Slovenian **Medical** Journal

Citomegalovirus infection in pregnancy

Okužba s citomegalovirusom v nosečnosti

Sara Vodopivec,[1] Miroslav Petrovec,[2] Lili Steblovnik[3]

Abstract

Cytomegalovirus (CMV) is the most common viral cause of *in utero* foetal infection. The virus is neurotropic, so it mainly causes neurological complications. It represents the most common non-genetic cause of sensorineural hearing loss, neurological abnormalities, and mental retardation, and is the cause of prematurity, intrauterine foetal death and neonatal mortality. The infection is confirmed by detecting CMV-specific IgM and IgG antibodies, and IgG antibody avidity is used for determining the onset of infection. The presence of the virus is detected by PCR. Congenital infection is the result of viraemia during primary or secondary maternal infection. An intrauterine infection may present itself with characteristic ultrasound features. Prenatal diagnosis of congenital CMV infection is carried out by amniocentesis. Up to 15% of infants of mothers with a confirmed infection during pregnancy are symptomatic at birth. In symptomatic newborns, 40-60% suffer permanent sequelae, the most common of which is sensorineural hearing loss. Counseling a pregnant woman with primary CMV infection is difficult as we cannot accurately predict the foetal outcome based on the currently available data and research results. Estimates of the severity of the infection and possible consequences are based primarily on the timing of the infection, the presence and type of foetal abnormality, and on laboratory parameters. Routine treatment of pregnant women with confirmed CMV infection with the virostatic valacyclovir or with hyperimmune globulins is not recommended in the absence of sufficient evidence of their effectiveness. All pregnant women should be informed about the risks of CMV infection and the preventive measures to protect themselves against CMV infection in pregnancy. The review article summarizes the known facts regarding screening, diagnosis and treatment of cytomegalovirus infection in pregnancy, citing the latest findings and evidence, and presents an adaptation of foreign guidelines for good clinical practice in Slovenia.

Izvleček

Citomegalovirus (CMV) je najpogostejši virusni vzrok okužbe ploda v maternici. Virus je nevrotropen, zato povzroča predvsem nevrološke zaplete. Je najpogostejši negenetski vzrok senzorinevralne naglušnosti, nevroloških nepravilnosti in umske zaostalosti, hkrati je vzrok tudi za nedonošenost, smrt ploda v maternici in umrljivost novorojenčkov. Okužbo s CMV

[1] Division of Gyneacology and Obstetrics, University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3] Department of Perinatal Medicine, Division of Gyneacology and Obstetrics , University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence / Korespondenca: Lili Steblovnik, e: lili.steblovnik@mf.uni-lj.si

Key words: seroconversion; fetal infection; antiviral agents; hyperimmune globulin; screening

Ključne besede: serokonverzija; okužba ploda; protivirusna zdravila; hiperimuni globulini; presejanje

Received / Prispelo: 20. 1. 2021 | **Accepted / Sprejeto:** 1. 4. 2021

Cite as / Citirajte kot: Vodopivec S, Petrovec M, Steblovnik L. Citomegalovirus infection in pregnancy. Zdrav Vestn. 2022;91(3–4):161–72.
DOI: https://doi.org/10.6016/ZdravVestn.3220

potrjujemo z dokazom za CMV specifičnih protiteles IgM in IgG. Prisotnost virusa dokazujemo s PCR. Za časovno opredelitev okužbe s CMV določamo avidnost protiteles IgG. Prirojena okužba je posledica viremije ob primarni ali sekundarni okužbi nosečnice. Ob znotrajmaternični okužbi so lahko prisotni značilni ultrazvočni znaki. Prenatalna diagnoza prirojene okužbe s CMV se postavi z amniocentezo. Simptome ob rojstvu ima do 15 % otrok mater s potrjeno okužbo v nosečnosti. Pri novorojenčkih s simptomi pride v 40–60 % do trajnih posledic, od katerih je najpogostejša senzorinevralna naglušnost. Svetovanje nosečnici s primarno okužbo s CMV je težavno, saj po doslej razpoložljivih podatkih in izsledkih raziskav izida za plod še ne znamo natančno napovedati. Ocene resnosti okužbe in možnih posledic temeljijo predvsem na časovni opredelitvi okužbe nosečnice, prisotnosti in vrsti nepravilnosti pri plodu in laboratorijskih parametrih. Rutinsko zdravljenje nosečnic s potrjeno okužbo s CMV z virostatikom valaciklovirjem ali s hiperimunimi globulini se zaradi pomanjkanja zadostnih dokazov o učinkovitosti ne priporoča. Vse nosečnice bi morale biti seznanjene o nevarnostih okužbe s CMV in preventivnih ukrepih za zaščito pred okužbo s CMV v nosečnosti. Pregledni članek povzema znana dejstva glede presejanja, diagnosticiranja in zdravljenja okužbe s CMV v nosečnosti z navajanjem najnovejših spoznanj in dokazov ter predstavlja prilagoditev tujih priporočil za dobro klinično prakso v Sloveniji.

1 Introduction

1.1 Cytomegalovirus (CMV)

Cytomegalovirus (CMV) or Human Herpesvirus 5 (HHV-5) belongs to the family of human herpesviruses, which are characterised by their ability to establish permanent (latent) infection after recovering from acute primary infection. It is most commonly transmitted through saliva and contact with contaminated objects (among children), semen and vaginal secretions (among adults), and has also been isolated from urine, faeces, breast milk, blood, and tears. Transmission by blood transfusion or transplantation of infected organs is also possible (1,2). The primary infection is systemic. The virus multiplies in salivary glands, kidneys, and the respiratory tract, and the latent phase is presented by the virus load in the bone marrow. It causes characteristic cytopathic effects with swelling and fusion of cells and the formation of multinucleated giant cells (2,3).

CMV is the most common viral cause of *in utero* foetal infection, i.e. congenital infection in the developed world. It occurs in 0.2–1.3% of live births (4). It is the most common non-genetic cause of sensorineural hearing loss, neurological abnormalities, and mental retardation. It is the cause of prematurity, foetal death *in utero*, and neonatal mortality. As such, it represents a major social, health, and economic burden on society (4-9).

1.2 Epidemiology

CMV is present all over the world and has no characteristic pattern of occurrence. The seroprevalence in women of childbearing age is higher in developing countries (2,8). A German study found that seroprevalence in women of childbearing age was 51.7% of (10).

According to the data of Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, CMV seroprevalence in Slovenian pregnant women was 70–80% in 2005 and 2006 (2). In a study in two maternity hospitals in eastern Slovenia, the incidence of new-borns with congenital CMV infection was approximately 0.14% (11). In the developed world, the prevalence of congenital CMV infection is 0.64% (4).

