No. 420, July 2021 (Replaces No. 240, April 2010)

Guideline No. 420: Cytomegalovirus Infection in Pregnancy

(En français : Infection à cytomégalovirus pendant la grossesse)

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

This clinical practice guideline was prepared by the authors and overseen by the SOGC Infectious Disease Committee. It was approved by the SOGC Guideline Management and Oversight Committee and SOGC Board of Directors.
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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed consent: Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that health care providers provide patients with information and support that is evidence-based, culturally appropriate, and personalized.

Language and inclusivity: The SOGC recognizes the importance to be fully inclusive and when context is appropriate, gender-neutral language will be used. In other circumstances, we continue to use gendered language because of our mission to advance women's health. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

Weeks Gestation Notation: The authors follow the World Health Organization's notation on gestational age: the first day of the last menstrual period is day 0 (of week 0); therefore, days 0 to 6 correspond to completed week 0, days 7 to 13 correspond to completed week 1, etc.

Keywords: cytomegalovirus infections; newborn screening; pregnancy

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RECOMMENDED CHANGES IN PRACTICE

1. Providers should educate patients of child-bearing age, pregnant patients, or patients planning a pregnancy about cytomegalovirus and its sequelae. This will encourage patients to take preventive measures to reduce cytomegalovirus acquisition.
2. Providers should discuss all treatment options with patients infected with cytomegalovirus, and decisions should be made in a shared process involving providers and patients.

KEY MESSAGES

1. Cytomegalovirus is the most common congenital infection. Despite the high prevalence and serious consequences of congenital cytomegalovirus infection, only 15% of pregnant patients in Canada are aware of cytomegalovirus and its sequelae.
2. There is a lack of strong and consistent evidence for maternal cytomegalovirus infection screening during pregnancy and/or for treatment of maternal infection (to prevent transmission to the fetus) or of established fetal infection. Therefore, awareness and prevention of cytomegalovirus acquisition are key. The recommended best practice is educating all pregnant patients or patients planning a pregnancy, and their families, about cytomegalovirus and the available preventive interventions.
3. Despite the challenges in diagnosing and treating congenital cytomegalovirus infection during pregnancy, cytomegalovirus-related disability can be mitigated, to some extent, through neonatal diagnosis and intervention, combined with Canada's well-established programs for early hearing detection and intervention.

DEFINITIONS

Primary CMV infection in pregnancy: new CMV infection in a person who was CMV IgG negative before the pregnancy
Non-primary CMV infection in pregnancy: active CMV infection in a person with a previous infection (who was previously CMV IgG positive)

ABSTRACT

Objective: To provide an update on current recommendations for cytomegalovirus (CMV) infection during pregnancy. The objectives of this guideline are:

- To improve perinatal care providers' awareness of the consequences of maternal CMV infection for the fetus and the infant;
- To emphasize the importance of educating patients about how to prevent CMV acquisition during pregnancy
- To raise perinatal care providers' awareness of new developments in CMV screening and treatment
- To highlight that a substantial proportion of disability due to congenital CMV (cCMV) can be modified to some extent

Target Population: Patients of child-bearing age, pregnant patients, and patients planning a pregnancy.

Benefits, Harms, and Costs: The patient partners urged us to make awareness of preventive strategies a high priority, despite concern that discussing CMV with patients could cause unnecessary anxiety. CMV educational interventions have shown benefits from increased awareness of cCMV prevalence and preventive strategies among providers, patients, and families.

Evidence: We searched MEDLINE, EMBASE, and CENTRAL databases for CMV in pregnancy. The search terms were developed using MeSH terms and keywords (**Appendix**).

The results were filtered for articles published between January 2010 and October 2020 and systematic reviews, meta-analyses, clinical trials, and observational studies.

The main inclusion criteria were pregnant patients and infants, as the target population, and CMV infection, as the diagnosis of interest. Recommendations are graded according to the U.S. Preventive Services Task Force grade of recommendations and level of certainty.

Validation Methods: We collaborated with patient partners, including members of CMV Canada (cmvcanada.com). In formulating our recommendations, we included patients' voices to add a unique and valuable perspective, thus ensuring that our recommendations are relevant to the patient–provider partnership.

Intended Audience: All perinatal health care providers.

RECOMMENDATIONS (grade and level of certainty in parentheses):

1. Pregnant patients with a mononucleosis-like illness or undifferentiated hepatitis should be investigated for cytomegalovirus infection (*C, low*).
2. To diagnose maternal cytomegalovirus infections and to differentiate primary from non-primary infections, this guideline recommends a combination of seroconversion (defined as documentation of a change from cytomegalovirus immunoglobulin G negative to positive), cytomegalovirus immunoglobulin M, and cytomegalovirus immunoglobulin G avidity testing (*B, moderate*).
3. A positive immunoglobulin M result alone should be interpreted with caution when determining when a CMV infection was acquired (*C, moderate*).
4. Breastfeeding is considered safe in patients who had CMV infection during pregnancy (*B, high*).
5. If primary maternal CMV infection is diagnosed during pregnancy, or abnormal sonographic findings suggest congenital CMV infection, pregnant patients should be offered an amniocentesis for confirmation of fetal congenital infection (cCMV) at least 8 weeks after the estimated time of maternal infection (*B, high*).
6. This guideline recommends discussing education and hygiene measures to prevent CMV acquisition with all patients, regardless of serologic status, before conception and through pregnancy, especially early in the antepartum period (*B, high*).
7. CMV hyperimmune globulin should not be used to prevent congenital CMV if a primary CVM infection is diagnosed during pregnancy (*B, low*).

