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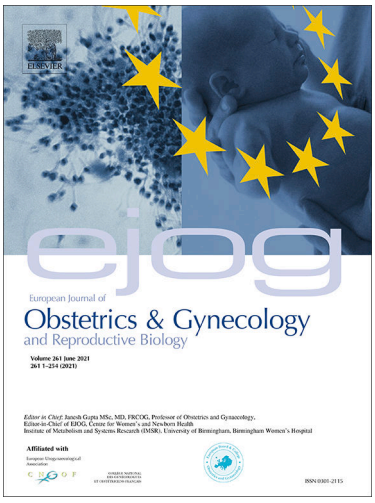

Review article

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Sara Sorrenti, Nouran Elbarbary, Francesco D'Antonio, Daniele Di Mascio, Asma Khalil

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Diagnosis and management of congenital Cytomegalovirus: Critical Appraisal of Clinical Practice Guidelines

Sara Sorrenti[1,2], Nouran Elbarbary[3], Francesco D'Antonio[4], Daniele Di Mascio[1], Asma Khalil[2,3,5]

1: Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Italy

2. Fetal Medicine Unit, Liverpool Women Hospital, Liverpool, United Kingdom

3. Fetal Medicine Unit, St George's Hospital, London, United Kingdom

4. Center for Fetal Care and High-Risk Pregnancy, Department of Obstetrics and Gynecology, University of Chieti, Italy

5. Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, United Kingdom

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Corresponding Author:

Professor Asma Khalil, MBBCH, MD, FRCOG

Department of Obstetrics and Gynecology

St. George's University Hospital

University of London

e-mail address: asmakhalil79@gmail.com

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Highlights:

- ◊ The diagnosis and management of congenital Cytomegalovirus (cCMV) are widely reported in the current Guidelines regarding CMV infection in pregnancy; on the other hand, screening is controversial among Guidelines
- ◊ With the new available evidence regarding the use of Valaciclovir in pregnancy in women with primary infection, Guidelines are changing recommendations regarding treatment in these cases
- ◊ New available treatment might change the recommendations regarding screening of CMV infection in pregnant women

ABSTRACT

Objectives: To review the currently available Clinical Practice Guidelines regarding the diagnosis and management of Cytomegalovirus (CMV) infection in pregnancy.

Methods: Medline, Turning Research into Practice (TRIP), Web of Science databases and scientific societies' websites were searched electronically up to April 2024. We included national and international Clinical Practice Guidelines regarding diagnosis, treatment and follow-up of CMV infection in pregnancy, published in English language. Quality assessment of the included guidelines was performed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool.

Results: Ten Clinical Practice Guidelines and two expert consensus statements were included. The review showed agreement among national and international guidelines about the diagnostic criteria for primary maternal CMV infection and about the gold standard for confirmation of fetal infection. Regarding treatment, only two societies recommended routine administration of Valaciclovir in case of primary infection in the clinical practing setting. Fetal surveillance including ultrasound and magnetic resonance imaging (MRI) in case of confirmed infection was found to be heterogeneous among the recommendations.

Conclusions: Although consensus was obtained regarding the diagnostic criteria for primary CMV infection in pregnancy, there was heterogeneity among Clinical Practice Guidelines with regards to other aspects of clinical management of CMV in pregnancy. In addition, some topics where not addressed in the current guidelines, including the treatment of non-confirmed fetal infection and the management of non-primary maternal infection. Recommendations regarding prevention of congenital CMV are rapidly evolving based on the new available evidence.

Introduction

Congenital Cytomegalovirus (CMV) affects up to 2% of live births and is the most common acquired cause of neurodevelopmental delay and sensorineural hearing impairment (1-3). Primary or non-primary infection in pregnancy may occur with direct contact with the saliva, urine, or blood of affected individuals. The most common route of infection in pregnant women is by young children, due to their longer excretion of the virus through urine and saliva (4). Vertical transmission of the virus in the case of primary infection is higher (5) and it occurs in 25-45% of cases if the infection is acquired periconceptionally or in the first trimester, 45% of cases if acquired in the second trimester, and 47-78% if acquired in the third trimester (6-7). The risk of congenital CMV in the newborn of primary infected mother is around 30-40% in the first and second trimester, and it reaches 70% in the third trimester. In the case of non-primary infection, the risk of fetal infection is much lower (1-2%). However, if acquired, the risk of postnatal neurological sequelae is similar to that of primary infection (8) and most symptomatic newborns with CMV are born from mothers with CMV reactivation. (9-10) Diagnosis of primary or non-primary infection is made with maternal serology, while fetal infection is demonstrated by the identification of viral DNA in the amniotic fluid sampled with amniocentesis (6). A recent study also showed a potential role for chorionic villus sampling (CVS) to detect CMV DNA through polymerase chain reaction (PCR) to rule out vertical transmission in case of early infection (11).

