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No. 240-Cytomegalovirus Infection in Pregnancy

This guideline was reviewed by the Maternal Fetal Medicine Committee and approved by the Executive and Council of The Society of Obstetricians and Gynaecologists of Canada.

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Key Words: Congenital infection, cytomegalovirus (CMV), prenatal diagnosis, intrauterine growth restriction (IUGR), microcephaly

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Abstract

Objectives: To review the principles of prenatal diagnosis of congenital cytomegalovirus (CMV) infection and to describe the outcomes of the affected pregnancies.

Outcomes: Effective management of fetal infection following primary and secondary maternal CMV infection during pregnancy. Neonatal signs include intrauterine growth restriction (IUGR), microcephaly, hepatosplenomegaly, petechiae, jaundice, chorioretinitis, thrombocytopenia and anemia, and long-term sequelae consist of sensorineural hearing loss, mental retardation, delay of psychomotor development, and visual impairment. These guidelines provide a framework for diagnosis and management of suspected CMV infections.

Evidence: Medline was searched for articles published in English from 1966 to 2009, using appropriate controlled vocabulary (congenital CMV infection) and key words (intrauterine growth restriction, microcephaly). Results were restricted to systematic reviews, randomized controlled trials/controlled clinical trials, and observational studies. Searches were updated on a regular basis and incorporated into the guideline. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Recommendations: The quality of evidence reported in this document has been assessed using the evaluation of evidence criteria in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

1. Diagnosis of primary maternal cytomegalovirus (CMV) infection in pregnancy should be based on de-novo appearance of virus-specific IgG in the serum of a pregnant woman who was previously seronegative, or on detection of specific IgM antibody associated with low IgG avidity (II-2A).

2. In case of primary maternal infection, parents should be informed about a 30% to 40% risk for intrauterine transmission and fetal infection, and a risk of 20% to 25% for development of sequelae postnatally if the fetus is infected (II-2A).
3. The prenatal diagnosis of fetal CMV infection should be based on amniocentesis, which should be done at least 7 weeks after presumed time of maternal infection and after 21 weeks of gestation. This interval is important because it takes 5 to 7 weeks following fetal infection and subsequent replication of the virus in the kidney for a detectable quantity of the virus to be secreted to the amniotic fluid (II-2A).
4. The diagnosis of secondary infection should be based on a significant rise of IgG antibody titre with or without the presence of IgM and high IgG avidity. In cases of proven secondary infection, amniocentesis may be considered, but the risk–benefit ratio is different because of the low transmission rate (III-C).
5. Following a diagnosis of fetal CMV infection, serial ultrasound examinations should be performed every 2 to 4 weeks to detect sonographic abnormalities, which may aid in determining the prognosis of the fetus, although it is important to be aware that the absence of sonographic findings does not guarantee a normal outcome (II-2B).
6. Quantitative determination of CMV DNA in the amniotic fluid may assist in predicting the fetal outcome (II-3B).
7. Routine screening of pregnant women for CMV by serology testing is currently not recommended (III-B).
8. Serologic testing for CMV may be considered for women who develop influenza-like illness during pregnancy or following detection of sonographic findings suggestive of CMV infection (III-B).
9. Seronegative health care and child care workers may be offered serologic monitoring during pregnancy. Monitoring may also be considered for seronegative pregnant women who have a young child in day care (III-B).

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group. II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	A. There is good evidence to recommend the clinical preventive action. B. There is fair evidence to recommend the clinical preventive action. C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making. D. There is fair evidence to recommend against the clinical preventive action. E. There is good evidence to recommend against the clinical preventive action. L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making.

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.

Taken from: Woolf SH, et al. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169:207–8.