8. In the case of documented primary CMV infection in the first trimester, early treatment with valacyclovir can be considered (*B, moderate*).
9. For established congenital CMV infections during pregnancy, decisions concerning treatment options should be made in a shared process involving patients and experienced teams (*C, low*).
10. In provinces where CMV IgG avidity testing is available, screening for CMV primary infection in the first trimester (using IgG and IgM antibodies followed by IgG avidity testing if the patient is IgM-positive) can be offered, especially in women at high risk (those who have a child under 3 years at home). CMV screening in pregnancy is not recommended in provinces where CMV IgG avidity testing is unavailable (*C, low*).

INTRODUCTION

Cytomegalovirus (CMV) is the most common infection acquired before birth (congenital infection). Congenital CMV infection (cCMV; defined as CMV infection that is acquired in utero [transplacentally] and is present at birth) is estimated to affect 1 of every 180 to 240 babies born in Canada[1,2] (Figure 1). Although most infants with cCMV are healthy at birth, approximately 15% to 20% have permanent neurologic sequelae, most commonly sensorineural hearing loss (SNHL); other sequelae include intellectual disability, cerebral palsy, visual impairment, and seizures.[3,4] This clinical practice guideline reviews the epidemiology, diagnosis, and prevention of CMV infection during pregnancy, and the pathogenesis and management of fetal CMV infection.

While this guideline does not make recommendations for the care of infants with sequelae of cCMV, it does highlight recent evidence supporting cCMV screening and treatment for newborns. We address the fact that a proportion of cCMV-related disability can be modified, to some extent, through neonatal diagnosis and intervention, combined with Canada's well-established services for early hearing detection and intervention.

EPIDEMIOLOGY OF MATERNAL AND CONGENITAL CMV INFECTIONS

CMV seroprevalence in patients of child-bearing age, defined as evidence of previous CMV infection (positive CMV immunoglobulin G [IgG]), is estimated to be 40% to 54% in Canada.[5,6] Seroprevalence is higher among patients born in low-resource settings and those with current or past sexually transmitted infections; seroprevalence increases with age and parity.[7,8] CMV seroprevalence is also higher in patients who are exposed to young children, such as daycare workers.[6,9] Rates of cCMV in neonates increase with higher seroprevalence in mothers.[10,11,12]

ABBREVIATIONS

CMV	cytomegalovirus
cCMV	congenital cytomegalovirus infection
CVS	chorionic villus sampling
ELISA	enzyme-linked immunosorbent assay
IUGR	intra uterine growth restriction
IgG	immunoglobulin G
IgM	immunoglobulin M
PCR	polymerase chain reaction
SGA	small for gestational age

Primary maternal CMV infection affects approximately 2% of pregnancies and is associated with the same factors driving CMV seroprevalence in patients of child-bearing age, mentioned above.[13,14,15] In particular, there is a higher risk of primary maternal CMV infection[16,17] if the interval between the mother's pregnancies is less than 3 years, as younger infants excrete CMV more frequently and increase the risk of the mother acquiring the infection.[18,19,20] Primary maternal infection during pregnancy carries a risk of cCMV of 30% to 40%. This risk, and the risk of associated sequelae, depend on the gestational age at which the mother acquires the infection[11,15,21,22] (Figure 2). In general, the likelihood of CMV transmission to the fetus increases proportionally with the gestational age at which the mother acquires the infection. However, the risk of long-term sequelae for the infant is inversely proportional to the gestational age at which cCMV is acquired.[23,24] Recent data suggest that exposure to CMV only in the first trimester of pregnancy is associated with sequelae in children at 2 years of age.[22]

Data show that intrauterine transmission of CMV occurs in 0.5% to 1.5% of pregnant patients with evidence of preconception immunity (non-primary infections).[11,25,26] The severity of cCMV due to non-primary maternal infection appears to be similar to that resulting from primary maternal infections.[3,10,12,27,28,29,30] Importantly, in regions with low seroprevalence, such as Canada, it is estimated that half of cCMV infections are due to non-primary maternal infections.[10,12,25,29,31]

PATHOGENESIS AND CLINICAL MANIFESTATIONS OF MATERNAL AND CONGENITAL CMV INFECTIONS

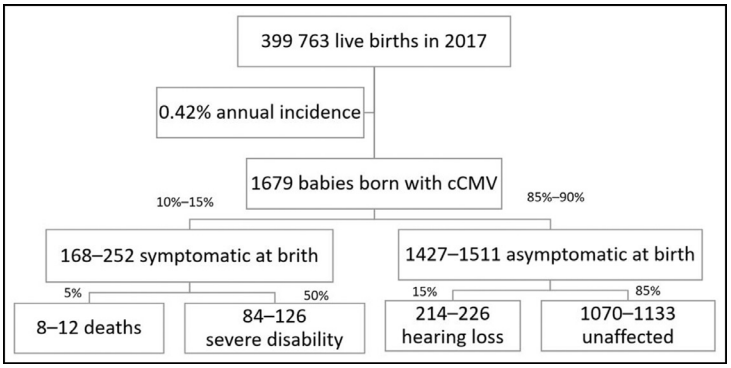
Primary CMV Infection

CMV is typically transmitted person-to-person through close contact with infectious virus shed in saliva, urine, genital secretions, and other body fluids; blood transfusion and organ transplantation are also recognized routes of infection. Primary CMV infection during pregnancy is asymptomatic in 95% of cases.[32] When CMV infection is symptomatic, the clinical presentation is the same as that in non-pregnant individuals. The incubation period ranges from 20 to 60 days, after which a mild mononucleosis-like syndrome ensues, with fever lasting 2 to 3 weeks, lymphadenopathy, high lymphocyte count, and abnormal liver enzyme results. Rare complications include hepatitis, Guillain-Barré syndrome, and myocarditis.[33]