1.3 Primary and secondary infection

The primary infection occurs upon first contact with the virus and is dangerous if it occurs during pregnancy. The incidence of primary infection in pregnancy is 0.64–4% (4,8,12).

The virus can reactivate later on, called a recurrent or secondary infection, and this also can cause morbidity and mortality in the foetus or new-born (2,13). Secondary infection (with pre-existing immunity to CMV) can also occur with another strain of CMV virus. The risk of CMV infection in pregnancy and the sequelae of the infection are shown in Figure 1.

1.4 Clinical picture in immunocompetent adults

The majority (90%) of healthy adults and preschool children with primary CMV infection have no symptoms or sequelae. The virus is excreted in saliva and urine for a long time after infection. In some, the infection manifests itself as a mononucleosis-like syndrome after four to eight weeks of incubation, with malaise, fever, muscle aches, swollen cervical lymph nodes, enlarged liver or spleen, with a third suffering from uncharacteristic skin rash. Liver tests may be slightly elevated and

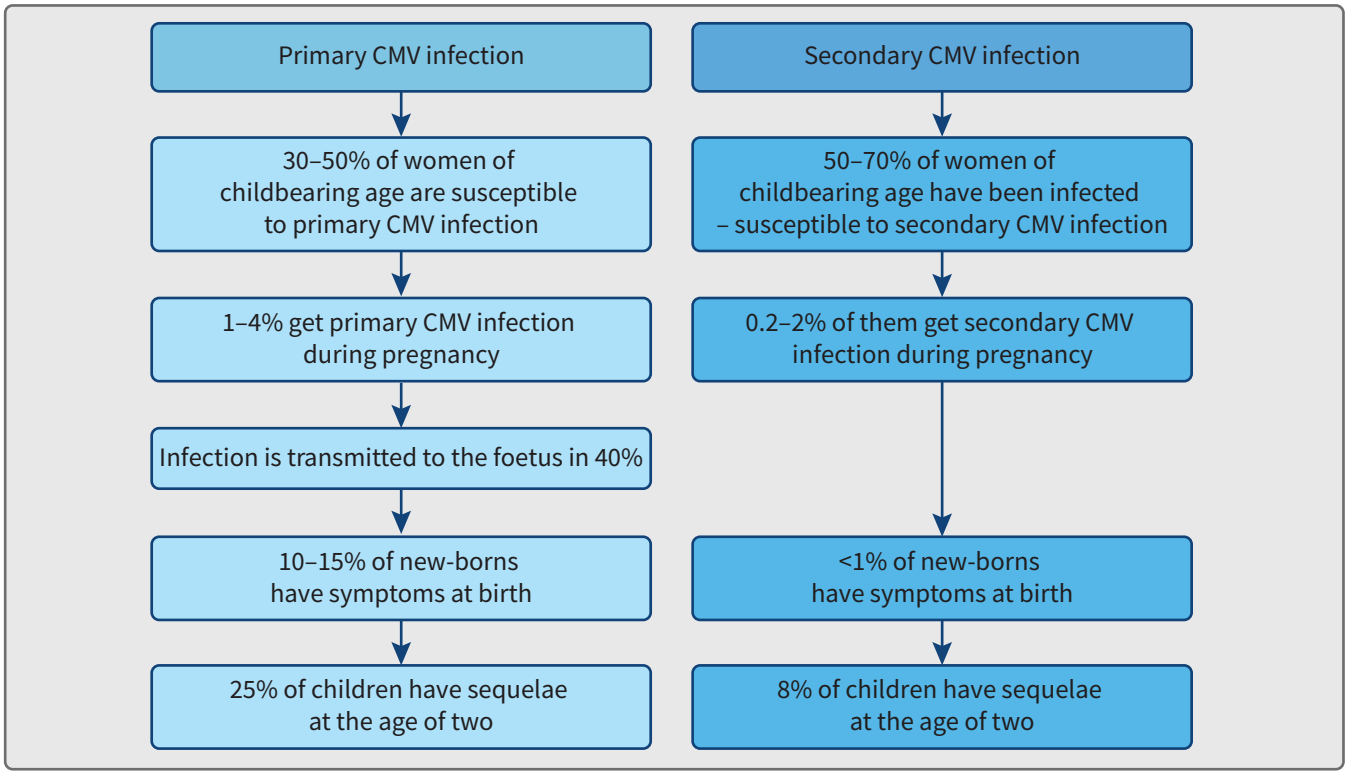

Figure 1: Risk of cytomegalovirus infection of a pregnant woman and foetus. Taken from SMFM. Congenital CMV diagnosis and antenatal management. Am J Obstet Gynecol 2016 (45).
Legend: CMV – cytomegalovirus.

lymphocytosis may be present. It is mostly a mild disease with no serious complications (2,14,15).

1.5 Clinical picture in pregnant women

About 20% of pregnant women with primary infection have symptoms (16). Usually it is a flu- or an infectious-mononucleosis-like syndrome with fever (the most pronounced sign of the disease), fatigue, muscle aches, enlarged cervical lymph nodes, sore throat, headache, enlarged liver or spleen (though rarely), hepatitis, pneumonia, skin rash, or gastrointestinal symptoms. Lymphocytosis (in 30–50%) and slightly elevated aminotransferases (in 40%) may stand out in laboratory results (15,17).

1.6 Diagnosis of cytomegalovirus infection

There should be close cooperation between a clinician and a microbiologist for confirming CMV infection in pregnancy: an agreement needs to be reached on the best time for taking the sample, correct collection and type of sample, storage and transportation of the sample for examination according to the evidence-based method, and to correctly interpret the results (18).

1.6.1 Serological testing

For most viral infections, evidence of seroconversion (that is, the appearance of specific IgM antibodies that are an acute response of the immune system to infection), is appropriate to confirm the primary infection. However, in the case of CMV infection, the following should be borne in mind:

- IgM antibodies may persist in serum for several months after primary CMV infection;
- Specific IgM antibodies may occur with secondary CMV infection;
- Cross-reactivity and CMV-specific IgM antibodies may occur due to another viral infection (e.g. Epstein-Barr virus infection);
- IgM antibodies may occur with non-specific polyclonal activation of the immune system (17,19,20).

Therefore, to estimate the timing of IgM-positive CMV infection, we also test the avidity of IgG antibodies that form later during the course of infection. If the IgG antibodies are negative, it is cross-reactivity and not CMV infection. A high IgG antibody avidity index (above 60%), which indicates a high antibody capacity to

bind to CMV antigen, is very likely to be associated with old (more than three months) or secondary infection. A low avidity index (below 30%) is more likely to indicate a fresh – primary infection (in the last three months) (17,21,22).

