GREGO, Katarzyna, GREGO, Mateusz, STOJAK, Łukasz, POPIELA, Dariusz, URBAŃSKA, Karina, KWIATKOWSKI, Filip, BACZEWSKI, Mateusz and CZYŻ, Witold. Congenital cytomegalovirus - current state of knowledge on the treatment and prevention of fetuses and newborns. Quality in Sport. 2025;37:57297. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.37.57297
https://apcz.umk.pl/QS/article/view/57297

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.12.2024. Revised: 10.01.2025. Accepted: 10.01.2025 Published: 15.01.2025.

Congenital cytomegalovirus - current state of knowledge on the treatment and prevention of fetuses and newborns

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ABSTRACT
Cytomegalovirus (CMV) is common pathogen in the human population and one of the most causes of intrauterine infections of the fetus. It is a component of the acronym TORCH describing pathogens which are a significant risk factor for miscarrings or serious damage to the fetus. Symptomatic congenital cytomegalovirus occurs in about 10% of infected newborns and, among of the other things, can cause hearing loosing, vision impairment or cognitive impairment in the children. Importantly, a child who is asymptomatic at the time of delivery is still at risk of developing dysfunctions in the future. Currently there is no effective vaccine against cytomegalovirus.

There are attempts to treat pregnant women with antiviral drugs and hyperimmunoglobulins. The treatment is intended to protect the fetus from vertical transmission of the virus or to reduce the effects of infection. An important aspect is the time of starting treatment for the woman and the seroprevalence of expectant mothers. The risk of fetal infection increases with the age of pregnancy. Primary infection of the mother poses a greater danger to the fetus than secondary infection. The key moment of treatment appear to be the first trimester of pregnancy, because it is during this period that the greatest devastation occurs in the rapidly developing fetus. For this reason, the greatest benefit from treatment may be obtained by pregnant women with primary CMV infection in the first trimester of pregnancy. Establishing a treatment regimen for pregnant women may reduce the number of births with disabilities caused by cytomegalovirus. Moreover, it is possible to consider introducing screening tests among pregnant women to identify the risk group as early as possible. In this article, we will present the problem of congenital cytomegalovirus and describe the current proposals for treatment and prophylaxis used in fetuses and newborns infected with cytomegalovirus. Moreover, we will present the current state of knowledge about potential side effects of its use. This review was conducted by searching scientific publications on PubMed and Google Scholar.

Keywords: Cytomegalovirus, CMV, congenital CMV, Hiperimmunoglobilin, Valacyclovir, Valgancyclovir, Newborn, Infant, Pregnancy, Fetus

INTRODUCTION

Cytomegalovirus (CMV) is a common pathogen in the human population. It is estimated that up to 80% of the Polish population has had contact with this pathogen. CMV infection spreads through contact with the body fluids of an infected person and vertically (intrauterine or during delivery). People working with children, newborns and people with weakened immunity (people after organ transplantation or HIV infection) are particularly at risk. (1, 2)

Immunocompetent people most often experience the infections asymptomatically or with mild symptoms such as sore throat, cough, fever, or swollen lymph nodes. In contrast, CMV infection poses a significant problem among people with weakened immunity, as well as among newborns and fetuses. The immune system of these people is unable to effectively initiate a response against the pathogen, resulting in a range of negative health outcomes and impacts on patient functioning. (2) In our article, we will focus on the issue of congenital CMV infection (cCMV) and its prevention and treatment.