In the last few years, there is growing evidence demonstrating that treatment with Valaciclovir can effectively reduce the vertical transmission of the disease, thus reducing the burden of this infection worldwide (12-16). However, not all current guidelines recommend this treatment as first line option (17-19), and despite the evidence of efficacy, maternal serological universal screening is not routinely recommended (20). In fact, diagnosis and management of CMV infection in pregnancy broadly vary among different clinical settings and the optimal clinical practice is still subject of debate.

This review aimed to evaluate the quality and consistency of available Clinical Practice Guidelines on diagnosis and management of CMV infection in pregnancy.

Methods

Search strategy

This systematic review was performed according to the a-prior protocol recommended for Systematic Review of Clinical Guidelines (21). Medline, Embase, and Web of Science databases were searched electronically up to April 1, 2024, using the combination of relevant keywords including "congenital cytomegalovirus", "CMV", "diagnosis", "prognosis", "management", "antenatal", "pregnant", "Guidelines", "Clinical practice". We also searched guideline databases, including the Guidelines International Network, International Guideline Library, National Institute of Health and Care Excellence (NICE), other professional societies that are partners in the Federation of Gynecology and Obstetrics (FIGO), the Turning Research into Practice (TRIP) database. The search was restricted to the English language. Reference lists of relevant studies were hand-searched for additional data.

Study selection and data extraction

Two authors (S.S., N.A.) independently screened titles and abstracts. Clinical Practice Guidelines about the diagnosis, prognosis, or management of congenital CMV in pregnancy were considered eligible for the analysis (Population, Intervention, Comparators, Attributes of Clinical Practice Guidelines, Recommendations characteristics; PICAR Statement), available in Supplemental material, S1. Furthermore, consensus statements published by a panel of experts, or national or international societies were included. Studies only about recommendations on screening for CMV in pregnancy were not within the scope of the study, so they were excluded. Non-Clinical Practice Guidelines articles on the topic of the study were excluded. When different versions of the same recommendations were found, the most recent edition was selected. Regional guidelines were excluded.

Full texts were evaluated by the same two authors for inclusion; disagreements were resolved by discussion and involvement of a third author (A.K.). Data extraction was performed by two authors (S.S., N.A.). Information about the year of publication, type of publication, organization or society releasing the recommendations, country of publication, and content of the recommendations were collected.

Quality assessment and risk of bias

Included Clinical Practice Guidelines were assessed with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool (22). This tool includes 6 domains (scope and purpose; stakeholder involvement; rigor of development; clarity of presentation; applicability; and editorial independence) and 23 items. Each of these items is assessed with a score from 1 (strongly disagree) to 7 (strongly agree). A quality score is calculated for each of the six domains. Also, 2 global rating items are part of the "overall assessment". AGREE II guidelines specify that each domain is independent, and scores should not be aggregated into a single quality score. (22)

Two reviewers independently assigned a score to each item; conflicts of more than 3 points for each item were resolved with a third reviewer (A.K.). The final score for each domain was calculated with the sum of scores of each item included in the domain and was expressed as the percentage of the maximum score. The AGREE II tool does not include any indication about how to classify included studies in terms of high or low quality based on the patterns of scores among the domains. Classification of low and high-quality guidelines should be individually defined by the reviewers (22). As previously reported (20), we used the cut-off score of >60 % to define each domain as adequately addressed; each Clinical Practice Guideline was evaluated as "high quality" if six domains had scored >60%, "moderate quality" if three to five domains scored >60%, and "low quality" if zero, one or two domains scored >60% (20).

