected infants compared with only 4.6% in control mothers of uninfected infants (24).

The traditional belief has been that most children with congenital CMV born to mothers who had secondary CMV infection are asymptomatic at birth, and fewer than 10% of them develop sequelae, mainly sensorineural hearing loss and chorioretinitis (16,25). There is, however, increasing evidence in recent years that the incidence of symptomatic infection in infants born to immune mothers following secondary infection may be higher than previously thought (25–27). Gaytant et al summarized 6 studies that reported on the type of maternal infection in relation to the outcome of congenital infection. There were 50 cases of congenital CMV following secondary infection, in which 45 (90%) were asymptomatic at birth. One (2%) developed minor symptoms (moderate psychomotor retardation, behavioral problems, clumsiness), and 4 (9%) developed major symptoms (severe mental retardation, hearing loss). Of the 5 infants who were symptomatic at birth, 2 (40%) developed major symptoms (3).

Prenatal Diagnosis

There are 2 important components in prenatal diagnosis of congenital CMV infection. The first is distinguishing between maternal primary and sec-

ondary infection based on serologic testing (16). The second is identifying whether fetal infection is present in women with proven CMV infection by using both noninvasive (ultrasound examination) and invasive (amniocentesis) prenatal testing (16).

Diagnosis of Maternal Infection

The diagnosis of primary CMV infection is clearly established when seroconversion can be documented. However, this is only possible with screening programs that identify seronegative women and then follow them prospectively and re-test them to identify seroconversion (25). When the immune status before pregnancy is unknown, determination of primary CMV infection should be based on detection of the specific IgM antibody. Unfortunately, this approach has limitations, since IgM can be detected in 10% of recurrent infections (28) and, unlike with many other infections, can be detected for months after primary infection (29). Therefore, in addition to primary infection during pregnancy, CMV IgM positivity may indicate either remote primary infection acquired before pregnancy or recurrent infection (20).

Because of these difficulties with interpreting the serology, the IgG avidity assay can be a useful tool to assist in distinguishing primary infection from past or recurrent infection and can assist in dating the time of infection (25,30). It is known that in the first few months after infection, virus-specific IgG of low avidity appears. Over time, the IgG antibody shows increasingly higher avidity. This high avidity is detectable only with remote or recurrent CMV infection (25). An avidity index $<30\%$ strongly suggests a primary infection of less than 3 months (30).

Using serology, a diagnosis of primary CMV infection during pregnancy is documented by either seroconversion (the appearance of CMV-specific IgG antibody in a previously seronegative woman) or detection of specific IgM antibody associated with low IgG avidity. Recurrent infection is diagnosed in women with detectable specific IgG antibodies without IgM antibodies before pregnancy and a significant increase of IgG antibody titer with or without the presence of specific IgM antibodies and high IgG avidity (31).

Diagnosis of Fetal Infection

Once maternal infection has been documented, it is important to determine whether fetal infection has also occurred, as this will help to guide the need for further evaluation and surveillance during pregnancy. Although ultrasound may be used, most ultrasound findings of CMV infection can also be seen with other infections or conditions affecting the fetus. In addition, these findings are only seen in less than 25% of infected fetuses (32). Ultrasound findings of fetal CMV infection consist of fetal growth restriction, cerebral ventriculomegaly, ascites, intracranial calcifications, abnormality of amniotic fluid volume (usually oligohydramnios), microcephaly, hyperechogenic bowel, hydrops fetalis, pleural effusion, and liver calcifications (32–34).

Compared with ultrasound findings, CMV isolation from amniotic fluid has a much higher sensitivity and specificity and is considered the gold standard for prenatal diagnosis of fetal CMV infection (13,25,35). Replication of the virus in the fetal kidney to produce sufficient quantity to be identified in amniotic fluid occurs only after 5 to 7 weeks from the onset of fetal infection. In addition, gestational age at time of amniocentesis has been shown to be an additional variable affecting sensitivity. Liesnard et al demonstrated a sensitivity of 30% if the first amniotic fluid sample was taken before 21 weeks of gestation, increasing to 71% thereafter (20). Therefore, amniocentesis should be performed at least 7 weeks after the onset of maternal infection and after 21 weeks of gestation (11,13,20). Amniocenteses performed too close to the onset of maternal infection carry a substantial risk of false negative results (36–38).