Non-Primary CMV Infection

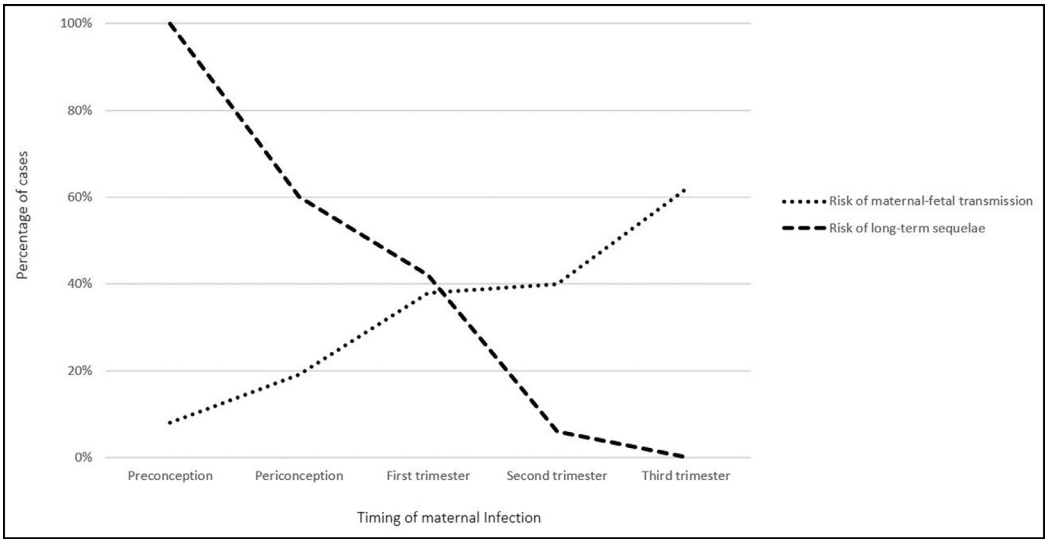
Non-primary CMV infection results from either reactivation of endogenous (latent) virus or re-infection by

Figure 1. Estimated congenital CMV infection burden in Canada. Rate 0.42% (1 in 240), extrapolated from Larke et al. (1980), for the city of Hamilton, Ontario



Canada 2017: approximately 250 to 334 babies affected by CMV-related disability.

Figure 2. Risk of fetal infection and risk of long-term infant sequelae in relation to gestational age



SOURCE: Adapted from Hutchinson BJ, Palma-Dias R, Walker SP. Universal cytomegalovirus screening: Time for reappraisal? Fetal and Maternal Medicine Review. 2014;25. Available from: https://www.cambridge.org/core/journals/fetal-and-maternal-medicine-review/article/universal-cytomegalovirus-screening-time-for-reappraisal/1A33E7C055351C2BB6AABA71D117C18E

exogenous virus.[34,35,36] Even in healthy individuals, CMV may periodically reactivate from latency, shedding at mucosal surfaces during reactivation.[32]

Congenital CMV Infection

cCMV refers to mother-to-child transmission of CMV in utero (transplacentally) that is present at birth, as determined by its presence in neonatal urine, blood, or saliva in the first 21 days of life.[37] cCMV can manifest in utero as intrauterine growth restriction, fetal hepatosplenomegaly, and intracranial white matter changes and calcifications, which are progressive over the gestation and depending on when the infection occurred.[32]

CMV can also be transmitted from mother to child through exposure to CMV-infected maternal blood or genital secretions during birth or, most commonly, through breastfeeding after birth. This is called postnatal infection and is more common than congenital infection.[38]

Postnatal infection is not associated with adverse infant outcomes, except among very-low-birthweight infants, who may present with end-organ disease and a sepsis-like

syndrome,[32] may develop chronic lung disease, and may have neurocognitive sequelae. However, the risk of long-term effects remains controversial.[39,40] Therefore, breastfeeding is considered safe in patients with CMV infection during pregnancy.