INTRODUCTION

Cytomegalovirus is the most common cause of intrauterine infection, occurring in 0.2% to 2.2% of all live births, and is a common cause of sensorineural hearing loss and mental retardation.[1,2]

Most healthy people who acquire CMV after birth experience few or no symptoms and no long-term sequelae. Some experience a mononucleosis-like syndrome with symptoms including malaise, persistent fever, myalgia, cervical lymphadenopathy, and, less commonly, pneumonia and hepatitis.[3] After the primary infection, defined as CMV infection in a previously seronegative person, the virus becomes dormant and exists in a latent state, from which it can be reactivated. This is designated as recurrent (secondary) infection.[4] In addition, there seem to be several strains of CMV that infect humans, so reinfection can occur, even in immunocompetent individuals. Therefore, secondary infection, defined as intermittent excretion of the virus in the presence of host immunity, may be due to either reacti- vation of an endogenous virus or exposure to a new virus strain from an exogenous source. Differentiation between these two kinds of secondary infection is not possible by serology but only by molecular analysis of virus isolates.[3–5] Seroconversion occurs in 1% to 4% of all pregnancies and is higher in women who are of low socioeconomic status or who have poor personal hygiene.[6,7]

Congenital infections are the result of transplacental transmission of CMV. Transmission to the fetus may occur because of primary or secondary maternal infection. The probability of intrauterine transmission following primary infection during pregnancy is 30% to 40%,[1,8] compared with only 1% following secondary infection.[1,8] Ten to fifteen percent of congenitally infected infants will have symptoms at birth including intrauterine growth restriction, microcephaly, hepatosplenomegaly, petechiae, jaundice, chorioretinitis, thrombocytopenia, and anemia, and 20% to 30% of them will die, mostly of disseminated intravascular coagulation, hepatic dysfunction, or bacterial superinfection.[8–10] Most of the congenitally infected infants (85–90%) have no signs or symptoms at birth, but 5% to 15% of them will develop sequelae such as sensorineural hearing loss, delay of psychomotor development, and visual impairment.[11,12]

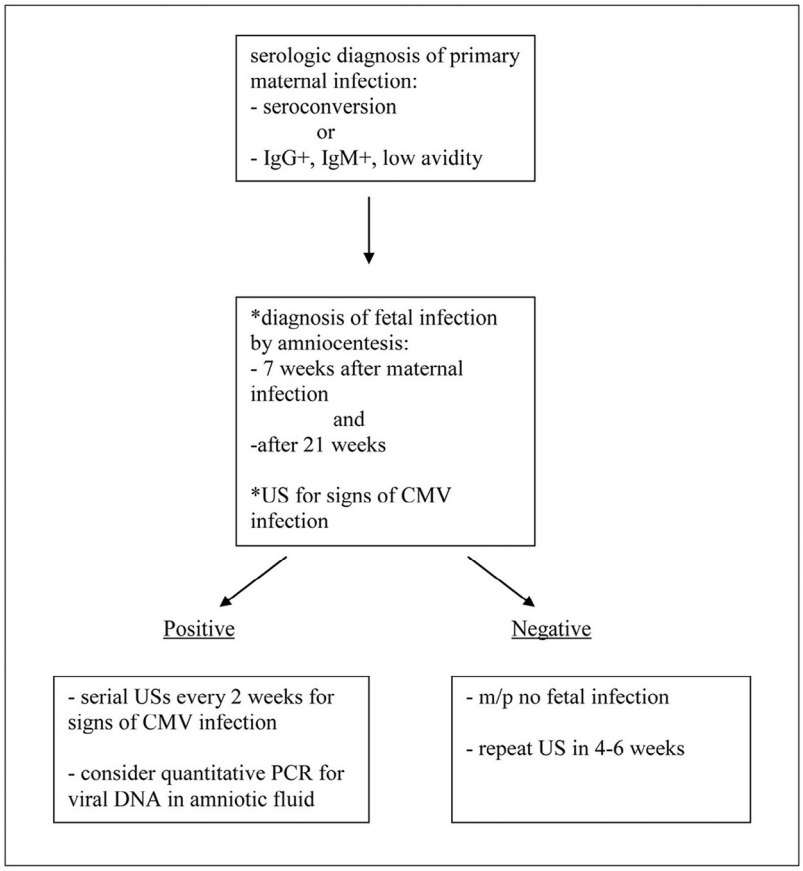
ABBREVIATIONS

CMV	cytomegalovirus
PCR	polymerase chain reaction
IUGR	intrauterine growth restriction

PRENATAL DIAGNOSIS

The first step in the prenatal diagnosis of congenital CMV infection is determination of maternal primary and secondary infection by serological testing.[12] In women with proven CMV infection, the second step is to identify fetal

Figure. Algorithm for prenatal diagnosis of congenital CMV



infection by non-invasive (ultrasound examination) and invasive (amniocentesis) prenatal tests[12] (Figure).