Statistical analysis

Simple statistical analysis was performed with descriptive purposes. The analysis was performed using Excel 16 (2021 Microsoft Corporation. All rights reserved.)

Results

Study selection and characteristics

The search identified 306 articles; 33 were assessed for eligibility and 12 Clinical Practice Guidelines were finally included in the systematic review (6, 18-19, 23-31). Characteristics of the included studies are reported in Table 1. Seven of them were national (18-19, 24, 26-29), five were international (6, 23, 25, 30-31) (Figure 1). Only one of them was published before 2010 (31), all the others were published in the last 10 years. All included guidelines reported information about the diagnosis of primary and non-primary maternal CMV infection in pregnancy and fetal infection; 10 out of 12 included information about the management of CMV infection in pregnancy; 5 out of 12 examined prevention strategies to reduce the rate of maternal infection; 10 out of 12 included recommendations about the screening in pregnant women, but the latter was not the topic of interest in the present systematic review.

Synthesis of results

Diagnosis

Synthesis of the recommendations are displayed in Table 2. The diagnosis of primary CMV infection in pregnancy was the object of all included Clinical Practice Guidelines, and consensus was achieved with regard to this point: all guidelines recommended the combination of positive CMV IgG, IgM and low IgG avidity as a criterion to define primary infection in pregnancy. Seroconversion, intended as the new onset of positive CMV IgG in a previously seronegative woman was reported as a criterion for primary infection in 10/12 studies (6,18-19, 25-28, 30-31). Moreover, the most recent guidelines suggested the test for CMV PCR in maternal blood in case of negative IgG and positive IgM, as a confirmation of very recent primary infection (23). Intermediate CMV IgG avidity was included in the definition of diagnosis of primary infection in 4/12 studies (26-27, 29-30). In addition, rising CMV IgG title in pregnancy was mentioned as a criterion of primary CMV infection in 2/12 guidelines (18, 27).

Some guidelines advised to investigate antenatal serology sampled earlier in pregnancy, when available (6/12 Clinical Practice Guidelines) (23,25,27-30).

Non-primary infection diagnostic criteria were reported by 3/12 studies (25, 28-29). They all defined possible non-primary infection in case of positive CMV IgG and IgM, with high IgG avidity; the Society of Gynecology of Canada (SOCG) also suggested possible secondary infection in case of raising IgG titer, negative IgM and high IgG avidity (28). On the contrary, the most recent European expert consensus stated that no valid laboratory can identify women with pre-existing immunity at risk of fetal infection (23). Similarly, both guidelines from the Royal College of Obstetrics and Gynecologists (RCOG) and ISUOG stated that maternal non-primary infection is diagnosed only in the presence of confirmed fetal infection (6, 24).

Full agreement was observed among included guidelines about the method of diagnosis of fetal infection: all studies recommended CMV PCR in the amniotic fluid sampled by amniocentesis as the gold standard to confirm fetal infection. The timing of amniocentesis in terms of gestational age at procedure and interval from the time of maternal infection was different among studies: ECCI and RCOG indicated 17 weeks of gestation, at least eight or six to eight weeks from the infection as the appropriate timing to perform the procedure, respectively. Seven guidelines defined the right timing for amniocentesis after 21 weeks of gestation (18-19, 25-27, 31); two guidelines indicated 20 weeks as the appropriate timing (6,30), and one study did not give any information about suggested gestational age at the procedure (28). Six-to-eight weeks were reported as the suitable time interval from infection to procedure in 2/12 guidelines (24,27); 4/12 of them indicated at least eight weeks (6,23,25,28) and 4/12 suggested at least six weeks after infection (19,26,29-30). One society reported five to six weeks from infection as enough to perform invasive testing (31), and one guideline did not specify any time frame from infection to amniocentesis (18).

The diagnostic criteria among the included Clinical Practice Guidelines are displayed in Figure 2.

Management

There was heterogeneity among the recommendations regarding fetal surveillance in case of confirmed infection. Serial ultrasound assessment in case of fetal infection was encouraged by 9/12 societies (6,18,23-28,31). Two guidelines did not include fetal assessment as the topic of

recommendations (29-30); guidelines from SMFM did not strongly recommend ultrasound surveillance or fetal magnetic resonance (MRI) as part of clinical management, instead highlighted limitations of both techniques (19). Fetal brain MRI was encouraged as a supplementary exam in case of fetal infection by 7/12 societies (6,23-27-31). The correct timing for MRI was pointed out in the third trimester, ranging from 28-34 among different guidelines.