DIAGNOSIS OF CMV INFECTION

Maternal Infection: Diagnosis

Women should be tested for CMV infection during pregnancy if there are fetal ultrasound abnormalities suggestive of cCMV,[41,42] or if pregnant patients have symptoms of CMV, including generalized illness (i.e., a mononucleosis-like syndrome) and undifferentiated hepatitis.[33]

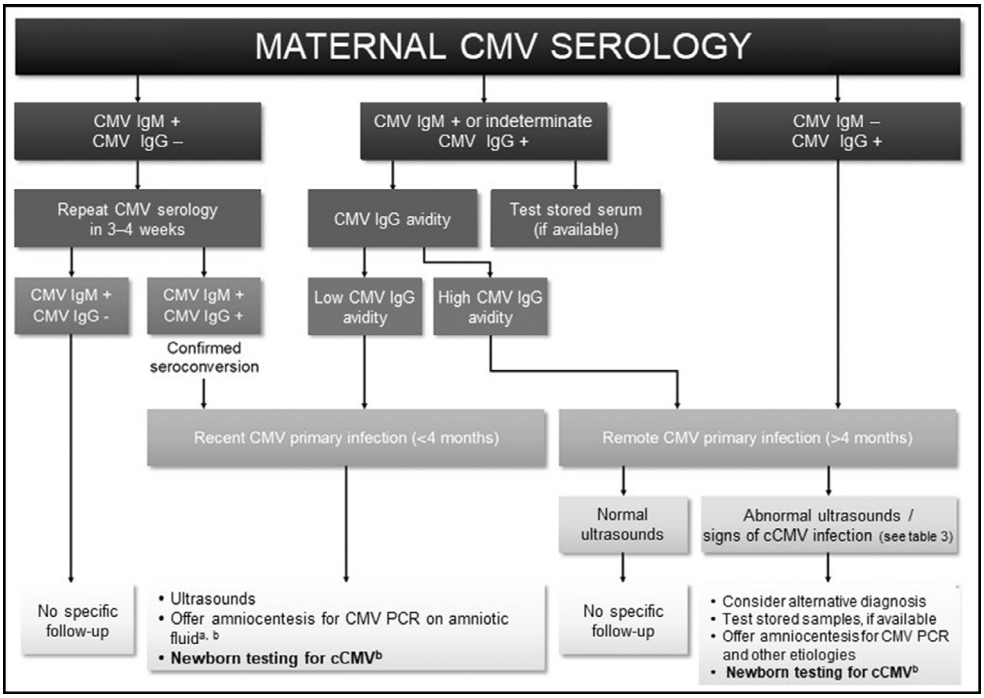
See Figure 3 for the recommended approach to testing for CMV infection during pregnancy. Currently available serologic tests are difficult to interpret; it is not always possible to determine when the maternal infection was acquired (see Table 1 for interpretation of serologic test results). The gold standard for diagnosing primary CMV infection is the documentation of a positive CMV IgG result in a person with previous documentation of a negative test result (seroconversion).[43,44] When a patient's previous immune status is unavailable, a combination of testing for CMV immunoglobulin M (IgM), CMV IgG, and CMV IgG avidity (where available) is recommended.

A positive result of a maternal CMV IgM test requires cautious interpretation because CMV IgM titres can be high for 1 to 3 months following a primary CMV infection[44] and can persist at low levels for 12 to 18 months following primary infection.[45] This makes it difficult to determine when the infection was acquired based solely on IgM presence. As well, CMV IgM levels can increase because of a non-primary infection.[44,46]

Furthermore, a negative result of maternal CMV IgM test does not rule out cCMV, as illustrated by a study of pregnancies in which fetal infection was confirmed following sonographic markers of congenital CMV infection. Among cases with a positive result of CMV on polymerase chain reaction (PCR) testing of amniotic fluid, the CMV IgM result was negative in 56%.[41] All of these infections were detected in either the second or third trimester. This evidence indicates either early first-trimester primary infection, as sonographic evidence of fetal infection takes several weeks to appear,[42] or non-primary infection.

CMV IgG avidity, the measure of how strongly IgG binds to CMV antigens, can help determine when the primary

Figure 3. Algorithm for approach to maternal CMV serologic testing during pregnancy



[a] At least 8 weeks after presumed infection.
[b] cCMV is defined as + CMV PCR amniotic fluid and/or + CMV PCR newborn urine, blood, or saliva.

Table 1. Interpretation of maternal cytomegalovirus (CMV) serologic tests

CMV serologic test result	CMV IgG avidity result	Interpretation	Implications
CMV IgM negative CMV IgG negative	N/A	Two possibilities: No evidence of infection Very early infection	Counsel patient concerning prevention of CMV acquisition during pregnancy Consider repeating in 4 weeks according to clinical situation
CMV IgM positive CMV IgG negative	N/A	Two possibilities: 1 Primary Infection 2 False-positive IgM result due to other infections, autoimmune disease, or laboratory methods[a]	Repeat in 4 weeks Test stored serum, if available
CMV IgM positive CMV IgG positive	Low[b]	Recent CMV infection	Test stored serum, if available, especially if avidity is unavailable: Seroconversion (negative CMV IgG in the past) is diagnostic of primary infection Counsel patient concerning risk of fetal infection and sequelae, and options for prenatal diagnosis (amniocentesis) and/or neonatal testing
CMV IgM positive CMV IgG positive	High[b]	Two possibilities: Past infection[a] Recent non-primary infection, if CMV IgG titres are rising	If sonographic anomalies are suggestive of cCMV, • Test stored serum, if available: A several-fold[c] rise of CMV IgG titres compared with stored sample or on serial samples performed with the same kit is suggestive of recent non-primary infection • Counsel patient concerning risk of fetal infection and possible sequelae, and options for prenatal diagnosis (amniocentesis) and/or neonatal testing
CMV IgM negative CMV IgG positive	High[b]	Two possibilities: Past infection Recent non-primary infection if CMV IgG titres are rising	If sonographic anomalies are suggestive of cCMV, • Test stored serum if available: A several-fold[c] rise of CMV IgG titre compared with prior sample or on serial samples performed with the same kit is indicative of recent non-primary infection • Counsel patient concerning low risk of fetal infection and possible sequelae and/or neonatal testing
CMV IgM negative CMV IgG positive	Low[b]	Unclear significance	Suggest consultation with specialist

[a] IgM can remain positive for up to 18 months.