1.6.2 Confirmation of infection

Proof of viral genome by polymerase chain reaction (PCR) is used to confirm infection (18).

2 Congenital infection

The incidence of congenital CMV infection in Western Europe, Canada, the United States and Australia is approximately 5–7/1,000 live births (23). Congenital infection is the result of viraemia during primary or secondary maternal infection, leading to placental infection and transmission of the virus through the placenta to the foetus, which occurs within four to eight weeks after the onset of viraemia (15,24).

2.1 Probability of congenital infection

The possibility of transmission to the foetus is higher with primary infection in pregnancy and increases with the duration of pregnancy:
- infection in the first trimester: 30–42%;
- infection in the second trimester: 38–44%;
- infection in the third trimester: 59–73% (7,24).

In secondary infection, the overall risk of infection of the foetus is low, 0.15–2%, but it can also be manifested by symptoms. As the population of seropositive women is large, more congenital infections occur in these pregnant women (13,25-28).

2.2 Symptoms and signs of congenital infection

In 85–90% of congenital infections, new-borns have no symptoms. Up to 15% of infected children have symptoms at birth, most of which occur during the primary infection of a pregnant woman in the first trimester of pregnancy. Mortality of new-borns with symptoms is 5–15% (25).

The virus is neurotropic, therefore causing mainly neurological complications (1). In new-borns with symptoms, 40–60% have permanent sequelae, the most common of which is sensorineural hearing loss (27,29).

Typical signs of congenital infection, that may be transient, are the following:
- small for gestational age;
- microcephaly;
- hepatomegaly;
- splenomegaly;
- petechiae;
- jaundice;
- thrombocytopenia;
- anaemia (17,30,31).

The long-term severe sequelae of congenital CMV infection are the following:
- sensorineural hearing loss;
- mental retardation;
- cerebral paralysis;
- visual impairment;
- epileptic seizures;
- cerebral or cerebellar atrophy and other disorders of neurological development (23,32-34).

However, when an infection occurs in the third trimester, new-borns rarely have symptoms (16,23,24,34). The risk of severe neurological sequelae decreases with the duration of pregnancy (16,24,34).

In new-borns with asymptomatic infection, neurological and developmental abnormalities occur in 15–25% of cases later in childhood, most often sensorineural hearing loss, less often psychomotor retardation, cognitive deficits, seizures, and visual impairment (2,27,33,35). A long-term prospective study of the association between congenital CMV infection showed an incidence of hearing loss in 12.7% of infected children. Hearing impairment is more common in cases of primary CMV infection in pregnant women in the first trimester and when signs of foetal or neonatal infection were seen by ultrasound (US) or magnetic resonance imaging (MRI) (36). Children with late sequelae of congenital infections account for the majority of the disease burden of congenital CMV infection (37).

3 Prenatal diagnosis

Testing a pregnant woman for CMV infection is in place in the case of:
- acute symptoms characteristic of a virus or a mononucleosis syndrome;
- foetal abnormalities, detected by ultrasound, characteristic of CMV infection (38,39).

3.1 Signs of cytomegalovirus infection on ultrasound

The positive predictive value of the ultrasound examination for the prognosis of congenital infection is 35% (38). Ultrasound signs are non-specific and present in less than 50% of infected foetuses (38,40). The most common are the following (frequency of occurrence, %):

- calcifications in the central nervous system, mainly periventricular (0.6–17.4);
- microcephaly (14.5);
- hyperechogenic bowel (4.5–13);
- intrauterine growth restriction (IUGR) (1.9–13);
- cerebral ventriculomegaly (4.5–11.6);
- ascites (8.7);
- pericardial effusion (7.2);
- hepatomegaly (4.3);
- hydrops foetalis (0.6);
- placentomegaly (4.3);
- calcifications in the liver;
- polymicrogyria;
- cerebellar hypoplasia (16,38,41).

3.2 Serological testing

The primary maternal CMV infection can be confirmed:

- by seroconversion – evidence of de novo appearance of CMV-specific IgG antibodies – gold standard (two serum samples, past and present, required);
- with evidence of CMV-specific IgM antibodies with concomitant low avidity of IgG antibodies (21,39,42).

To identify the infection, microbiological laboratories often use serums taken earlier for screening for toxoplasmosis, syphilis or hepatitis B, which have been archived for at least one year (43).

3.3 Magnetic Resonance Imaging (MRI) of the foetus

In the presence of ultrasound signs of central nervous system (CNS) abnormalities, an additional diagnostic method is MRI (44). In foetuses with confirmed infection, the use of ultrasound and MRI is 95% sensitive to the detection of structural abnormalities of the CNS. If the MRI result is within normal limits, the outcome is generally good for the foetus. However, a normal MRI of the foetal head does not reliably predict a good neurological development for the foetus, as sensorineural hearing loss in the case of congenital CMV infection is developing progressively (45,46).

3.4 Confirming foetal infection

Prenatal diagnosis of congenital CMV infection is confirmed by amniocentesis to prove viral DNA in amniotic fluid by PCR (42,47,48). For optimal sensitivity of the method, it is important to perform amniocentesis six to eight weeks after the onset of maternal infection/after proven seroconversion (thus allowing time for sufficient replication of the virus in the infected foetus and its excretion in the foetal urine) and after the 20th week of pregnancy, when the foetal urination is established (17,42,47).

Amniocentesis to prove infection should be performed in pregnant women with primary CMV infection. In pregnant women with secondary infection, there is no consensus on whether confirmation of foetal infection is reasonable, as the risk of transmitting the infection to the foetus is very low. However, the literature does also describe cases of severe sequelae for the foetus in the case of secondary maternal infection, so amniocentesis should be considered in these cases as well (49,50).

If performed within the recommended time window, a negative PCR result for CMV is 97–100% sensitive (47,51). If the test is performed earlier than recommended, the likelihood of a false-negative outcome is higher (20). In the absence of ultrasound signs of infection and a negative amniocentesis result, the likelihood of infection with symptoms and neurological sequelae in these new-borns is significantly lower (52). According to the data available so far, quantitative determination of DNA for CMV in the amniotic sac is not relevant for predicting the outcome of the disease (53).

The main limitation of prenatal diagnosis of congenital CMV infection is that confirmation of infection cannot predict whether a new-born will have symptoms and whether he or she will develop late neurological sequelae (45,53,54).