The diagnosis of fetal CMV infection should be based on culture and/or PCR performed on amniotic fluid samples. Some culture techniques allow detection of the virus 16 to 24 hours after amniotic fluid collection (11,39,40).

With the advent of PCR, which allows the amplification to a detectable level of minute amounts of viral DNA present in the amniotic fluid, the sensitivity of prenatal diagnosis of fetal infection has increased. Revello and Gerna have reported that the sensitivity, specificity, and positive and negative predictive values of DNA detection in amniotic fluid obtained in a series of 102 pregnant women were 90.2%, 100%, 100%, and 90.4%, respectively (11). Despite the use of a very sensitive technique such as PCR, it is reasonable to assume that a delay in intrauterine transmission of the infection may represent a major obstacle to achieving 100% sensitivity (25). However, several studies have indicated that the detection of even small amounts of viral DNA in the amniotic fluid correlate with congenital infection at birth, explaining the 100% specificity of this test (41,42).

Another tool available for diagnosis is the use of fetal CMV IgM. However, this is not recommended because cordocentesis is associated with risk, and there is poor sensitivity, as it is often late in pregnancy that many fetuses develop specific IgM (9,37). Lipitz et al studied 63 pregnant women with primary CMV infection, in whom fetal diagnosis was made by amniocentesis and fetal blood sampling or amniocentesis only. Thirteen of 22 patients with evidence of fetal infection by amniocentesis underwent cordocentesis, and 10 of the 13 (77%) showed positive IgM results in the fetal blood. No case of positive fetal serum IgM with negative amniotic fluid culture or PCR was recorded, indicating that the information yielded by cordocentesis did not increase the ability to accurately diagnose intrauterine infection (37).

In a large series of 237 women who had primary CMV infection studied by amniocentesis with or without cordocentesis, the best sensitivity and 100% specificity were achieved by PCR done on amniotic fluid sampled after 21 weeks of gestation with a mean interval of 7 weeks between maternal infection and amniocentesis (20).

Amniocentesis may be used in cases of either primary or secondary maternal CMV infection. Although the risk of fetal infection is lower with secondary infection, it may occasionally result in severe sequelae. Therefore, the risk/benefit ratio of performing this invasive diagnostic test must be considered carefully in cases of secondary infection.

Prognostic Markers of CMV Disease

Although prenatal testing can identify infection, the presence of the virus in the amniotic fluid does not reliably predict fetal outcomes. Detection of sonographic abnormalities may aid in determining fetal prognosis, but there is no guarantee of a normal fetus/infant with no sequelae if these findings are absent.

Lipitz et al have studied the outcomes of 50 pregnancies with documented intrauterine CMV infection, in which 17 pregnancies (18 fetuses) continued to term. Four fetuses had neurologic abnormalities, of which 3 had normal prenatal ultrasound findings, giving a risk of 19% (3 of 16) for postnatal neurologic abnormalities. These problems included hearing loss, chorioretinitis, and developmental delay, even when there were no prenatal sonographic abnormalities (32).

Guerra et al have recently reported on the effectiveness of ultrasound in the antenatal prediction of symptomatic congenital CMV infection in 600 women with primary infection. Twenty-three (15%) of 154 fetuses with congenital infection had abnormal sonographic findings, of whom 18 (78%) were symptomatic, whereas among the 131 infected fetuses without abnormal sonographic findings, 68 fetuses/neonates (52%) were classified as symptomatic, resulting in a negative predictive value of only 48% (43). Therefore, although ultrasound is a valuable tool in evaluating a fetus with CMV infection, its limitations should be mentioned when counseling patients.