[b] If unavailable, test stored serum sample taken preconception or in early pregnancy.

[c] Traditionally, a 4-fold increase has been considered suggestive of recent infection, but this can vary according to the test used. Consult a local virologist regarding assay performance.

cCMV: congenital cytomegalovirus infection; IgG: immunoglobulin G; IgM: immunoglobulin M; N/A: not applicable.

infection was acquired and should be performed primarily in cases where IgG and IgM are positive, or considered when IgM is negative and IgG is positive but there are concerning clinical features for congenital CMV infection (e.g., abnormal ultrasound findings). IgG avidity is low in early CMV infections, becoming high 5 to 6 months following primary infection.[47,48] In addition to levels "high" and "low," avidity is referred to as "indeterminate" at a transition from low to high. However, there are some diagnostic dilemmas with avidity testing as well. Low levels of IgG in

the sample can result in falsely low avidity levels.[49] As of November 2020, avidity testing is available in 3 Canadian provinces: Ontario, Québec, and Alberta.

Patients in the second trimester or later with sonographic findings suggestive of cCMV and low avidity should be offered further amniocentesis and/or newborn testing (See Box); these findings may indicate an infection acquired or reactivated during early pregnancy.[47,50,51,52] CMV PCR testing of maternal urine is not part of routine testing for CMV infection during pregnancy and should be reserved to specialists in maternal–fetal medicine, reproductive infectious diseases, and infectious diseases.

RECOMMENDATIONS 1, 2, 3, and 4

Fetal Infection: Diagnosis and Prognosis of Fetal Infection

Abnormal fetal sonographic findings (Box) are a common indication for testing for cCMV.[52] However, these findings are not specific for cCMV. Further, sonography is not a sensitive diagnostic tool, as less than of 50% of fetal infections exhibit findings on sonography.[42,53] Even when there are abnormal sonographic findings, there may be a delay before they are seen.[42]

The gold standard for diagnosing in utero cCMV infection is a positive result of a CMV PCR test of amniotic fluid obtained by amniocentesis.[52,54] The sensitivity and negative predictive value of a negative PCR result of amniotic fluid is 93%;[44] the specificity of a positive amniotic fluid PCR result for cCMV is 100%.

Timing of amniocentesis is important; traditionally, it has been recommended after 21 weeks gestation and at least 6 weeks after suspected maternal infection.[52,55,56] In a recent study by Enders et al., there was no difference in sensitivity in amniocentesis-based testing performed at 17 weeks or at 20 weeks gestation, as long as at least 8 weeks had elapsed after suspected maternal infection.[57] cCMV-related fetal abnormalities, especially the central nervous system findings, can evolve, and fetal sonography and magnetic resonance imaging (MRI) have been used to predict neurologic impairment, with inconsistent results.[58,59,60,61] Abnormal fetal sonographic and MRI findings may be seen in children with normal outcomes. However, consistently normal fetal sonographic and MRI findings confer a low risk of long-term neurologic deficits. A normal third-trimester fetal MRI has been reported to have a high negative predictive value for SNHL.[62]

Viral load in amniotic fluid has been investigated as a potential marker for predicting neonatal outcomes, with conflicting results.[50,63,64] Some studies have found an association between higher viral loads and the severity of the disease, while others have not. Ultimately, studies have not consistently shown that low levels or even negative amniotic fluid PCR results rule out neurologic impairment or SNHL.[65,66]

RECOMMENDATION 5

SUMMARY

Diagnosis of both maternal CMV infection and cCMV can be challenging, and involving experts in this area, through a multidisciplinary team approach, is recommended. Ideally, if stored sera are available, maternal infection can be documented by demonstrating seroconversion. If this is not possible, maternal testing for IgM, IgG, and IgG avidity (where available) is recommended. Sonographic findings may suggest cCMV, but are not specific for this diagnosis. Fetal infection is documented by positive CMV

Box. Common sonographic findings in congenital cytomegalovirus infection

Central nervous system	Cardiac	Abdominal	Placenta	Other
• Ventriculomegaly • Calcifications • Microcephaly • Subependymal/ periventricular cysts • Periventricular hyperechogenicity • Cerebellar aplasia • Porencephaly • Lissencephaly	• Cardiomegaly • Pericardial effusion • Calcifications	• Hepatomegaly • Splenomegaly • Calcifications • Ascites • Echogenic bowel	• Placentomegaly • Small placenta • Oligohydramnios	• Intrauterine growth restriction • Death • Pelvic cysts

SOURCE: Adapted from Society for Maternal-Fetal Medicine, Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. Am J Obstet Gynecol. 2016;214:B5-B11. Available from: https://pubmed.ncbi.nlm.nih.gov/26902990/

PCR results from amniotic fluid. See Figure 3 for algorithms to assist with the approach to maternal serologic testing and sonographic findings.