3.5 Confirmation of infection after birth

To prove congenital infection, the gold standard is to isolate the virus and its DNA from the urine of the new-born taken in the first three weeks after birth (2,17,55). It is also possible to confirm viral DNA in dried blood samples on paper cards taken for screening for detecting metabolic diseases, but this method is less sensitive than detecting the virus from a fresh sample (42). Children

under the age of two excrete the virus in saliva and urine for an average of 24 months and can thus be an important source of infection for their surroundings (56).

4 Prevention of cytomegalovirus infection in pregnancy and prevention of its sequelae

4.1 Screening

Various international recommendations do not recommend routine CMV screening of pregnant women because:

- there is no effective vaccine to prevent infection in seronegative women;
- in seropositive pregnant women, it is difficult to distinguish between primary and secondary infection;
- seropositive women are not protected against infection and may experience reactivation of the virus or become infected with another strain, which can also lead to a congenital infection;
- we do not have a proven effective treatment that could be offered to pregnant women;
- despite the proven infection of the foetus, the sequelae for its health cannot be predicted;
- routine screening could lead to unnecessary, potentially harmful, measures (3,45,53).

In some countries, despite clear recommendations, screening is carried out in some centres (57). In France, screening was carried out by 14% of hospitals in 2012 (58). In Germany, recommendations for the diagnosis of viral infections in pregnancy are followed, which recommend screening in early pregnancy for women at high risk of CMV infection due to occupational or family exposure to young children (59).

4.2 Primary prevention – prevention of cytomegalovirus infection in pregnancy

Research has shown that consistent counselling on the importance of preventing CMV infection in pregnancy reduces seroconversion rates in previously seronegative pregnant women (54). As contact with the bodily secretions of young children is the greatest risk for women of childbearing age, preventive hygiene measures to prevent primary infection in pregnant women and thus congenital CMV infections are essential (60).

Pregnant women should avoid contact with the saliva, urine and tears of children. It is important they wash their hands regularly with soap and water after contact with body secretions, to avoid kissing pre-schoolers on the mouth, to not share food, drinks, cutlery with children, and to regularly clean toys and other surfaces that come in contact with the bodily secretions of children (23,54,60).

4.3 Secondary prevention – prevention of transmission of infection from a mother to the foetus and treatment of foetal infections during pregnancy

When maternal infection is confirmed, the goal is to prevent the transmission of the infection to the foetus (3). In recent years, the possibilities of treatment with immunotherapy and virostatics have been intensively studied.

4.3.1 CMV-specific hyperimmune globulins (HIG)

At the time of primary infection, the pregnant woman has no developed effective antibodies to prevent transmission of the infection to the foetus. A promising method of treatment is passive immunisation, this is intravenous injection of high doses of highly avid CMV-specific antibodies – hyperimmune globulins (HIG) (7).

The results of observational and randomised studies do not yet support the routine use of HIG to treat pregnant women with primary CMV infection. For now, the decision to treat with HIG is made individually and for research purposes (17,31).

In a review article on the treatment of CMV infection in pregnancy, Rawlinson et al. analysed the data from research showing that there is a trend towards the effectiveness of HIG administration in preventing foetal transmission and treating foetal infection (61). A large randomised prospective study is underway in the United States to evaluate the effectiveness of HIG in reducing the transmission of primary CMV infection in pregnancy to the foetus, which could provide acceptable answers regarding the use of HIG in primary CMV infection in pregnancy (clinicaltrials.gov: NCT01376778). However, according to the published protocol, lower doses of HIG (100 IU/kg) are used in this study and only once a month, which is contrary to the pharmacokinetic findings of Kagan et al. This could be reflected in underestimating the results of the study or lower efficacy of HIG compared to a dose of 200 IU/kg every 14 days (3).

Based on the data available in the literature, the manufacturer of HIG (Cytocect ® CP) recommends:

- "off-label use" of HIG in pregnancy to prevent infection of the foetus, as experts only recommend it in

research situations;
- informing the manufacturer of the intention to use Cytotect to treat a pregnant woman;
- the manufacturer records the use of Cytotect during pregnancy and is available to assist with treatment protocol decisions.

4.3.2 Virostatics

The only virostatic that does not cause teratogenic and toxic effects is valaciclovir, which has poor effect against CMV (17). To date, two studies have been published examining the efficacy of antiviral therapy with valaciclovir (62). The use of valaciclovir (8g daily) was associated with a significantly higher proportion of asymptomatic new-borns with congenital infection compared with the historical cohort (62). A major randomised study is currently underway to evaluate the effectiveness of valaciclovir in the transmission of primary CMV infection from a pregnant woman to the foetus. Routine prenatal treatment with valaciclovir is not recommended due to lack of evidence of efficacy (31,45).

4.3.3 Vaccine

Despite active research, the CMV vaccine is not yet available (3). The problem with doing research on a suitable vaccine is the fact that even new-borns of seropositive mothers (with pronounced immunity to CMV) may develop symptomatic infection and have long-term neurological sequelae.

4.4 Tertiary prevention – treatment of new-borns with confirmed congenital cytomegalovirus infection

New-borns with symptomatic congenital CMV infection should be treated, as research has shown that antiviral therapy reduces or prevents the progression of hearing loss and improves long-term neurodevelopmental sequelae (63). The treatment of choice is oral valganciclovir, but if the new-born is receiving parenteral feeding, ganciclovir is given intravenously. The drugs act virostatically; they prevent viral replication by inhibiting viral DNA synthesis. The treatment should be started within the first month after birth. The recommended duration of treatment is from six weeks to six months, depending on the severity of symptoms. Children treated for congenital CMV infection should be monitored by audiologists and ophthalmologists until the age of six (37,63).

5 Management of a pregnancy, complicated with cytomegalovirus infection

Councelling to a pregnant woman with CMV infection is complex as we cannot accurately predict the foetal outcome based on currently available data and research results.

Estimates of the severity of the infection and the possible sequelae are based primarily on:
- the timing of a maternal infection;
- the presence and type of foetal anomalies;
- laboratory parameters (17).

Once foetal CMV infection has been confirmed, regular ultrasound examinations every two to four weeks are required to monitor for signs of CMV infection in the foetus (17,53). Based on current knowledge, the most important ultrasound predictor for predicting foetal status seems to be the presence of brain abnormalities (64,65).