Recent progress in the field of magnetic resonance imaging (MRI) has contributed to the development of detailed fetal imaging. Two recent studies have evaluated the contribution of MRI to the diagnosis of fetal brain abnormalities in CMV-infected fetuses (44,45). The first series included 11 cases with no ultrasound features, in which MRI always confirmed the absence of visceral or cerebral anomalies. However, in 13 cases with extracerebral features without cerebral abnormalities at ultrasound, MRI revealed cerebral anomalies in 6 cases (46%) and therefore modified the prognosis. Termination of pregnancy was performed in 5 of these 6 fetuses (encephalitis was found at fetopathological examination in all 5 cases), and 1 child is mentally retarded (44). Benoist et al have shown that the best positive predictive value (88.9%) for prenatal diagnosis of cerebral lesions was obtained with a combination of abnormal ultrasound and MRI findings, but the MRI did not improve the negative predictive value obtained by normal ultrasound findings (45).

Another marker which has been studied as a prognostic factor is CMV viral load in amniotic fluid. Guerra et al reported that a CMV viral load $>10^3$ genome equivalents was 100% predictive of fetal infection, whereas a level $>10^5$ was predictive of symptomatic CMV disease (46). Similarly, other studies have also shown significantly higher CMV DNA load values in amniotic fluid samples in the group of symptomatic fetuses, as opposed to the asymptomatic group. However, there was great overlap between viral load values in the symptomatic and asymptomatic groups, and other variables such as gestational age at time of amniocentesis and time elapsed since maternal infection were found to influence viral load irrespective of fetal outcome (41,42). Therefore, more study is needed on the prognostic value of CMV DNA viral load levels.

Determination of a few parameters in the fetal blood, such as CMV-specific IgM, viral load, as well as assessment of biochemical and hematological parameters, might also assist in predicting fetal out-

come. A significant correlation between high levels of virus-specific IgM and adverse fetal outcome has been reported (47,48). Moreover, all virologic parameters tested to determine viral load in fetal blood were found to be higher in fetuses with abnormalities compared to fetuses with normal findings (48). These data might indicate that congenitally infected fetuses with normal biochemical, hematological, and ultrasound findings and low viral load in blood, together with low IgM antibody, may have a more favorable outcome (48).

Thus, fetal blood sampling, although not sensitive enough to justify its use for the detection of intrauterine infection, may provide important prognostic information. More studies are needed to validate these fetal blood measures as prognostic markers and, therefore, fetal blood sampling should not be routinely performed in the prenatal evaluation of congenital CMV infection.

Prenatal Treatment and Prevention of Congenital CMV Infection

Although there are several tools available for the prenatal diagnosis of congenital CMV infection, there is no effective treatment to offer once a diagnosis has been made. The use of CMV-specific hyperimmune globulin for treatment was evaluated recently in 157 pregnant women with primary CMV infection (49).

After amniocentesis, CMV was found in the amniotic fluid of 45 women with primary infection more than 6 weeks before enrolment. Of the 31 women who elected to receive intravenous treatment with CMV hyperimmune globulin (200 U per kilogram of the mother's body weight), only one (1/31) had an infant with clinical CMV disease at birth. Fifteen of the 31 had abnormal ultrasound findings. Of the 14 women who declined treatment, 7 (7/14) had infants who were symptomatic at delivery.

In the prevention group, 37 women received hyperimmune globulin and 6 (16%) of them had infants with congenital CMV infection. In comparison, 19 of 47 women (40%) who did not receive hyperimmune globulin had infected infants. No adverse effects of the hyperimmune globulin were observed (49). These results are provocative, and this may be the first effective antenatal treatment that is available. However, it is important to note that this was not a randomized controlled trial and further study is necessary. Prenatal administration of ganciclovir into the umbilical vein has also been reported but its value in improving the prognosis is not well established (50).