1. Cytomegalovirus in pregnant women and their children

The most common pathogens threatening the fetus are described by the acronym TORCH, which includes Toxoplasma gondii, Rubella virus, Cytomegalovirus, Herpes simplex virus, and others. CMV is the most frequently diagnosed cause of congenital infections in newborns, with an incidence of about 0.7% among live births. Pregnant patients often experience the infection asymptomatically; however, the virus poses a serious threat to the fetus. Symptomatic congenital cytomegalovirus occurs in about 10% of infected newborns and can lead to hearing and vision impairments, as well as cognitive function disorders in the child. Importantly, an asymptomatic child at birth is still at risk for developing dysfunctions in the future. (2-6)

The degree of risk to the fetus depends on many factors. One of them is the seroprevalence of women of childbearing age. Reinfection or reactivation of CMV infection in a woman poses a lower risk to the fetus than primary infection. Studies show that in cases of primary infection, there is a higher incidence of births of sick children. Unfortunately, IgG antibodies in women do not provide protection to the child against intrauterine infection. (7, 8)
Another factor influencing the degree of risk to the fetus is the manner in which the child became infected (during birth, breastfeeding, or in utero) and the stage of pregnancy at which the infection occurred. The risk of transmission increases with gestational age; however, it is during the first trimester that a range of developmental disorders in the fetus is most commonly observed. Depending on the timing of the infection, the condition of the newborn can vary.In cases of infection during the third trimester, the newborn may not show any signs of infection, but they may experience long-term complications from CMV infection (such as hearing loss, motor disorders, learning difficulties, etc.). In contrast, infections occurring in the first trimester more frequently result in severe cases of intrauterine infection, which can even lead to miscarriage or fetal demise. The most commonly described complications of congenital CMV include hearing loss, neurological disorders, seizures, microcephaly, hepatosplenomegaly, chorioretinitis, and others. (4, 5, 9-12)

2. Diagnosis of cCMV

Currently, there are no widespread screening tests for CMV infection among pregnant women. Suspicions of intrauterine infection may first arise from abnormal results in prenatal ultrasound examinations. The changes observed in the fetal image are not specific to CMV infection. Confirmation of virus transmission to the fetus can be obtained through amniocentesis; however, this is an invasive procedure and carries the risk of complications. Additionally, there are time constraints for performing amniocentesis - 6-8 weeks after maternal infection and after the 21st week of pregnancy. Another method to confirm congenital cytomegalovirus is testing the child's bodily fluids after birth. Tests can utilize the child's urine, saliva, cerebrospinal fluid, and blood. The preferred method is molecular testing using PCR, which detects CMV DNA. Biological material should be collected within 3 weeks of birth. This is the period during which we detect antibodies following the child's intrauterine contact with the virus, rather than as a result of postnatal CMV infection. An older and less commonly used method today is tissue culture, which is time-consuming and has been largely replaced by more modern laboratory techniques. (5, 10, 13)

3. Treatment Methods for cCMV

Currently, there is no vaccine available that would enable primary prevention regarding the fetus. The recommended way to prevent the consequences of congenital CMV infection is through proper hygiene among pregnant women. There are attempts to treat cCMV involving the administration of antiviral medications and immunoglobulins to pregnant women. However, neither of these methods guarantees protection for the child against intrauterine infection.
Numerous studies describe treatment regimens using ganciclovir, valganciclovir, valacyclovir, and immunoglobulins, which offer hope for improving quality of life and mitigating the effects caused by congenital CMV in the fetus. In this article, we will present the current knowledge on treatment and prevention methods for congenital cytomegalovirus infection in newborns.

Discussion

Congenital CMV infections present a challenging issue for doctors and parents of affected children. Currently, treatment regimens are being sought that would allow for the protection of the child against vertical transmission from the mother. Timely initiation of therapy is crucial in mitigating the effects of the infection in the newborn. Studies show that the greatest benefits from treatment are observed when initiated in the first trimester of pregnancy. (7, 8) Currently, the recommended treatment method is antiviral therapy using valacyclovir; however, this therapy is lengthy, and the preventive effect of antiviral medications is not entirely effective. An interesting and promising treatment option appears to be hyperimmunoglobulin. Unfortunately, studies regarding its efficacy are very inconsistent, and there are no clear recommendations for its use. In the future, it may be possible to develop a vaccine against CMV, which seems to be the best solution for primary prevention concerning the fetus. As of today, research on this treatment method is still ongoing. (14, 15)