PREVENTION OF MATERNAL CMV INFECTION DURING PREGNANCY

Ultimately, the best strategy to prevent cCMV would be an effective vaccine against CMV. While there is optimism that such a vaccine will be developed, current candidates are still in early-phase trials.[67] One randomized, double-blinded, placebo-controlled trial showed promising results, with a significantly lower infection rate among patients who received the vaccine (8% in the vaccine group compared with 14% in the placebo group, $P = 0.02$).[68] Until a safe and effective CMV vaccine is clinically available, primary prevention of cCMV relies on patient education and hygiene measures.

Studies conducted in North America and Europe have repeatedly demonstrated that awareness of cCMV among the general population and pregnant patients is low, and that behaviour that raises the risk of maternal CMV acquisition is common. Two studies have demonstrated that pregnant and postpartum patients are less aware of cCMV than they are of other congenitally acquired infections.[69,70] In Canada, only 15% to 25% of pregnant patients report awareness of CMV and its implications for pregnancy,[5] but once informed, 74% want CMV screening in pregnancy.[71]

Similarly, awareness of and counselling about cCMV remain low among perinatal care providers.[72,73] A 2012 study of 800 perinatal care providers in France identified knowledge gaps, particularly regarding the mode of transmission of CMV and the availability of effective in utero therapy. In the Netherlands, 41% of 330 midwives reported never informing a patient about CMV, and midwives cited that the most common reason for avoiding this discussion was that they did not have enough information.[70,72,73]

Results from several studies, including 1 randomized controlled trial, provide evidence that education about hygiene measures may be an effective means of reducing the incidence of primary CMV infection among patients who are seronegative.[74,75,76,77] Studies considering whether such interventions could be effective for pregnant patients more broadly, (i.e., regardless of their serologic status) are sparse. Price et al. carried out a web-intervention for 809 patients of reproductive age in the U.S., in which participants completed surveys before and after they either read a fact sheet or viewed an educational video.[78] Both the fact sheet and the video increased knowledge and acceptance of behavioural interventions. Seventy-two percent of patients reported motivation to adopt these behaviours after either intervention (fact sheet or video). In this study, obstetricians and pediatricians were the most frequently mentioned "preferred channels" for communicating information about CMV. Thackeray et al. conducted a study to characterize further the acceptability of behavioural measures among patients in the U.S. who were of reproductive age and had young children at home.[79,80] They randomly assigned 840 patients to read 1 of 4 CMV fact sheets and complete and questionnaires about knowledge and intended behaviours before and after reading. The authors found that, while most patients adopted positive attitudes toward protective behaviours, the least favoured behaviours were avoiding kissing on the lips and avoiding sharing food.[79]

There is evidence that educational interventions to promote hygiene measures may reduce primary CMV acquisition during pregnancy. However, most data come from studies involving patients who are aware of their susceptibility to primary CMV during pregnancy, which may be an essential motivator to adopt hygiene measures. Given the importance of non-primary maternal infection for cCMV,[10,12,25,29,31] more data are needed to assess the impact of educational interventions to prevent cCMV in seropositive patients. However, preventive measures effective against primary infection are likely to reduce reinfection as well. As these education and hygienic interventions are inexpensive and straightforward, they should be considered for all pregnant patients, regardless of serologic status.

Although CMV seroprevalence is higher in daycare workers than in the general population, reliable data is lacking regarding their risk of CMV primary infection. CMV seroprevalence and primary CMV infection incidence are not increased among health care workers. Therefore, we do not recommend that pregnant patients who are working with children younger than 3 years of age take time off work. Instead, we recommend that any worker who is pregnant or who may become pregnant and works with children younger than 3 years of age be provided with education regarding strategies to prevent CMV acquisition.[81]

RECOMMENDATION 6

PRENATAL TREATMENT AND PREVENTION OF FETAL INFECTION

Despite advances in the diagnosis of fetal CMV infection, treatment options during pregnancy remain limited. Both oral valacyclovir and CMV-specific hyperimmune globulin

(CMV-HIG) have been studied to prevent fetal CMV infection (i.e., mother-to-child transmission) or treat established fetal infection. Studies have included only primary maternal CMV infections.

Maternal Antiviral Therapy to Treat or Prevent Congenital CMV Infection

Valacyclovir appears safe for use in pregnancy, even in the first trimester.[82,83] At a dosage of 8 g per day, it results in therapeutic concentrations in amniotic fluid and fetal blood.[84]

However, the available evidence is insufficient to recommend routine maternal antiviral therapy for fetal infection. A recent double-blind, randomized controlled trial reported on 90 pregnant patients with primary CMV infection acquired during the periconceptional period or the first trimester of pregnancy. Patients were randomly assigned to receive either oral valacyclovir (8 g per day) or placebo. Fetal infection rates determined by CMV PCR of amniotic fluid were 29.8% in the placebo group and 11.1% in valacyclovir group (OR 0.29; 95% CI 0.09−0.9)[85] The benefit was limited to those with infection acquired during the first trimester; there was no significant difference in fetal infection among patients with periconceptional infection. While the results of this small, single-centre study are highly suggestive of valacyclovir's efficacy in preventing cCMV among patients with first-trimester primary infection, they need to be replicated in other trials. Two prior studies looking at antiviral medications to prevent cCMV-associated sequelae among pregnancies with confirmed cCMV showed conflicting results. One documented less likelihood of symptomatic disease at birth among infants whose mothers were treated during pregnancy, but the other found no difference. [86,87]

Maternal CMV-HIG Immunotherapy to Treat or Prevent Congenital CMV Infection

Seven studies, including 2 randomized controlled trials, have reported on the use of CMV-HIG among pregnant patients with primary CMV infection and without evidence of fetal infection (amniocentesis either not done or results negative for CMV) to prevent cCMV (Table 2).[88,89,90,91,92,93,94] Following earlier studies with inconsistent results, a recent, high-quality, multi-centre, double-blind randomized placebo-controlled trial found CMV-HIG ineffective in decreasing the risk of cCMV or fetal death among patients with primary CMV infection in early pregnancy. The trial was stopped early at the recommendation of the study's data and safety monitoring committee.