RCOG proposes to divide foetuses with confirmed congenital infection into three prognostic categories, according to the ultrasound report (17):
1. Asymptomatic foetuses – without symptoms no ultrasound abnormalities are found, MRI of the CNS is normal. The prognosis is good, there is only the possibility of sensorineural hearing loss.
2. Foetuses with mild to moderate symptoms – no ultrasound abnormalities of the CNS, with the presence of other individual ultrasound abnormalities. The prediction of the outcome is uncertain, so it is necessary to continue ultrasound and MRI monitoring for a better prediction of the outcome. It can be explained to the parents that there is no unequivocal evidence of the effectiveness of the treatment, but we can offer treatment. It is necessary to talk about the possibility of terminating the pregnancy.
3. Foetuses with severe symptoms – with ultrasound abnormalities of the CNS. The prognosis of the outcome is extremely poor. A pregnant woman has the option to decide to terminate the pregnancy (17,53).

Leruez-Ville et al. tried to predict the risk of neurological sequelae in congenital infection based on ultrasound findings, dividing them into three categories:
- severe CNS abnormalities (microcephaly, severe ventriculomegaly >15 mm);
- mild CNS abnormalities (borderline ventriculomegaly);
- ultrasound findings outside the CNS (hyperechogenic bowel, hepatomegaly, IUGR).

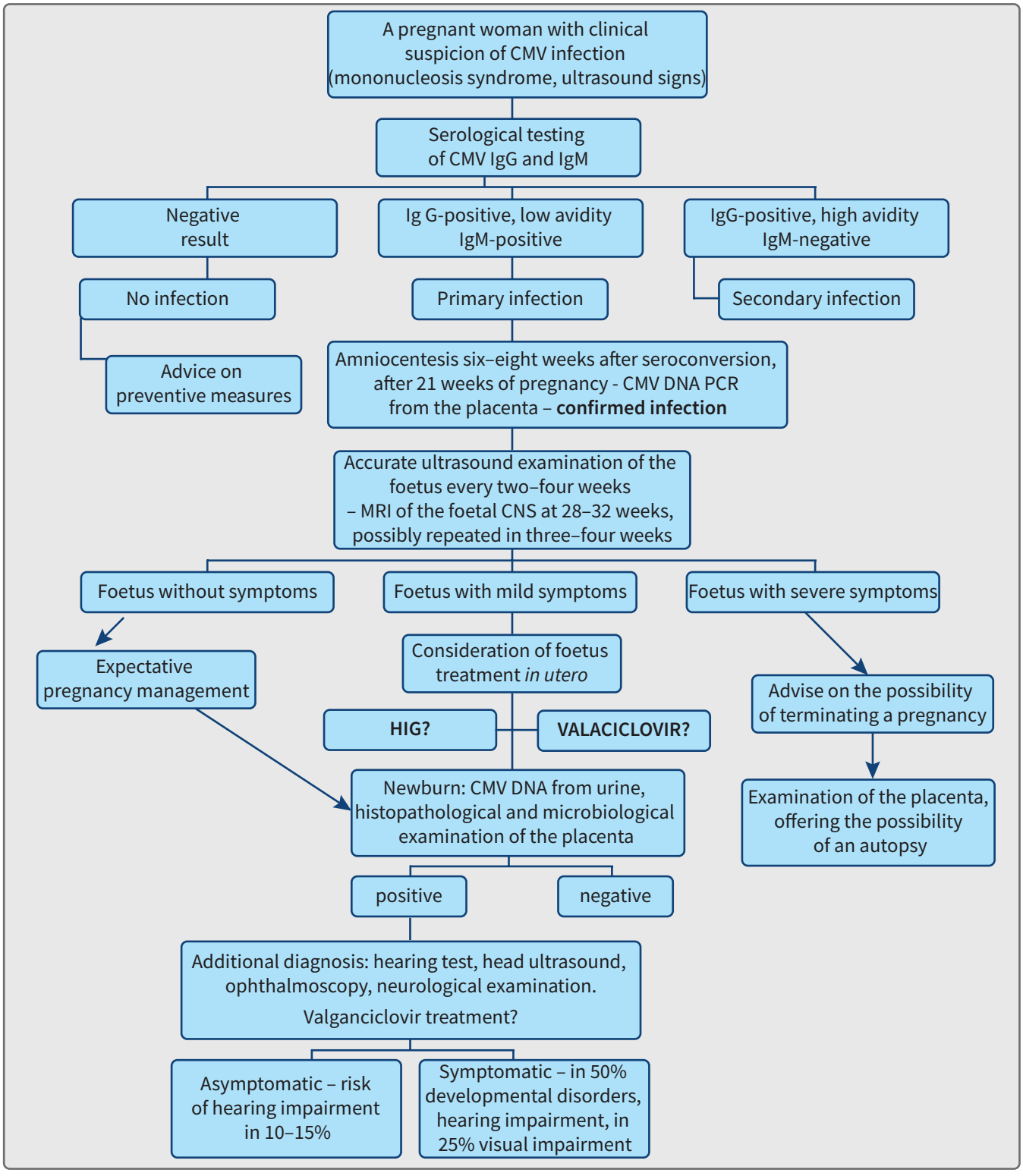

Figure 2: Scheme of intervention in case of established primary cytomegalovirus infection in pregnancy. Taken from RCOG 2018, Tanimura 2019 (18,39).

Legend: CMV – cytomegalovirus; MRI – magnetic resonance imaging; CNS – central nervous system; HIG – human immunoglobulin.

The results have shown that women from the first group most often terminated the pregnancy. In the second group, the probability of giving birth to a new-born with symptoms was 60%, and in the case of the third group this possibility was 10% (66).

Women with CMV infection during pregnancy can breast-feed, as most new-borns will be infected with the virus sooner or later, and most will be asymptomatic (67).

6 Recommendations for good clinical practice in the treatment of primary cytomegalovirus infection in pregnancy

The recommendations are taken from (17,31,45,53). The recommended action scheme is summarised in Figure 2.

6.1 Prevention of congenital cytomegalovirus infection

- All pregnant women should be informed about the dangers of CMV infection and about preventive measures for protection against CMV infection during pregnancy.
- Routine screening of pregnant women for CMV infection with serological testing is not recommended.
- Seronegative pregnant women who work with children (in kindergartens, in health care) may be offered serological monitoring during pregnancy in the future. Seronegative pregnant women who have children in kindergarten could also be serologically monitored.

6.2 Diagnosis of primary infection in pregnancy

Serological testing of pregnant women for CMV infection is performed in cases where the pregnant woman suffers from mononucleosis-like symptoms and signs that cannot be explained otherwise, or when ultrasound examination of the foetus reveals abnormalities characteristic of congenital CMV infection which also cannot be explained otherwise.