The possible scenarios of negative amniocentesis or non-confirmed fetal infection were explicitly discussed in Clinical Practice Guidelines from ECCI and RCOG, respectively (23,24). The first society advocated providing usual antenatal care in case of negative amniocentesis (23), whereas the latter advised serial ultrasound surveillance including MRI assessment in case of both confirmed and non-confirmed fetal infection (24).

Additional fetal testing was only suggested by two societies as a possible option: RCOG advocated considering fetal blood sampling for platelet count (24); WAPM specified that fetal blood sampling can be considered only for prognostic assessment, not for diagnostic purposes (31). One society recommended against the routine fetal blood sampling for informative purposes (26); ISUOG defined fetal blood sampling as indicated in the intermediate prognostic group, with normal ultrasound findings and patients wishing as much information as possible (6).

Referral to a tertiary unit with high expertise in fetal infections was advised by 7/12 of the included guidelines (18,24-28,30).

Treatment

Regarding treatment, the guidelines showed different trends over the years. Before 2022, only one out of seven societies suggested considering treatment with Valaciclovir in case of primary infection acquired in the first trimester (28); the other societies did not recommend the use of antivirals outside the setting of a research protocol. In exception, ACOG recommended treatment with antivirals (such as valganciclovir, ganciclovir or foscarnet) in patients with acquired immunodeficiency (i.e., AIDS) or organ transplant (18).

From 2022, only one out of five guidelines did not recommend any treatment to prevent fetal infection (25); two guidelines encouraged to consider treatment with Valaciclovir in case of primary infection (26) or in case of positive amniocentesis, after multidisciplinary discussion (27). The most recent guidelines, published in 2023 and 2024 (RCOG and ECCI, respectively) advised prompt treatment with Valaciclovir in case of primary infection to prevent vertical transmission (8g/day, administered as 2gr/4 times a day) (23,24). The European consensus stated to also consider continuing treatment with Valaciclovir in case of confirmed fetal infection, after discussion with an expert team (23).

Six out of 12 Guidelines (23-28) were published after the clinical trial regarding the role of Valaciclovir in the treatment of primary CMV infection in pregnancy (14); the remaining were developed earlier than the publication of the trial (6,18-19, 29-31).

On the other hand, the role of the CMV hyperimmune globulins has been included in 9/12 Clinical Practice Guidelines (6,18-19,23-24,26,28,30-31): all of them did not recommend or recommended against the use of such treatment in case of primary infection; however, one of them advised to consider treatment with globulins in case of fetal infection (26) and one suggested to consider hyperimmune globulin at the dose of 200 IU/Kg every 2 weeks in case of very recent-first trimester primary infection (23).

Fetal surveillance and treatment options are illustrated in Figure 3.

Data about post-natal testing for CMV infection are reported in the Supplemental materials (S2). Pediatric assessment including hearing tests, ophthalmological assessment, and radiological imaging was not the focus of the present review.

Quality assessment of Clinical Practice Guidelines

The AGREE II domains are summarized in Table 3. Eight out of 12 guidelines were evaluated as high-quality (6,19,23-25,27-29), three were moderate quality (18,26,30), one was rated as low quality (31). The domains with the lowest scores was the Rigor of Development and Applicability, reflecting that often clinical practice guidelines fail to describe in detail the process of development of the recommendations and lack to extensively advice regarding the facilitation and application of them.

Discussion

Main findings

The findings from the present systematic review showed that there is agreement among national and international guidelines about the diagnostic criteria for primary maternal CMV infection and about the gold standard for confirmation of fetal infection. However, the timing of amniocentesis and management of fetal infection in terms of surveillance did not reach a consensus among included CPGs. Moreover, only two societies recommended routine administration of Valaciclovir in case of primary infection in the clinical practicing setting. However, only 50% of the included guidelines were developed after the randomized controlled trial about the use of Valaciclovir in secondary prevention of congenital CMV was published in 2020 (14).