Nine studies have reported on fetal outcomes after CMV-HIG treatment during pregnancies with fetal infection confirmed by amniocentesis (Table 3).[88,89,91,92,95,96,97,98,99] The findings, taken as a whole, show a trend toward decreased morbidity for fetuses whose mothers received CMV-HIG, even though there were no statistically significant differences.

Overall, among pregnant patients with first-trimester primary CMV infections, there are limited data to support the use of valacyclovir 8 g per day for the prevention of fetal CMV infection, and high-quality evidence to recommend against use of CMV-HIG for the same purpose.

For established cCMV infections during pregnancy, the available evidence is insufficient to recommend using either CMV-HIG or antiviral medications to reduce sequelae in infected fetuses. These therapies should be used only by experienced teams after appropriate counselling, ensuring active patient participation in the decision-making process.

RECOMMENDATIONS 7, 8, and 9

Counselling of Patients with a Prior Pregnancy Resulting in Congenital CMV Infection

There are no data on pregnancy and infant outcomes in subsequent pregnancies following a pregnancy affected by cCMV. Although affected patients have CMV-specific immunity, they can still acquire a CMV infection and transmit the infection to their fetuses,[11,25,26] and this congenital infection can result in sequelae comparable to those arising from primary infections. [3,10,12,27,28,29,30] The crucial point to convey to these pregnant patients is that their risk of cCMV (given pre-conception immunity) is far lower, at 0.5% to 1.5%, compared with primary infections.[11,25,26]

In this context, educating these women on hygiene measures is critical (see Prevention of Maternal CMV Infection During Pregnancy), and maternal serologic testing is not helpful (Table 1).

Screening for Maternal CMV Serologic Status

Screening for maternal CMV serologic status in pregnancy is controversial, because of the absence of reproducible and readily interpretable diagnostic tests, and because non-primary CMV maternal infections pose a risk of cCMV similar to that of primary infections.

However, there are several points to consider. Congenital CMV acquired during the first trimester is associated with the highest risk of long-term neurodevelopmental sequelae. Given the relatively low seroprevalence of CMV in Canada, primary infections contribute to half of the cases of cCMV. Limited but good-quality data support the use of valacyclovir to prevent cCMV infection resulting from primary

Table 2. Published literature on cytomegalovirus-specific hyperimmune globulin (CMV-HIG) for prevention of congenital CMV infection (cCMV)

Author, year of publication	Country	Methods	Intravenous HIG group	Control group	Rate of cCMV (% HIG / % control)
Nigro et al., 2005[88]	Italy	Prospective cohort	n = 37 monthly 100 UI/kg	n = 47	16% / 40% (P = 0.02)
Buxmann et al., 2012[89]	Germany	Case series	n = 37 (1 twin pregnancy) 200 UI/kg	None	24% in the HIG group
Revello et al., 2014[90]	Italy	Randomized double-blind trial	n = 61 monthly Cytotect 100 UI/kg	n = 62 Placebo	30% / 44% (P = 0.130)
Minsart et al., 2018[91]	Canada	Retrospective cohort	n = 5 monthly Cytogam 150 mg/kg	n = 26	20% / 38.5% (P = 0.631)
Blazquez-Gamero et al., 2019[92]	Spain	Retrospective cohort	n = 17 monthly Cytotect 100 UI/kg	None	41%
Kagan et al., 2019[93]	Belgium Germany	Prospective cohort / historical controls	n = 40 biweekly Cytotect 200 UI/kg before 14 weeks	n = 108	7.5% / 35.2% (P < 0.0001)
Hughes, 2019[94]	USA	Randomized double-blind trial	n = 206 monthly Cytogam 100 UI/kg	n = 193	22.7% / 19.4% (P = 0.424)

maternal CMV infections in the first trimester[85] (see Prenatal Treatment and Prevention of Fetal Infection for a detailed discussion).

Pregnant patients, especially those at high risk of CMV primary infection (patients in contact with children 3 years old and younger) can be offered CMV serologic testing in the first trimester to screen for CMV primary infection. Importantly, pregnant patients with positive results of serologic testing remain at risk for cCMV in their fetus. A message that such patients are "CMV-immune" could be misleading and provide false reassurance. Rather, CMV prevention strategies should be discussed with all patients, regardless of their serologic status, to reduce the risk of cCMV through maternal infection or reinfection during pregnancy.

The cost-effectiveness of CMV screening strategies during pregnancy needs to be further evaluated.

