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Cytomegalovirus infection in pregnant women - threats, diagnosis and treatment

Arkadiusz Grunwald
Medical University of Lublin
https://orcid.org/0000-0002-9792-1118
Kinga Brzuszkiewicz
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0003-3941-027X
Katarzyna Nowak
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0002-8289-1681
Małgorzata Satora
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0002-6010-9732
Jakub Klas
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0002-4795-1909
Gracjan Rudziński
Uniwersytet Medyczny w Lublinie
https://orcid.org/0000-0001-8911-9144

Abstract

Cytomegalovirus is one of the most widespread DNA viruses, with 90% of women of childbearing age in Poland infected with it. Infection poses a risk to the mother as well as the fetus, as the virus can cross the placenta and damage the fetus. The purpose of this paper is to review scientific publications from 2017-2022, which describe the course of cytomegalovirus infection in pregnant women, the risks to the mother and fetus associated with the infection, methods of diagnosing the infection in the pregnant woman and the fetus, as well as treatment of cytomegalovirus infection and directions for vaccine research.

The most common complications of congenital cytomegalovirus infection include hearing loss, mental developmental delays and miscarriage. The infection can be detected in the pregnant woman by immunological testing, while polymerase chain reaction is used in the fetus and newborn. Early detection of infection in a pregnant woman allows the implementation of treatment which includes ganciclovir, valganciclovir, acyclovir and valacyclovir. A vaccine against cytomegalovirus has not been developed. Particularly important in the prevention of infection is to conduct educational activities regarding the routes of transmission of the virus and the consequences of congenital infection for the fetus.

Cytomegalovirus infections among pregnant women. It is important to monitor fetal development and possibly diagnose for congenital CMV infection in case of abnormalities, and the best diagnostic method is polymerase chain reaction testing. For the treatment of congenital CMV infection, acyclovir and valacyclovir are preferred, and therapy should be implemented for specific indications. Attention should be paid to educating women about infections caused by cytomegalovirus.
Keywords: cytomegalovirus, congenital cytomegaly infection, pregnancy, diagnostics, treatment

1. Introduction.

Cytomegalovirus is one of the most well-known and widespread DNA viruses due to its ease of transmission through our body's secretions and excretions. It belongs to the family *Herpesviridae* and the subfamily *Betaherpesvirinae*, so this virus like the whole group has the ability to cause latent infections and the ability to reactivate. Currently, there are several different species of cytomegaloviruses specific for different mammalian species, the most common of which is human cytomegalovirus (HCMV), also classified as human betaherpesvirus-5 (HHV-5). Cytomegalovirus shows tropism to T lymphocytes and bone marrow stromal cells. The virus replicates only in human cells, such as fibroblasts, epithelial cells and macrophages. In the general population, CMV infection is classified as a sexually transmitted disease. CMV transmission is also possible via blood and in organ transplantation. Latent infections affect immunocompromised patients, especially patients after transplantations and patients with AIDS. Clinical manifestations can have different localisations: lungs, brain, gastrointestinal tract. At the risk of active infection are pregnant women. Primary infections in adulthood during pregnancy, as well as reactivation of the infection during pregnancy, pose a risk to the mother as well as the fetus, as the virus can cross the placenta and damage the fetus. Congenital CMV infections, among the most common intrauterine infections, affect 0.3-2.5% of live-born newborns [1]. Vertical infections can occur during pregnancy, as well as during labor and after delivery. Postpartum infections due to breastfeeding are also common, but healthy newborns, born on time, do not present any symptoms of infection at that time.

2. Purpose.

The purpose of this paper is to review scientific publications from 2017-2022, which describe the course of cytomegalovirus infection in pregnant women, the risks to the mother and fetus associated with the infection, methods of diagnosing the infection in the pregnant woman and the fetus, as well as the treatment of cytomegalovirus infection and future directions in vaccine research.

3. Epidemiology of cytomegalovirus infection in pregnant women and fetuses.

Cytomegalovirus is widespread worldwide. In the United States, CMV infection affects 1 in 3 children by age 5. Nearly half of adults in their 40s are already infected with CMV [2]. In Poland, nearly 70% of people are infected, including 90% of women of reproductive age [3]. The live birth rate in the United States and Europe is 0.5-1%. In 85-90% of newborns, the infection is asymptomatic, 10% have hearing loss, and 10-15% have symptomatic infections, which means hearing loss, psychomotor retardation, choroid and retinal inflammation and learning disabilities [4]. Table 1. shows the average seroprevalence of cytomegalovirus among women of childbearing age.