Clinical and research implications

Congenital CMV infection is the most common cause of non-genetic congenital neurodevelopmental delay and hearing loss. Across different clinical settings, screening and management of maternal and fetal infection can vary, leading to high heterogeneity of practice in the presence of the same condition. (32)

The agreement regarding the diagnostic criteria for maternal and fetal infection supports the use of these criteria in clinical practice. However, in case of confirmed infection, different scientific societies do not agree on the surveillance and management of these cases. The role of ultrasound in detecting fetal abnormalities potentially associated with CMV infection has been extensively reported in the current literature (33-35). Although most Clinical Practice Guidelines recommend the use of fetal ultrasound in case of fetal infection, the timing and frequency of such surveillance are scarcely reported among the guidelines. We would advocate that the development of specific pathways for fetal surveillance should be implemented in every clinical setting.

Similarly, the treatment of maternal infection to prevent vertical transmission and possibly the treatment of fetal infection are still the subject of controversies among Clinical Practice Guidelines in the last 10 years. As aforementioned, there has been a progressive implementation of support for the use of antivirals in women with primary CMV infection over the years. This observation reflects the recent evidence that has been published supporting the use of this treatment in pregnancy: a double-blind controlled trial included 90 women with primary CMV infection acquired in the periconceptional period or first trimester of pregnancy and showed that the administration of Valaciclovir was associated with a reduction of the rate of fetal infection by 71% (14).

Moreover, a very recent individual patient meta-analysis on the use of Valaciclovir in secondary prevention of congenital CMV in women with primary infection acquired in the periconceptional period or first trimester demonstrated that a regime of 8g/daily of Valaciclovir reduced the rate of vertical transmission (OR 0.34, 95% CI 0.18-0.61), neonatal infection (0.30, 95% CI 0.19-0.47) and termination of pregnancy due to severe signs of fetal infection (0.23, 95% CI 0.22-0.24) (15). These findings confirm what was previously reported by another meta-analysis about the effectiveness and safety of Valaciclovir in secondary prevention of fetal infection in case of maternal CMV infection (14).

On the other hand, only a few studies investigated the role of antivirals in the treatment of fetal infection (36-37), with promising results observed with high-dose Valaciclovir in the improvement of moderately symptomatic infected fetuses.

In this scenario, it is of great importance to reconsider the screening for CMV infection in pregnancy; although not object of the present study, this practice has been object of a recent study (20), which reported that the majority of present guidelines do not recommend routine screening for CMV in pregnancy (20). With the emerging evidence regarding the benefits of early treatment in case of maternal CMV infection, the available recommendation should be revised, and larger studies are needed in order to provide enough strong evidence to change clinical practice.

Another controversial point regarded the use of fetal brain MRI as a diagnostic tool in case of fetal infection. Recent evidence has suggested the encouraging role of MRI in detecting brain anomalies that could be missed with only ultrasound assessment (38-44).

A multicentric cohort study of cases with confirmed fetal infection showed 10.5% of structural anomalies detected solely at MRI examination: these included malformations of cortical

development, destructive encephalopathy, intracranial calcifications of the germinal matrix and complex brain anomalies (42). Similarly, a large meta-analysis including 1178 cases of CMV fetal infection with normal ultrasound at diagnosis found that follow-up scans detected brain abnormalities in 4.4% (95% CI, 1.4-8.8%) of cases, whereas the rate of abnormalities in the central nervous system only diagnosed with fetal MRI was 5.8% (95% CI, 1.9-11.5%) (45). Nevertheless, only less than 60% of guidelines included in the present systematic review advised to perform MRI in case of fetal infection.

Some clinical practice points were not addressed in the current guidelines, including the choice of treatment in case of fetal signs of infection but without confirmed infection by amniocentesis (i.e. if declined by maternal choice). Similarly, the pathway of clinical surveillance in case of signs of fetal infection is not clearly defined by the available practice guidelines. Large multicenter studies are needed to investigate the optimal algorithm for fetal assessment in case of confirmed fetal infection.