RECOMMENDATION 10

POSTNATAL MANAGEMENT OF CONGENITAL CMV INFECTION

A detailed discussion of the care of infants with cCMV is outside the scope of this guideline. However, it is noteworthy that there is level I evidence for the benefit of antiviral treatment for selected infants with symptomatic cCMV,[100,101] which is now the standard of care.[37,43] Furthermore, early diagnosis of cCMV appears to be beneficial, even in the absence of medical treatment, as it allows for appropriate monitoring and support for hearing loss and developmental delay.[37,102,103] CMV testing of newborns who fail the newborn hearing screen (i.e., targeted screening) has become widely adopted,[104,105] including at some Canadian centres. The province of Ontario added CMV to the universal newborn screening panel in 2019, as an adjunct to its well-established newborn hearing screening program. However, targeted CMV screening still misses over half of all infants with cCMV who develop SNHL after birth.[106] It is estimated to be substantially less cost-effective than universal newborn CMV screening, which could identify all infected newborns, allowing for early intervention and appropriate anticipatory guidance.[102,103] Management of infants with cCMV requires a multidisciplinary approach and should be undertaken in consultation with an expert in pediatric infectious diseases.[37,105]

CONCLUSIONS

CMV is the most common congenital infection. Even though most infants born with congenital CMV infection are healthy at birth, approximately 1 in 5 to 6 will suffer permanent neurologic sequelae like hearing loss. Simple strategies can prevent its acquisition. Therefore, we recommend raising awareness of CMV among all patients of

Table 3. Published literature on cytomegalovirus-specific hyperimmune globulin (CMV-HIG) for prevention of congenital CMV infection – associated sequelae

Author, year of publication	Country	Methods	Intervention	Symptoms at birth (% HIG / % control)	Adverse neurodevelopmental outcome (% HIG / % control)
Nigro et al., 2005[88]	Italy	Prospective cohort n = 31 HIG n = 14 no treatment	IV HIG (200 UI/kg), repeated + HIG intra–umbilical-cord or intra-amniotic infusion if persistent sonographic signs	3% / 50% ($P = 0.001$)	3% / 42% (+ 2 perinatal death)
Nigro et al., 2008[95]	Italy	Case series n = 3 HIG n = 2 no treatment	IV HIG (Cytotect, 200 UI/kg) every 2 to 3 weeks + intra-amniotic HIG infusion	0 % / 100%	0% / 100%
Nigro et al., 2012[98,a]	Italy	Case series n = 8 HIG n = 8 no HIG	IV HIG (Cytotect, 200 UI/kg) repeated if persistent sonographic signs	12 % /100%	12% / 100% ($P < 0.0004$)
Visentin et al., 2012[97]	Italy	Prospective cohort n = 31 HIG n = 36 no HIG	IV HIG (Cytotect, 200 UI/kg) once	Unknown	13% / 43% ($P < 0.01$)
Buxmann et al., 2012[89]	Germany	Retrospective case series n = 3[b]	IV HIG + fetal intra-umbilical cord or intra-amniotic HIG infusion	0%	100% normal at 1 year old
Japanese Congenital Cytomegalovirus Infection Immunoglobulin Fetal Therapy Study Group 2012[99]	Japan	Prospective case series n = 5[c]	Weekly IV HIG (7.5–15.0 g) and/or HIG injection into the fetal peritoneal cavity	80%	20% (+ 1 early neonatal death)
Nigro et al., 2012[96]	Italy	Case-control	IV CMV HIG every 2 to 4 weeks (200 UI/kg)		32 cases: hearing deficit and/or neurodevelop mental sequelae 32 controls: no sequelae, matched for timing of CMV infection and age at the last evaluation Cases more likely to be born of patients not treated with CMV-HIG during pregnancy (87.5% vs. 15.6%, $P < 0.0001$)
Minsart et al., 2018[91]	Canada	Retrospective cohort n = 11 HIG n = 29 no HIG	Monthly IV CMV HIG (Cytogam 150 mg/kg)	72.7% / 34.5% ($P = 0.003$)	45.5% / 17.2% ($P = 0.103$)
Blazquez-Gamero et al., 2019[92]	Spain	Retrospective cohort n = 19	IV HIG (Cytotect 200 UI/kg) repeated once if abnormal sonographic signs	50%	20%[d]

[a] Nine of these 16 patients were included in previous publications.

[b] Cases without IV HIG (fetal intra-umbilical or intra-amniotic HIG infusion only) are not included.

[c] Cases without IV HIG (fetal intra-umbilical or intra-amniotic HIG infusion only) are not included.

[d] Three cases were lost to follow-up.

IV: intravenous.

child-bearing age and perinatal health care providers. We involved patients' voices in the development of these guidelines, and our patient partners urged us to make awareness of preventive strategies a high priority. Serologic tests to diagnose CMV infection in pregnancy require cautious interpretation. When primary CMV infection during

pregnancy or cCMV is suspected, a referral to a maternal–fetal medicine and/or a reproductive infectious disease specialist is warranted. Early diagnosis of cCMV appears to be beneficial, as it allows for assessment of treatment eligibility as well as appropriate monitoring and support for hearing loss and developmental delay.

GUIDELINE TOOLKIT

SOGC members can visit the Guideline Resource Kit webpage on sogc.org to find complementary tools and resources and to participate in accredited continuing professional development activities.

SUPPLEMENTARY MATERIAL

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jogc.2021.05.015.

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