Diagnosis of Maternal Infection

Revello and Gerna[13] state:

> *The diagnosis of primary CMV infection is ascer- tained when seroconversion is documented, i.e., the de novo appearance of virus-specific IgG in the serum of a pregnant woman who was previously seronegative. However, such an approach is feasible only when a screening program is adopted and seronegative women are identified and prospec- tively monitored[13] [or when maternal serum specimens are saved].*

When the immune status before pregnancy is unknown, determination of primary CMV infection should be based on detection of specific IgM antibody. However, IgM can also be detected in 10% of recurrent infections[14] and can be detected for months after primary infection.[15] Therefore, the group of women designated CMV-IgM positive could include women with primary infection acquired before pregnancy and a few women with recurrent infections.[16] The IgG avidity assay can help distinguish primary infec-tion from past or recurrent infection and can assist in deter- mining when infection occurred.[13,17]

> *This assay is based on the observation that virus-specific IgG of low avidity is produced during the first months after onset of infection, whereas subsequently a maturation process occurs by which IgG antibody of increasingly higher avidity is generated. IgG antibody of high avidity is detected only in subjects with remote or recurrent CMV infection. Avidity levels are reported as the avidity index, expressing the percentage of IgG bound to the antigen following treatment with denaturing agents.[13]*

An avidity index >60% is highly suggestive of past or secondary infection, while an avidity index <30% is highly suggestive of a recent primary infection (duration <3 months).[17] Hence, serologic 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.

Women who have detectable specific IgG antibodies without IgM antibodies before pregnancy and a significant rise

of IgG antibody titre with or without the presence of specific IgM antibodies and with high IgG avidity can be classified as having recurrent infection.[18]

Diagnosis of Fetal Infection

Since intrauterine transmission of the virus occurs in only 30% to 40% of pregnancies in women with primary infection and at a significantly lower rate in women with secondary infection, it is important in cases of proven maternal infection to find out if the fetus is infected.

Ultrasonographic findings are helpful but not diagnostic because CMV has features in common with other intrauterine infections and with other fetal diseases. Moreover, these abnormalities are observed in less than 25% of infected fetuses.[19] The most frequently reported sonographic findings of fetal CMV infection include 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[19–21] (Table 2).

Because of its high sensitivity and specificity, CMV isolation from amniotic fluid has been recognized as the gold standard for prenatal diagnosis of fetal CMV infection.[9,13,22] To achieve the highest sensitivity, the amniocentesis should be per- formed until at least 7 weeks after the onset of maternal infection and after 21 weeks of gestation because a detectable quantity of the virus is not secreted to the amniotic fluid until 5 to 7 weeks after fetal infection and replication of the virus in the kidney.[9,16,23] It has been repeatedly reported that prenatal diagnosis procedures performed too close to the onset of maternal infection carry a substantial risk of false negative results.[24–26] The diagnosis of fetal CMV infection should be based on the results of culture and PCR testing of amniotic fluid samples. CMV isolation can be done by con- ventional culture on fibroblasts or by the shell vial tech- nique, which uses monoclonal antibodies to the major immediate early protein p72 and enables detection of the virus 16 to 24 hours after amniotic fluid collection.[23,27,28]

Table 2. Congenital CMV infection-sonographic finding

IUGR
Cerebral ventriculomegaly
Microcephaly
Intracranial calcifications Ascites/pleural effusion Hydrop fetalis
Oligohydramnios/polyhydramnios
Hyperechogenic bowel
Liver calcifications

Diagnosis of fetal infection by testing for fetal IgM is not recommended not only because of the risk associated with cordocentesis but also because many fetuses infected by CMV do not develop specific IgM until late in pregnancy, resulting in poor sensitivity.[5,25]