The management of non-primary infection is not extensively addressed in the available Clinical Practice Guidelines. Although the rate of vertical transmission has been reported to be very low (7), recent evidence showed that fetal infection in case of non-primary maternal infection may be as severe as transmission after primary infection (7-9). Moreover, it has been reported that the majority of neonates with symptomatic congenital CMV infection were born to mothers with CMV reactivation (9). However, only the European expert consensus published in 2024 recommended testing neonates for congenital CMV in both cases of mothers with primary or non-primary infection (23). However, we believe that prenatal management of the latter should be included as a topic of prenatal recommendations.

Strengths and limitations

The extensive literature search, the inclusion of very recent guidelines and the detailed quality assessment of included guidelines represent strengths of this review. Moreover, the assessment of different aspects of CMV infection represents another strength of this work.

The main limitations of this review include the inclusion of low-quality guidelines and the restriction to only English-written guidelines. Also, these guidelines were all published in different periods (despite only one before 2010): as the evidence changes (i.e. in terms of treatment with antiviral therapy), it is entirely plausible that these guidelines will be updated, hopefully sharing similar recommendations.

Conclusions

Although consensus was obtained regarding the diagnostic criteria for primary CMV infection in pregnancy, there is heterogeneity among Clinical Practice Guidelines in the timing of invasive testing for the diagnosis of fetal infection, ultrasound surveillance of infected fetuses, and further assessment

with fetal brain MRI. Treatment recommendations have shown a specific trend over the past few years, with the progressive inclusion of antiviral therapy in clinical practice.

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531 **Table 1.** Characteristics of included CPGs

	Authors	Scientific society	Year of publication (year of last update)	Country	Topic of interest	Methodology
1	Leruez-Ville et al.[23]	European congenital infection initiative (ECCI)	2024	Europe	Diagnosis, treatment, screening, primary and secondary prevention, neonatal follow-up	Systematic and comprehensive literature search of relevant databases including PubMed, Scopus, Cochrane library; expert consensus
2	Khalil et al.[24]	Royal College of Obstetricians and Gynaecologists (RCOG)	2023	UK	Diagnosis, treatment, screening	Search on available literature, original studies, review articles; expert opinion
3	Women's Health Commettee[25]	Royal Australian College of Obstetricians & Gynaecologists (RANZCOG)	2023	Australia/New Zealand	Prevention, screening, diagnosis, management	Consensus-based
4	Palasanthiran et al.[26]	Australasian Society for Infectious Diseases (ASID)	2022	Australia	Diagnosis, treatment, screening	Evidence and consensus-based
5	SA Maternal, Neonatal & Gynaecology Community of Practice[27]	South Australian Maternal, Neonatal & Gynaecology Community of Practice (SA)	2022	South Australia	Screening, diagnosis and counselling	Review of published evidence and expert opinions

6	Boucoiran et al.[28]	Society of Obstetricians and Gynecologists of Canada (SOGC)	2021	Canada	Prevention, screening, diagnosis, treatment	Systematic review of MEDLINE, EMBASE, and CENTRAL databases for CMV in pregnancy
7	Khalil et al.[6]	International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)	2020	International	Diagnosis, treatment, screening	Practice Guidelines and Consensus Statements developed by the the ISUOG Clinical Standards Committee (CSC)
8	Standards Units, National Infection Service[29]	UK Standards for Microbiology Investigations	2019	UK	Diagnosis	Developed by the Standards Unit, National Infection Service, Public Health England
9	Rawlinson et al.[30]	International Congenital Cytomegalovirus Recommendations Group	2017	International (Europe, USA and Australia)	Prevention, diagnosis, treatment	Consensus discussion and review of the literature
10	Hughes et al.[19]	Society of Maternal-Fetal Medicine (SMFM)	2016	USA	Diagnosis, management, screening	Search included national and international guidelines on the topic
11	Practice Bulletin[18]	American College of Obstetrics and Gynecologists (ACOG)	2015	USA	Diagnosis, management, counselling, screening	Search included original research, review articles, commentaries, Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists, expert opinions
12	Coll et al.[31]	World Association of Perinatal Medicine (WAPM)	2009	International	Prevention, screening, diagnosis, management	-

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534 **Table 2.** Synthesis of recommendations