- The diagnosis of primary infection in pregnancy is made on the basis of confirmed seroconversion – the occurrence of CMV-specific IgG antibodies in the serum of previously seronegative pregnant women – or when there is evidence of CMV-specific IgM antibodies in the presence of low-avidity IgG antibodies.
- The diagnosis of secondary infection is made with a significant increase in IgG antibody titre with or without the presence of specific IgM antibodies. Once secondary infection is confirmed, amniocentesis can be performed, but the likelihood of transmission to the foetus is lower than with primary infection, and the risk-benefit ratio of amniocentesis is lower than with primary infection.
- With the primary infection of the pregnant woman, parents should be informed that the possibility of transmission of the infection to the foetus is 30–40%, and the possibility of sequelae for the infected foetus is 20–25%.

6.3 Intervention

- Prenatal diagnosis of congenital CMV infection is made by amniocentesis, which is performed at least six weeks after the estimated time of primary maternal infection and after the 21st week of pregnancy.
- In the case of confirmed congenital CMV infection, regular ultrasound examinations of the foetus every two to three weeks before delivery are necessary in order to detect characteristic changes or abnormalities of the foetus, which can help us assess the prognosis of the outcome for the foetus. The absence of abnormalities visible with ultrasound is not a reliable predictor of a favourable course of infection (no symptoms).
- Diagnosis of CMV infection in the new-born and early monitoring of the child with the possibility of contracting CMV *in utero* (determination of viraemia through urine, check-ups at an infectologist, ENT, etc.).

6.4 Treatment

- Routine treatment of pregnant women with valaciclovir to prevent transmission of the infection to the foetus or to prevent sequelae in a foetus with confirmed infection is not recommended due to a lack of sufficient evidence of efficacy.
- Routine treatment of pregnant women with hyperimmune globulins to prevent transmission of the infection to the foetus or to prevent sequelae in a foetus with confirmed infection is not recommended due to a lack of sufficient evidence of efficacy.
- Treatment of a pregnant woman with antiviremics or hyperimmune globulins should be given careful consideration when the benefits outweigh the risks, although no reliable efficacy data are available.
- In cases of severe CNS abnormalities and poor prognosis, termination of pregnancy may be considered.

7 Conclusion

CMV is the most common cause of viral foetal infection *in utero* in the developed world and the most common nongenetic cause of sensorineural hearing loss. That is why pregnant women should be informed about preventive measures for protection against CMV infection during pregnancy. We should consider serological testing for CMV infectionin pregnancy in case of a characteristic maternal clinical picture (mononucleosis-like symptoms, unexplained hepatitis) or in case of ultrasound signs of foetal infection (calcification in the central nervous system, microcephaly, hyperechogenic bowel, foetal growth restriction). CMV foetal infection is confirmed by proving the presence of the virus in the amniotic fluid (amniocentesis) at least six weeks after the estimated time of primary maternal infection and after the 21st week of pregnancy. Drugs (virostatics and hyperimmune globulins) are available to prevent the transmission of infection to the foetus and for treatment, but due to lack of evidence of efficacy, they have not yet been accepted for routine use.

Conflict of interest

None declared.

References

1. Cheeran MC, Lokensgard JR, Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clin Microbiol Rev. 2009;22(1):99-126. DOI: 10.1128/CMR.00023-08 PMID: 19136436
2. Poljak M, Petrovec M. Medicinska virologija. Ljubljana: Medicinski razgledi; 2011.
3. Kagan KO, Sonek J, Hamprecht K. Antenatal treatment options for primary cytomegalovirus infections. Curr Opin Obstet Gynecol. 2018;30(6):355-60. DOI: 10.1097/GCO.0000000000000486 PMID: 30169462
4. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007;17(4):253-76. DOI: 10.1002/rmv.535 PMID: 17579921
5. Pultoo A, Jankee H, Meetoo G, Pyndiah MN, Khittoo G. Detection of cytomegalovirus in urine of hearing-impaired and mentally retarded children by PCR and cell culture. J Commun Dis. 2000;32(2):101-8. PMID: 11198394
6. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. Clin Infect Dis. 2013;56(9):1232-9. DOI: 10.1093/cid/cit018 PMID: 23334811
7. Nigro G. Hyperimmune globulin in pregnancy for the prevention of congenital cytomegalovirus disease. Expert Rev Anti Infect Ther. 2017;15(11):977-86. DOI: 10.1080/14787210.2017.1398081 PMID: 29072089
8. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013;26(1):86-102. DOI: 10.1128/CMR.00062-12 PMID: 23297260
9. Bristow BN, O'Keefe KA, Shafir SC, Sorvillo FJ. Congenital cytomegalovirus mortality in the United States, 1990-2006. PLoS Negl Trop Dis. 2011;5(4):e1140. DOI: 10.1371/journal.pntd.0001140 PMID: 21541359
10. Lachmann R, Loenenbach A, Waterboer T, Brenner N, Pawlita M, Michel A, et al. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS One. 2018;13(7):e0200267. DOI: 10.1371/journal.pone.0200267 PMID: 30044826
11. Paradiž KR, Seme K, Puklavec E, Paro-Panjan D, Poljak M. Prevalence of congenital cytomegalovirus infection in Slovenia: a study on 2,841 newborns. J Med Virol. 2012;84(1):109-15. DOI: 10.1002/jmv.22230 PMID: 22028094
12. Stagno S, Pass RF, Cloud G, Britt WJ, Henderson RE, Walton PD, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. JAMA. 1986;256(14):1904-8. DOI: 10.1001/jama.1986.03380140074025 PMID: 3020264
13. Wang C, Zhang X, Bialek S, Cannon MJ. Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. Clin Infect Dis. 2011;52(2):e11-3. DOI: 10.1093/cid/ciq085 PMID: 21288834
14. Cohen JI, Corey GR. Cytomegalovirus infection in the normal host. Medicine (Baltimore). 1985;64(2):100-14. DOI: 10.1097/00005792-198503000-00003 PMID: 2983175
15. Nigro G, Anceschi MM, Cosmi EV, Group CC; Congenital Cytomegalic Disease Collaborating Group. Clinical manifestations and abnormal laboratory findings in pregnant women with primary cytomegalovirus infection. BJOG. 2003;110(6):572-7. DOI: 10.1046/j.1471-0528.2003.01302.x PMID: 12798474
16. Picone O, Vauloup-Fellous C, Cordier AG, Guitton S, Senat MV, Fuchs F, et al. A series of 238 cytomegalovirus primary infections during pregnancy: description and outcome. Prenat Diagn. 2013;33(8):751-8. DOI: 10.1002/pd.4118 PMID: 23553686
17. Khalil A HP, Jones C, Soe A, Ville YG. Congenital cytomegalovirus infection: update on treatment. Microorganisms. 2020;8(10):1516. DOI: 10.3390/microorganisms8101516 PMID: 33019752
18. Revello MG, Gerna G. Pathogenesis and prenatal diagnosis of human cytomegalovirus infection. J Clin Virol. 2004;29(2):71-83. DOI: 10.1016/j.jcv.2003.09.012 PMID: 14747024
19. Revello Mg, Fabbri E, Furione M, Zavattoni M, Lilleríi C, Tassis B, et al. Role of prenatal diagnosis and counseling in the management of 735 pregnancies complicated by primary human cytomegalovirus infection: a 20-year experience. 2011;50(4):303-7. DOI: 10.1016/j.jcv.2010.12.012 PMID: 21277825
20. Lazzarotto T, Guerra B, Gabrielli L, Lanari M, Landini Mp. Update on the prevention, diagnosis and management of cytomegalovirus infection during pregnancy. Clin Microbiol Infect. 2011;17(9):1285-93. DOI: 10.1111/j.1469-0691.2011.03564.x PMID: 21631642
21. Grangeot-Keros L, Mayaux MJ, Lebon P, Freymuth F, Eugene G, Stricker R, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. J Infect Dis. 1997;175(4):944-6. DOI: 10.1086/513996 PMID: 9086155
22. Kanengisser-Pines B, Hazan Y, Pines G, Appelman Z. High cytomegalovirus IgG avidity is a reliable indicator of past infection in patients with positive IgM detected during the first trimester of pregnancy. J Perinat Med. 2009;37(1):15-8. DOI: 10.1515/JPM.2009.012 PMID: 18673093
23. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. Semin Perinatol. 2018;42(3):149-54. DOI: 10.1053/j.semperi.2018.02.002 PMID: 29503048