In addition to prenatal therapy, there is also an option of treatment after birth for symptomatic infants. Some evidence has suggested limited benefit with ganciclovir treatment of neonates with symptomatic congenital CMV infection. A study carried out on a group of 47 infants with congenital infection, who were treated with ganciclovir for 6 weeks, showed hearing improvement in 5 of 30 infants (16%) after 6 months of follow-up. The most common side effects were neutropenia and elevation of liver enzymes (51). In another more recent study, ganciclovir was given within the first month at 12 mg/kg/d intravenously for 6 weeks (52). Of the 42 infants followed, evaluation at 6 months and 1 year showed significantly less hearing deterioration in treated infants compared with control infants (52). Similarly, Michaels et al found no progression of hearing loss at a median age of 2 in 9 treated children with congenital CMV, 5 of whom had hearing loss before therapy was started. However, there was no evidence of improvement in neurodevelopmental sequelae (53).

The best prevention for congenital CMV infection is primary prevention, and this could be accomplished with a vaccine. Vaccination of seronegative women of childbearing age could prevent the occurrence of primary CMV infection during pregnancy. In a phase 2, placebo-controlled, randomized, double-blind trial, Pass et al have evaluated the efficacy of the CMV glycoprotein B vaccine compared with a placebo. The vaccine group was more likely to remain uninfected during a 42-month period than the placebo group ($P = 0.002$). However, the sample size of this study was too small to determine the efficacy of the vaccine in preventing congenital infection (54). Therefore, until the efficacy of this vaccine is established, recommendations for avoiding infection revolve mostly around personal hygiene practices, such as thorough handwashing after diaper changes, and avoiding intimate contact with salivary secretions and urine from young children (55).

To determine if protective behavior prevents child-to-mother transmission of CMV during pregnancy, Adler et al studied 166 seronegative mothers with a child <36 months of age attending a daycare facility (56). Mothers, either pregnant or attempting pregnancy, were randomly assigned to either a control or intervention group, in which the mothers received instructions for handwashing, glove use, and avoiding intimate contact with their children. The proportion of women seroconverting was the same in both the intervention and control groups, at 7.8% of women. However, for 41 women attempting pregnancy at

enrolment with a child shedding CMV, 10 of 24 became infected compared with only 1 of 17 women who were already pregnant at enrolment (56). According to this study, intervention before pregnancy was found to be ineffective, but intervention for pregnant women may be effective, as pregnant women may be more motivated than nonpregnant women to adhere to recommendations to protect their unborn children (57).

The Issue of Screening

There is no consensus on the issue of screening for CMV by serology. No public health authority has ever recommended routine serologic screening for pregnant women (25). The time for screening would be at the beginning of pregnancy or in advance of pregnancy. In the case of a seronegative woman, serologic testing for CMV would need to be repeated during pregnancy to rule out seroconversion.

Arguments against screening include the fact that there is no effective vaccine and no treatment that has been proven effective. For infections with effective vaccines, screening is usually done either before or at the beginning of pregnancy. As there is no effective prenatal treatment, the choices with regard to an infected fetus are to terminate the pregnancy or to observe the fetus until delivery. On the other hand, with prenatal testing women can be educated about behavior and prevention with respect to seronegative women (58).

Finally, routine antibody testing, especially if done before pregnancy, may help to differentiate between primary and secondary infection in cases of suspected CMV infection during pregnancy (4). Naessens et al evaluated a CMV screening program in which serological testing was performed at the first prenatal visit. With this program, screening detected 82% of all congenital CMV infections (59). However, as long as there is no available vaccine or effective prenatal treatment, it will be difficult to justify serological screening for CMV in terms of cost-effectiveness. Therefore, routine serologic testing of all pregnant women for CMV, to identify primary infection in pregnancy, is not recommended.

CONCLUSION

Congenital CMV infection is a substantial concern in pregnant women. Following a diagnosis of, primary maternal CMV infection, fetal infection may be confirmed by amniocentesis. However, our ability to predict the outcome of an infected fetus is quite limited. Until an effective and safe vaccine becomes available, research should be focused on identifying reliable prognostic markers and on validating the promising reports on the effectiveness of CMV-specific hyperimmune globulin in treating the disease antenatally.

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