CPG	Diagnosis of primary infection	Diagnosis of secondary infection	Diagnosis of fetal infection	Investigations in pregnancy	Treatment	Follow-up
ECCI[23]	- Positive CMV IgG and IgM with low avidity - Repeat avidity if intermediate - No need for testing for CMV PCR in blood and urine if IgG and IgM positive Test for CMV PCR in blood if only IgM positive (if positive, confirms primary infection)	no valid laboratory test to identify women with preexisting immunity at risk of fetal infection	CMV PCR in amniotic fluid collected from 17 + 0 weeks gestation, provided that maternal infection occurred at least 8 weeks earlier	- Negative amniocentesis: usual antenatal care - Positive amniocentesis for fetal infection: serial US and fetal brain MRI in the third trimester	- administration of oral valacyclovir at a dose of 8 g/day in cases of maternal primary infection in the periconceptional period or the first trimester of pregnancy, as early as possible after the diagnosis and until the result of the CMV PCR in amniocentesis - recommend against the administration of hyperimmune globulin (100 IU/kg every 4 weeks) in primary infection - Administration of hyperimmune globulin at dose of 200 IU/kg every 2 weeks, in women with very recent primary CMV infection in the first trimester may be considered In case of confirmed fetal infection, fetal treatment with valacyclovir 8 g/day may be considered after discussion with an expert team	-

RCOG[24]	- CMV IgG seroconversion - Positive CMV IgM, positive IgG, and low IgG avidity	Only possible when fetal infection is diagnosed	PCR on amniotic fluid; amniocentesis to be performed >17 weeks of gestation, 6-8 weeks after maternal infection	- Serial US surveillance every 2–3 weeks until birth, with detailed assessment of the fetal brain (in confirmed and non-confirmed fetal infections) - Fetal brain MRI at 28-32 weeks (repeated if necessary) - Consider fetal blood samples for platelet count -	- Oral valaciclovir following primary infection in the first trimester - Treatment with Hyperimmune globulin (HIG) not routinely recommended -	Every 2-3 weeks
RANZCOG[25]	- New appearance of CMV IgG in a previously seronegative woman - Positive IgM with low IgG avidity	Possible with positive IgG and IgM and high IgG avidity	CMV PCR on amniocentesis performed after 21 weeks, >8 weeks after infection	- Serial US surveillance and MRI recommended in case in case of positive amniocentesis	- No recommended treatment to prevent fetal infection	-
ASID[26]	- Seroconversion or rise in IgG - Positive CMV IgG and IgM and low or intermediate avidity	-	Amniocentesis (CMV PCR) to be performed 6 weeks after infection, >21 weeks of gestation	- Fetal US - Fetal MRI to consider in case of confirmed fetal infection - Fetal blood sampling not recommended	- Use of CMV immunoglobulin not routinely recommended; can be considered in case of infected fetus - Valaciclovir not routinely recommended but can be considered in primary infection	-

SA[27]	- Seroconversion or rise in IgG titre - Positive IgG and IgM, low or intermediate IgG avidity	-	Amniocentesis >21 weeks, after 6-8 weeks following infection	- Serial fetal US - Consider MRI in addition to fetal US	- Valaciclovir may be offered if amniocentesis for CMV PCR after 21 weeks gestation is positive, after fetal medicine and paediatric infectious disease subspecialist consultation	-
SOGC[28]	- Positive CMV IgG result in a person with previous documentation of a negative test result (seroconversion) - Combination of CMV IgM, CMV IgG, and CMV IgG avidity (where available)	Positive IgG (raising titre), positive IgM and high IgG avidity Or Positive IgG (raising titre), negative IgM and high IgG avidity	Gold standard is positive CMV PCR test on amniocentesis at least 8 weeks after maternal infection	- Fetal US - No strong recommendation on MRI	- CMV hyperimmune globulin should not be used to prevent congenital CMV in case of primary infection - In the case of primary infection in the first trimester, early treatment with valacyclovir can be considered	-
ISUOG[6]	- CMV-specific IgG in a woman who was previously seronegative; - detection of CMV IgM antibody and low IgG avidity	Only possible when fetal infection is diagnosed	CMV DNA on PCR analysis of the amniotic fluid. Amniocentesis should be performed at least 8 weeks after estimated time of maternal infection and after 20gestational weeks	- detailed ultrasound follow-up (every 2–4weeks) for the remainder of the pregnancy - Consider fetal brain MRI at 28-32 weeks - Fetal platelet count to be considered only in intermediate prognostic group, in case of normal US and mother wishing more information	- high-dose valaciclovir not routinely recommended (only in context of research) - CMV-specific hyperimmune globulin (HIG) not routinely recommended (only in context of research)	Every 2-4 weeks