24. Enders G, Daiminger A, Bäder U, Exler S, Enders M. Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age. J Clin Virol. 2011;52(3):244-6. DOI: 10.1016/j.jcv.2011.07.005 PMID: 21820954
25. Gaytant MA, Rours GI, Steegers EA, Galama JM, Semmekrot BA. Congenital cytomegalovirus infection after recurrent infection: case reports and review of the literature. Eur J Pediatr. 2003;162(4):248-53. DOI: 10.1007/s00431-002-1115-5 PMID: 12647198
26. Mussi-Pinhata MM, Yamamoto AY, Aragon DC, Duarte G, Fowler KB, Boppana S, et al. Seroconversion for Cytomegalovirus Infection During Pregnancy and Fetal Infection in a Highly Seropositive Population: "The BraCHS Study". J Infect Dis. 2018;218(8):1200-4. DOI: 10.1093/infdis/jiy321 PMID: 29868783
27. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med. 1992;326(10):663-7. DOI: 10.1056/NEJM199203053261003 PMID: 1310525
28. Tanimura K, Tairaku S, Morioka I, Ozaki K, Nagamata S, Morizane M, et al. Universal Screening With Use of Immunoglobulin G Avidity for Congenital Cytomegalovirus Infection. Clin Infect Dis. 2017;65(10):1652-8. DOI: 10.1093/cid/cix621 PMID: 29020153
29. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. J Clin Virol. 2006;35(2):226-31. DOI: 10.1016/j.jcv.2005.09.016 PMID: 16386462
30. Pass RF, Arav-Boger R. Maternal and fetal cytomegalovirus infection: diagnosis, management, and prevention. F1000 Res. 2018;7:255. DOI: 10.12688/f1000research.12517.1 PMID: 29560263
31. Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017;17(6):e177-88. DOI: 10.1016/S1473-3099(17)30143-3 PMID: 28291720
32. Stagno S, Whitley RJ. Herpesvirus infections of pregnancy. Part I: cytomegalovirus and Epstein-Barr virus infections. N Engl J Med. 1985;313(20):1270-4. DOI: 10.1056/NEJM198511143132006 PMID: 2997607
33. Pass RF. Cytomegalovirus infection. Pediatr Rev. 2002;23(5):163-70. DOI: 10.1542/pir.23-5-163 PMID: 11986492
34. Pass RF, Fowler KB, Boppana SB, Britt WJ, Stagno S. Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome. J Clin Virol. 2006;35(2):216-20. DOI: 10.1016/j.jcv.2005.09.015 PMID: 16368262
35. Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. Pediatrics. 1999;104(1 Pt 1):55-60. DOI: 10.1542/peds.104.1.55 PMID: 10390260
36. Foulon I, De Brucker Y, Buyl R, Lichtert E, Verbruggen K, Piérard D, et al. Hearing Loss With Congenital Cytomegalovirus Infection. Pediatrics. 2019;144(2):e20183095. DOI: 10.1542/peds.2018-3095 PMID: 31266824
37. Lim Y, Lyall H. Congenital cytomegalovirus - who, when, what-with and why to treat? J Infect. 2017;74:S89-94. DOI: 10.1016/S0163-4453(17)30197-4 PMID: 28646968
38. Guerra B, Simonazzi G, Puccetti C, Lanari M, Farina A, Lazzarotto T, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol. 2008;198(4):380.e1-7. DOI: 10.1016/j.ajog.2007.09.052 PMID: 18191802
39. Tanimura K, Yamada H. Maternal and neonatal screening methods for congenital cytomegalovirus infection. J Obstet Gynaecol Res. 2019;45(3):514-21. DOI: 10.1111/jog.13889 PMID: 30590863
40. Picone O, Teissier N, Cordier AG, Vauloup-Fellous C, Adle-Biassette H, Martinovic J, et al. Detailed in utero ultrasound description of 30 cases of congenital cytomegalovirus infection. Prenat Diagn. 2014;34(6):518-24. DOI: 10.1002/pd.4340 PMID: 24532345
41. Malinger G, Lev D, Lerman-Sagie T. Imaging of fetal cytomegalovirus infection. Fetal Diagn Ther. 2011;29(2):117-26. DOI: 10.1159/000321346 PMID: 21088375
42. Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. Clin Microbiol Rev. 2002;15(4):680-715. DOI: 10.1128/CMR.15.4.680-715.2002 PMID: 12364375
43. Petrovec M. Virusne okužbe pri nosečnici, plodu in novorojenčku. Med Razgl. 2014(53):173-84.
44. de Vries LS, Gunardi H, Barth PG, Bok LA, Verboon-Maciolek MA, Groenendaal F. The spectrum of cranial ultrasound and magnetic resonance imaging abnormalities in congenital cytomegalovirus infection. Neuropediatrics. 2004;35(2):113-9. DOI: 10.1055/s-2004-815833 PMID: 15127310
45. Hughes BL, Gyamfi-Bannerman C; Society for Maternal-Fetal Medicine (SMFM). Diagnosis and antenatal management of congenital cytomegalovirus infection. Am J Obstet Gynecol. 2016;214(6):B5-11. DOI: 10.1016/j.ajog.2016.02.042 PMID: 26902990
46. Lipitz S, Hoffmann C, Feldman B, Tepperberg-Dikawa M, Schiff E, Weisz B. Value of prenatal ultrasound and magnetic resonance imaging in assessment of congenital primary cytomegalovirus infection. Ultrasound Obstet Gynecol. 2010;36(6):709-17. DOI: 10.1002/uog.7657 PMID: 20503234
47. Liesnard C, Donner C, Brancart F, Gosselin F, Delforge ML, Rodesch F. Prenatal diagnosis of congenital cytomegalovirus infection: prospective study of 237 pregnancies at risk. Obstet Gynecol. 2000;95(6 Pt 1):881-8. DOI: 10.1097/00006250-200006000-00019 PMID: 10831985
48. Lazzarotto T, Guerra B, Lanari M, Gabrielli L, Landini MP. New advances in the diagnosis of congenital cytomegalovirus infection. J Clin Virol. 2008;41(3):192-7. DOI: 10.1016/j.jcv.2007.10.015 PMID: 18054840
49. Ornoy A, Diav-Citrin O. Fetal effects of primary and secondary cytomegalovirus infection in pregnancy. Reprod Toxicol. 2006;21(4):399-409. DOI: 10.1016/j.reprotox.2005.02.002 PMID: 16580941
50. Paixão P, Brito MJ, Virella D, Neto MT. Recurrent maternal CMV infection associated with symptomatic congenital infection: results from a questionnaire study in Portugal. BMJ Paediatr Open. 2019;3(1):e000455. DOI: 10.1136/bmjpo-2019-000455 PMID: 31263791
51. Enders G, Bäder U, Lindemann L, Schalasta G, Daiminger A. Prenatal diagnosis of congenital cytomegalovirus infection in 189 pregnancies with known outcome. Prenat Diagn. 2001;21(5):362-77. DOI: 10.1002/pd.59 PMID: 11360277
52. Bilavsky E, Pardo J, Attias J, Levy I, Magny JF, Ville Y, et al. Clinical Implications for Children Born With Congenital Cytomegalovirus Infection Following a Negative Amniocentesis. Clin Infect Dis. 2016;63(1):33-8. DOI: 10.1093/cid/ciw237 PMID: 27114380
53. Yinon Y, Farine D, Yudin MH. No. 240-Cytomegalovirus Infection in Pregnancy. J Obstet Gynaecol Can. 2018;40(2):e134-41. DOI: 10.1016/j.jogc.2017.11.018 PMID: 29447718
54. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. J Pediatr. 2004;145(4):485-91. DOI: 10.1016/j.jpeds.2004.05.041 PMID: 15480372
55. Yamada H, Tanimura K, Tairaku S, Morioka I, Deguchi M, Morizane M, et al. Clinical factor associated with congenital cytomegalovirus infection in pregnant women with non-primary infection. J Infect Chemother. 2018;24(9):702-6. DOI: 10.1016/j.jiac.2018.04.010 PMID: 29735300
56. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. Semin Perinatol. 2007;31(1):10-8. DOI: 10.1053/j.semperi.2007.01.002 PMID: 17317422
57. Blázquez-Gamero D, Galindo Izquierdo A, Del Rosal T, Baquero-Artigao F, Izquierdo Méndez N, Soriano-Ramos M, et al. Prevention and treatment of fetal cytomegalovirus infection with cytomegalovirus hyperimmune globulin: a multicenter study in Madrid. J Matern Fetal Neonatal Med. 2019;32(4):617-25. DOI: 10.1080/14767058.2017.1387890 PMID: 28978246
58. Seror J, Bordes P, Luton D. Routine screening for CMV during pregnancy: practices assessment in Île-de-France. Gynécol Obstét Fertil. 2013;41(10):578-82. DOI: 10.1016/j.gyobfe.2013.07.009 PMID: 24099656

59. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K. Primary human cytomegalovirus (HCMV) infection in pregnancy. Dtsch Arztebl Int. 2017;114(4):45-52. DOI: 10.3238/arztebl.2017.0045 PMID: 28211317

60. Revello MG, Tibaldi C, Masuelli G, Frisina V, Sacchi A, Furione M, et al.; CCPE Study Group. Prevention of Primary Cytomegalovirus Infection in Pregnancy. EBioMedicine. 2015;2(9):1205-10. DOI: 10.1016/j.ebiom.2015.08.003 PMID: 26501119

61. Rawlinson WD, Hamilton ST, van Zuylen WJ. Update on treatment of cytomegalovirus infection in pregnancy and of the newborn with congenital cytomegalovirus. Curr Opin Infect Dis. 2016;29(6):615-24. DOI: 10.1097/QCO.0000000000000317 PMID: 27607910

62. Leruez-Ville M, Ghout I, Bussieres L, Stirnemann J, Magny JF, Couderc S, et al. In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. Am J Obstet Gynecol. 2016;215(4):462.e1-e.10. DOI: 10.1016/j.ajog.2016.04.003 PMID: 27083761

63. Kimberlin DW, Aban I, Acosta EP. Valganciclovir for Congenital Cytomegalovirus. N Engl J Med. 2015;372(25):2463. DOI: 10.1056/NEJMc1504937 PMID: 26083215

64. Tanimura K, Tairaku S, Ebina Y, Morioka I, Nagamata S, Deguchi K, et al. Prediction of Congenital Cytomegalovirus Infection in High-Risk Pregnant Women. Clin Infect Dis. 2017;64(2):159-65. DOI: 10.1093/cid/ciw707 PMID: 27986675

65. Farkas N, Hoffmann C, Ben-Sira L, Lev D, Schweiger A, Kidron D, et al. Does normal fetal brain ultrasound predict normal neurodevelopmental outcome in congenital cytomegalovirus infection? Prenat Diagn. 2011;31(4):360-6. DOI: 10.1002/pd.2694 PMID: 21413035

66. Leruez-Ville M, Ville Y. Fetal cytomegalovirus infection. Best Pract Res Clin Obstet Gynaecol. 2017;38:97-107. DOI: 10.1016/j.bpobgyn.2016.10.005 PMID: 27923540

67. Hamprecht K, Goelz R. Postnatal Cytomegalovirus Infection Through Human Milk in Preterm Infants: Transmission, Clinical Presentation, and Prevention. Clin Perinatol. 2017;44(1):121-30. DOI: 10.1016/j.clp.2016.11.012 PMID: 28159200