World Health Organization regions	**Women of childbearing age [%]**
Europe Region	66
America Region	75
Southeast Asia Region	86
Africa Region	88
Western Pacific Region	88
Eastern Mediterranean Region	90
World	**83**

Table 1. Estimated average seroprevalence of cytomegalovirus among women of childbearing age in World Health Organization regions [5] (*own compilation).*

Increased incidence of infection is observed during three periods: early childhood, adolescence and reproductive period [6]. The virus is isolated from urine, blood, pharyngeal washings, saliva, tears, milk, semen, feces, amniotic fluid, vaginal and cervical secretions, tissues taken for transplantation, and the multitude of fluids and body secretions in which it is found promotes its spread. Congenital infections of the fetus are caused by both primary and secondary infections. The transmission rate in primary infections is 30-40%, while in secondary infections it is 1%. Secondary infections are responsible for most of the pathological conditions that occur in newborns due to CMV infection [7]. The low awareness of cytomegalovirus in the modern world is alarming. Of the 726 women surveyed, aged 18-44, only 20% had heard of cytomegalovirus infection in the past, but after receiving information about it, up to 96% of women considered screening during pregnancy and shortly after the birth of their child as necessary [8].

4. Screening for cytomegalovirus infection.

Despite the prevalence of cytomegalovirus infection in women of childbearing age and the potential negative effects of infection on the fetus and newborn, universal screening for CMV infection is not recommended, although in some European countries, the United States, Australia and Israel, such tests are performed independently from screening programs [9]. Both pregnant women and newborns are screened. In pregnant women, specific IgG and IgM antibodies to the virus can be detected, which is the preferred screening method for detecting primary infections [10]. Amniocentesis is also performed for the detection of cytomegalovirus DNA by polymerase chain reaction (PCR) in amniotic fluid, which is the preferred method for detecting fetal infections [11]. Newborn screening appears to be important because of the predominantly asymptomatic course of congenital infections and the high risk of sensorineural deafness (SNHL) in later life. Viral DNA is contained in the urine and saliva of infected newborns, with the highest sensitivity and specificity being the Real Time-PCR (RT-PCR) test performed in saliva [12]. PCR testing using a dry blood droplet is also performed. The lack of screening in pregnant women in Poland and other European countries delays the diagnosis and treatment of cytomegalovirus infection [13].

5. Clinical course of cytomegalovirus infection in pregnant women.

Among CMV infections, a distinction can be made between primary and secondary infections. Due to the later risk of birth defects in the fetus, cytomegalovirus is particularly dangerous for women of childbearing age. Contact with infected body secretions, especially in child contact and in the home environment, is identified as the most common source of infection for women [14]. Even in seronegative women, 1-2% of these women may seroconvert during pregnancy [15]. The spread of the virus by the bloodborne route and its replication are not subject to control by the host, while the virus remains dormant in monocytes after primary infection. In immunocompetent individuals, the virus rarely causes any clinical symptoms, while infections in immunocompromised individuals are characterized by a more severe course. Heterophilic antibody-negative mononucleosis syndrome is possible, and symptoms are similar to those caused by Epstein-Barr virus (EBV), with less pronounced pharyngitis and lymphadenopathy. The virus is detected in body secretions during primary infection and whenever the infection is reactivated [16].

6. Congenital cytomegalovirus infections.

Approximately 10% of newborns with congenital CMV infection show signs of infection - microcephalus or hydrocephalus, encephalitis, nervous system damage, spastic paresis, retinitis pigmentosa, optic nerve atrophy, hearing loss or deafness, liver and spleen enlargement, jaundice, interstitial pneumonia, decreased platelet count and hemorrhagic diathesis, and death in the first weeks of life is also possible. Fetal death and spontaneous abortion are also possible [17]. These symptoms indicate the existence of congenital CMV infection, in those cases a full diagnostic workup is necessary. However, 90% of infected newborns have no symptoms of infection, the infection is asymptomatic. As many as 40-60% of newborns with symptomatic infection and 10-15% of newborns with asymptomatic infection develop sensorineural deafness as a complication of the infection [11]. It has been shown that the risk of neonatal symptoms is the highest when a pregnant woman's CMV infection occurs at conception or during the first trimester of pregnancy [18]. The pathophysiological basis for hearing loss in CMV-infected neonates is

not clear. Direct cytolysis of the components of the vagus, loss of neurons of the cochlear spiral ganglion, as well as immune damage due to the host immune response and pro-inflammatory chemokines encoded by viral genes are indicated.