UK Standards for Microbiology Investigations[29]	- Positive IgG and IgM, low or intemediate IgG avidity - Refer to earlier antenatal serum if available	Possible if IgG and IgM positive and high IgG avidity	CMV PCR with amniocentesis >21 weeks, at least 6 weeks earlier	-	-	-
International Congenital Cytomegalovirus Recommendations Group[30]	- Seroconversion in previously seronegative woman - Positive IgG, IgM and low or moderate IgG avidity	-	CMV PCR on amniotic fluid (amniocentesis at 20-21 weeks, at least 6 weeks from infection	-	CMV hyperimmunoglobulin or antiviral treatment not recommended to prevent fetal infection in infected mothers or to treat fetal infection	-
SMFM[19]	- CMV IgG seroconversion - Positive CMV IgM, positive IgG, and low IgG avidity	-	PCR on amniotic fluid; amniocentesis to be performed >21 weeks of gestation, 6 weeks after maternal infection	- MRI not recommended in clinical practice	- Treatment with ganciclovir or valacyclovir not recommend - any antenatal therapy, either with antivirals or CMV hyperimmune globulin, only to be offered as part of a research protocol -	-
ACOG[18]	- Seroconversion from negative to positive or a significant increase (greater than fourfold) in anti-CMV IgG titers	-	Culture or PCR on amniotic fluid; amniocentesis to be performed >21 weeks of gestation	Serial US surveillance (assessment of fetal anatomy and growth)	- Antiviral medications such as ganciclovir, valganciclovir, and foscarnet recommended only in patients with acquired immunodeficiency syndrome (AIDS) or organ transplants	-

	- Low IgG avidity combined with IgM titers				- Antivirals are not not recommended in routine clinical care - CMV-specific hyperimmune globulin is not recommended	
WAPM[31]	IgG seroconversion (*de novo* appearance of IgG in the serum of a pregnant woman previously seronegative) Positive IgG and IgM, low IgG avidity	-	PCR in amniotic fluid (amniocentesis >21 weeks, at least 5-6 weeks after infection)	Fetal blood sampling should not be performed for diagnosis; can be considered to assess prognosis Fetal US to assess brain anatomy MRI at 32-34 weeks can be considered	Antivirals and intravenous CMV hyperimmune globulin: very promising but currently their use not is not recommended outside randomized controlled trials	-

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536 Table 3. AGREE II assessment

Guideline		Domain (%)							
Scope and purpose	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity and presentation	Applicability	Editorial independence	Overall assessment	Domains >60%	Quality
ECCI[23]	100%	70%	93%	100%	83%	100%	85% Y:2	6	High

RCOG[24]	97%	89%	86%	100%	96%	75%	100% Y:2	6	High
RANZCOG[25]	100%	94%	83%	100%	98%	100%	100% Y:2	6	High
ASID[26]	100%	80%	53%	100%	58%	42%	42% Y:1 YwM:1	3	Moderate
SA[27]	100%	78%	63%	100%	83%	71%	71% Y:2	6	High
SOGC[28]	100%	100%	96%	100%	98%	100%	100% Y:2	6	High
ISUOG[6]	100%	89%	85%	100%	83%	100%	100% Y:2	6	High
UK Standards[29]	100%	80%	87%	100%	96%	83%	71% Y:2	6	High
International CMV recomm group[30]	100%	86%	84%	92%	74%	54%	71% Y:1 YwM:1	5	Moderate

SMFM[19]	78%	64%	71%	100%	87%	100%	71% Y:2	6	High
ACOG[18]	69%	72%	82%	100%	72%	54%	41% YwM:2	5	Moderate
WAPM[31]	8%	39%	17%	100%	35%	100%	14% N:2	2	Low

Y: yes (number of appraisers that have given that recommendation; YwM: Yes with modifications)

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