Although it is accepted that amniocentesis in primary maternal CMV infection is warranted because of the high risk of fetal infection, there is no consensus on whether to perform amniotic fluid viral studies in cases of secondary infection, when the risk of fetal infection is low. However, there are several cases of secondary infection with severe sequelae described in the literature; therefore, amniocentesis for prenatal diagnosis of fetal infection may be considered even in cases of secondary infection.[3,29]

Prognostic Markers of CMV Disease

One of the major limitations of prenatal diagnosis of CMV is that positive results of amniotic fluid tests such as viral isolation and PCR do not discriminate between infants who will have symptoms at birth and those who will not.

The severity of the sonographically detected abnormalities may aid in determining the prognosis of the fetus, but the absence of sonographic findings does not guarantee a normal outcome. Once fetal infection is diagnosed, serial ultra- sound examinations should be done every 2 to 4 weeks to look for signs of CMV infection (Table 2) that might help in predicting the outcome. The ultrasound follow-ups should be performed in a laboratory that is capable of diagnosing the abnormalities outlined in Table 2, and preferably in a referral centre.

Fetal MRI may improve the prognostic evaluation, espe- cially when brain abnormalities are detected by ultrasound. However, the role of fetal MRI in providing useful information in fetuses with CMV still needs to be determined.[30,31]

The clinical significance of the viral load in amniotic fluid as a prognostic factor has been investigated by several studies, which showed that the CMV DNA load values in amniotic fluid samples were significantly higher in the group of symptomatic than in the group of asymptomatic fetuses.[32] However, a great number of values were found to overlap between the two groups[33,34]; thus the role of quantitative determination of CMV DNA in the amniotic fluid as a prognostic factor of CMV disease still awaits confirmation.

PRENATAL TREATMENT AND PREVENTION OF CONGENITAL CMV INFECTION

Despite advances in the diagnosis of fetal CMV infection, there is no effective therapy, and the option of pregnancy

termination is often raised once fetal infection is detected by ultrasound or amniocentesis or once a fetus is determined or suspected to be affected.

A recent multicentre prospective cohort study of 157 pregnant women with confirmed primary CMV infection evaluated the use of CMV-specific hyperimmune globulin for the treatment and prevention of fetal CMV infection.[32] Forty-five women had a primary infection more than 6 weeks before enrolment, underwent amniocentesis, and had CMV detected in the amniotic fluid. Thirty-one of these women elected to receive intravenous treatment with CMV-hyperimmune globulin (200 U/kg of the mother's body weight). Fourteen women declined treatment with hyperimmune globulin, and 7 of them had infants who were symptomatic at delivery. In contrast, only 1 of the 31 treated women had an infant with clinical CMV disease at birth although 15 of them were carrying fetuses with ultrasonographic evidence of CMV disease.[32] In the prevention group, 37 received hyperimmune globulin, 6 (16%) of whom had infants with congenital CMV infection, compared with 19 of 47 women (40%) who did not receive hyperimmune globulin. No adverse effects of hyperimmune globulin were observed.[32] These results offer a potential measure to treat and prevent congenital CMV infection. However, this was not a randomized controlled trial, and further study is necessary prior to widespread adoption of this strategy.

Regarding postnatal therapy, there is some evidence suggesting a limited beneficial role for ganciclovir treatment of neonates with symptomatic congenital CMV infection. A few studies have demonstrated some hearing improvement and less hearing deterioration in infants treated with ganciclovir.[33–35]

The ultimate goal in prevention of congenital CMV infection is to develop a vaccine, which would be administered to seronegative women of childbearing age to prevent the occurrence of primary CMV infection during pregnancy. Until an effective vaccine is available, recommendations for seronegative pregnant women with respect to CMV infection include practising good personal hygiene such as avoiding intimate contact with salivary secretions and urine from young children and careful hand washing after changing diapers and wiping secretions.[33] Despite our assumption that changing protective behaviours prevents child to mother transmission of CMV during pregnancy, Adler et al. did not show any benefit for such intervention.[34] However, their data also demonstrated that intervention is more effective during pregnancy than before pregnancy, because pregnant women are more motivated to adhere to recommendations than non-pregnant women.[35]