7. Diagnosis of cytomegalovirus infection in pregnant women.

Because of the risks that congenital CMV infection poses to a child's development, it is important to detect the infection as early as possible in the pregnant woman in order to consider treatment. Flu-like symptoms and fever in a pregnant woman should always arouse vigilance, as they may indicate either primary infection or reinfection with CMV [19]. Testing for antibodies to CMV then seems reasonable. Preferably, IgM antibodies should be detected first, and when positive, IgG antibodies should be tested [20]. The presence of IgM antibodies alone does not indicate recent infection, so it is useful to determine the avidity of IgG antibodies to distinguish primary and secondary infections. To date, the usefulness of determining CMV DNA in the blood, saliva and urine of pregnant women has not been determined. Chronic chorioamnionitis is more frequently observed in pregnant women with CMV infection. The result can be intrauterine fetal growth restriction (FGR), even without fetal infection. Biomarkers of inflammation can be elevated levels of C-reactive protein (CRP) and serum amyloid A (SAA). In this situation, hemopirolactam (HPL) levels are reduced, which can also be a useful biomarker of placental inflammation [21].

8. Diagnosis of cytomegalovirus infection in fetuses and newborns.

If abnormal findings are detected in a pregnant woman and there is a risk of CMV infection, the next step should be the diagnosis of infection in the fetus and newborn. Ultrasound examinations in this case are characterized by
low sensitivity. They are useful when an infection is found in a pregnant woman, in order to evaluate potential abnormalities in the fetus. In this case, it is difficult to determine pathognomonic features for CMV infection, but hyperechogenicity of the intestine and ventriculomegaly are the most common signs of primary CMV infection in the fetus [22]. The preferred method is amniocentesis for PCR testing to detect CMV DNA in amniotic fluid, with the highest sensitivity after 21 weeks of gestation. When the test is performed with a negative result before this date or before 8 weeks after the estimated date of seroconversion in the mother, it should be repeated [11, 20]. For diagnosis by amniocentesis, ultrasound and magnetic resonance imaging are useful for predicting the course of infection and the risk of hearing loss [20]. For children, the primary sample for PCR testing is either urine or saliva. Because of reports of false-positive results from saliva samples, any such positive result should be confirmed by testing from a urine sample [23]. PCR testing can also be performed in an umbilical cord blood sample, but it has a lower sensitivity in detecting the virus compared to tests performed in amniotic fluid, as well as urine and saliva in children [7]. Also, testing using a dry blood droplet has lower sensitivity than using a saliva sample, but is useful for performing common screening, including retrospective studies. Figure 1. shows the summative algorithm for the diagnosis of cytomegalovirus infection in the pregnant woman, fetus and newborn.

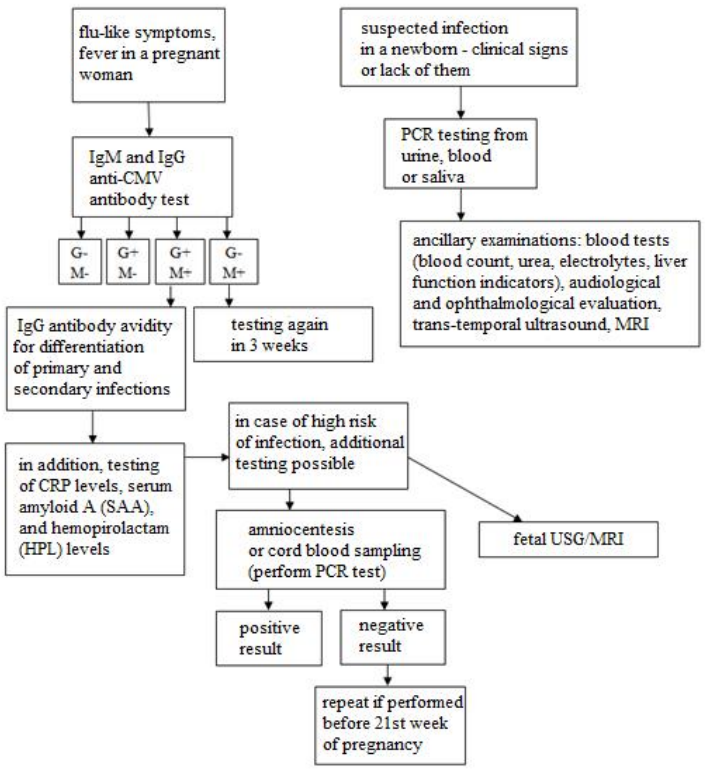

Figure 1. Algorithm for the diagnosis of CMV infection in the pregnant woman, fetus and neonate *(own compilation).*

9. Treatment of cytomegalovirus infection.

Ganciclovir, valganciclovir, acyclovir and valacyclovir are used in antiviral therapy. For infants with clinical symptoms at birth, combination therapy with ganciclovir or valganciclovir can prevent hearing loss and has a better prognosis, but is associated with a risk of neutropenia [20]. According to the 2017 recommendations of the International Congenital Cytomegalovirus Recommendations Group, oral valganciclovir treatment should be used in infants with moderate to severe conditions. In European practice, treatment is implemented for central nervous system symptoms, life-threatening conditions, severe disease involving a single organ or involvement of multiple organs [24]. Ganciclovir and valganciclovir are teratogenic drugs, so any use should be preceded by a thorough evaluation of potential opportunities and risks. Valganciclovir, as a pro-drug of ganciclovir, has less toxicity and is well absorbed and rapidly metabolized after oral administration [4]. They can also be used prenatally, as acyclovir and valacyclovir, and acyclovir has the best safety profile of the aforementioned drugs [25]. Studies have proven that valacyclovir crosses the placenta and affects a higher percentage of asymptomatic
newborns than when it is not used (82% to 43%) [26]. Letermovir is an inhibitor of viral terminase, which is necessary for the process of viral replication, and has no teratogenic effect. To date, it has been used for the prevention of CMV infection in allogeneic bone marrow transplant

recipients, but its potential efficacy in the treatment of congenital CMV infection should be investigated. If infection is detected in a pregnant woman, hyperimmunized globulin (HIG) may be effective in preventing CMV transmission to the fetus. The data from a non-randomized study have shown that biweekly administration of HIG up to 20 weeks of pregnancy prevents transmission of primary infection from mother to fetus [27]. To be able to use this therapy on a large scale, it is necessary to confirm its effect in a randomized clinical trial. A non-randomized study showed that combination therapy with HIG and valacyclovir can prevent the appearance of new brain damage and the progression of existing damage in CMV-infected fetuses [28]. There is a need for further research into the therapeutic options for congenital CMV infections. This is also supported by the economic aspect, because with effective therapy, screening for CMV infection in the woman and the fetus will then become recommended for economic reasons.

10. Prevention of cytomegalovirus infection in pregnant women.

Congenital CMV infection is a serious disease, with lifelong implications, so it is reasonable to prevent infection first in pregnant women, but also the transmission of infection from mother to fetus. To date, no vaccine has been developed to prevent infection in pregnant women, so it is crucial to increase the focus on education and development of strategies to prevent infection, involving women planning to become pregnant, pregnant women and health care workers [20]. International studies show that women's knowledge of CMV and the routes of transmission is limited. In a study of 457 women in Australia, only 73 of them (16%) had heard of CMV, 58% regularly kissed their baby on the mouth, 57% did not wash their hands after every diaper change. After reading an informational pamphlet, women's knowledge of CMV improved [29]. Pre-pregnancy screening and personal hygiene advice has been shown to effectively reduce exposure to CMV [30]. There is a need for further vaccine research, but the effects of any vaccination will have to wait decades due to the transience of generations. An ideal vaccine should induce a strong humoral response, as well as HCMV-specific CD4+ and CD8+ responses from T cells [31].

11. Conclusions.

CMV infections among pregnant women is a current problem, due to the impact on fetal and child development - requiring the implementation of appropriate measures. Screening is still not recommended due to the unprofitability and lack of effective treatment of CMV infection in women and newborns. It is important to monitor fetal development and possible diagnosis for congenital CMV infection in case of abnormalities. The best diagnostic method is PCR testing to detect CMV DNA in amniotic fluid. For the treatment of congenital CMV infection in the fetus, acyclovir and valacyclovir are preferred due to their better safety profile than ganciclovir and valganciclovir, and treatment should be implemented for specific indications. Further research is required on the efficacy of letermovir in congenital CMV infections in the fetus, as well as on the efficacy of HIG to prevent transmission of infection from mother to fetus. At this point, special attention should be paid to educating women about CMV infections, as well as reminding them of basic hygiene rules during childbearing age to minimize the risk of CMV infection.

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