The Question of Screening

Screening for CMV by serology has been and still is a debated issue. Routine serologic screening for pregnant women has never been recommended by any public health authority.[13] The screening, if done, should be performed at the beginning of pregnancy or even prior to a planned pregnancy. If a woman is seronegative, repeated examinations during pregnancy should be done when there is clinical suspicion. However, screening is usually done before pregnancy for diseases such as rubella and varicella against which immunization can be provided, whereas there is currently no effective and safe immunization against CMV. Moreover, because effective prenatal treatment options are not yet available, the choices when a women is carrying a baby with CMV infection or disease are limited to elective termination of the pregnancy or expectant observation until delivery. Prenatal testing, however, offers an opportunity to educate women about behaviours, and precautionary measures can be suggested to seronegative women.[36] Moreover, 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.[29] Naessens et al. evaluated a screening program for CMV in which serological testing was performed at the first prenatal visit; they showed that such screening allows the detection of 82% of all congenital CMV infections.[37] Nevertheless, routine serologic testing of all pregnant women for CMV to identify those who have acquired primary infection during pregnancy is not currently recommended. Therefore, serological testing for CMV should be used only in women who develop influenza-like symptoms during pregnancy or following detection of sonographic findings that are suggestive of CMV infection and that cannot be explained by another cause (placental insufficiency in case of IUGR and oligohydramnios and fetal anemia in case of ascites etc.).

SUMMARY

Congenital CMV infection is the leading infectious cause of mental retardation and sensorineural deafness. Once primary maternal CMV infection has been diagnosed, fetal infection can be accurately determined by amniocentesis. Prenatal counselling in case of fetal infection is difficult because of our limited ability to predict outcome. Because 20% to 25% of infected fetuses will develop sequelae, termination of pregnancy should be discussed as one of the management options. Currently, routine serologic testing of all pregnant women is not recommended, and use of serologic testing should be used only in pregnant women who develop influenza-like illness or following detection of sonographic findings suggestive of CMV infection.

Recommendations

The quality of evidence reported in this document has been assessed using the evaluation of evidence criteria in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

1. Diagnosis of primary maternal cytomegalovirus (CMV) infection in pregnancy should be based on de-novo appearance of virus-specific IgG in the serum of a preg- nant woman who was previously seronegative, or on detection of specific IgM antibody associated with low IgG avidity (II-2A).
2. In case of primary maternal infection, parents should be informed about a 30% to 40% risk for intrauterine trans- mission and fetal infection, and a risk of 20% to 25% for development of sequelae postnatally if the fetus is infected (II-2A).
3. The prenatal diagnosis of fetal CMV infection should be based on amniocentesis, which should be done at least 7 weeks after presumed time of maternal infection and after 21 weeks of gestation. This interval is important because it takes 5 to 7 weeks following fetal infection and subsequent replication of the virus in the kidney for a detectable quantity of the virus to be secreted to the amniotic fluid (II-2A).
4. The diagnosis of secondary infection should be based on a significant rise of IgG antibody titre with or without the presence of IgM and high IgG avidity. In cases of proven secondary infection, amniocentesis may be considered, but the risk–benefit ratio is different because of the low transmission rate. (III-C)
5. Following a diagnosis of fetal CMV infection, serial ultra- sound examinations should be performed every 2 to 4 weeks to detect sonographic abnormalities, which may aid in determining the prognosis of the fetus, although it is important to be aware that the absence of sonographic findings does not guarantee a normal outcome (II-2B).
6. Quantitative determination of CMV DNA in the amniotic fluid may assist in predicting the fetal outcome (II-3B).
7. Routine screening of pregnant women for CMV by serol- ogy testing is currently not recommended (III-B).
8. Serologic testing for CMV may be considered for women who develop influenza-like illness during pregnancy or following detection of sonographic findings suggestive of CMV infection (III-B).
9. Seronegative health care and child care workers may be offered serologic monitoring during pregnancy. Moni- toring may also be considered for seronegative pregnant women who have a young child in day care (III-B).

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