1. Antiviral medications

Antiviral medications administered vary depending on the period in which they are used. In the case of treating pregnant women and protecting the child from vertical transmission of CMV, valacyclovir appears to be the safest option. The proposed regimen involves administering this drug in high doses (8g/day). The mechanism of action of valacyclovir is based on inhibiting the viral DNA polymerase. (16) There are many studies discussing the effectiveness of such therapy in reducing vertical transmission from mother to child. It seems that the use of valacyclovir is relatively safe and does not carry serious side effects for either the mother or the child. Research describes the possibility of acute renal failure occurring in the mother; however, symptoms resolve after discontinuation of the medication. (14, 17, 18)

In 2020, a randomized study was published that examined the effectiveness of valacyclovir in preventing CMV transmission to the fetus. The drug was administered to pregnant women with confirmed primary infection during the periconceptional period and in the first trimester, up until the time of amniocentesis. The analysis of the results showed a significant decrease in CMV transmission to the fetus in women treated compared to those receiving placebo (from 30% in the placebo group to 11% in the valacyclovir-treated group, $p = 0.027$; odds ratio 0.29, 95% CI 0.09–0.90 for vertical transmission of cytomegalovirus). (19) Similar studies based on administering valacyclovir at a dose of 8g/day during the early stages of pregnancy have confirmed the above results. (20-22) Furthermore, subsequent studies have demonstrated that shortening the interval between the time of infection and the administration of the drug improves treatment outcomes. (23)

In the case of newborns who could not be protected from CMV infection, treatment with valganciclovir can be applied. This drug is a derivative of ganciclovir, and its action is also based on inhibiting the viral DNA polymerase.

The advantage of valganciclovir over ganciclovir lies in the method of administration. Valganciclovir is administered orally, thereby avoiding the prolonged venous catheterization that occurs with ganciclovir treatment. (24, 25)

Children born with symptomatic, moderate, or severe congenital CMV should undergo long-term treatment. Recommendations indicate a 6-week course of valganciclovir at a dose of 16 mg/kg/dose every 12 hours. Extension of treatment for up to 6 months is considered.

Such an approach may help limit further progression of dysfunctions caused by cytomegalovirus, such as hearing loss. (22, 24, 26, 27)
Complications associated with the use of valganciclovir include neutropenia and elevated liver parameters; therefore, during treatment, regular complete blood counts and monitoring of liver enzyme and creatinine levels should be performed. (24, 26)

2. Hyperimmunoglobulins

Hiperimmunoglobulina (HIG) is a pooled plasma from donors with high titers of antibodies against CMV. It is commonly used in individuals who have undergone kidney, lung, or heart transplants. (28, 29)
Data on the effectiveness of hyperimmunoglobulins in pregnant women is conflicting. Some observations contradict the efficacy of HIG in protecting the fetus from CMV. (30, 31)
Research conducted in 2005 by Nigro et al. initially raised hopes for finding an effective method of prevention against CMV during the fetal period. The study was conducted in a non-randomized manner, and its results showed a significant reduction in congenital CMV from 40% in the control group to 16% in the group receiving hyperimmunoglobulin (HIG). (32) Subsequent analyses, however, raised uncertainty regarding the appropriateness of using HIG in pregnant women. (33, 34) In 2014, Revello et al. challenged reports regarding hyperimmunoglobulins by conducting a randomized study. According to their observations, the use of HIG not only failed to produce the expected effect but also caused a number of side effects in patients and their children. Complications such as premature birth, preeclampsia, and fetal growth restriction were noted. (35) Shortly after the publication of this study, a certain discrepancy was identified that could have significantly impacted the results regarding the efficacy of HIG. An important aspect was the half-life of the drug, which was found to be half as long as initially reported, as well as the dosage of 100 IU/kg, which proved to be insufficient. (36) Another aspect highlighting the need for further knowledge about hyperimmunoglobulins in pregnant women is the dependence of treatment efficacy on the timing of maternal infection and the initiation of therapy. As is well known, the first trimester poses the greatest risk to the fetus, and it is during this period that the most significant benefits from the use of HIG are expected.
Considering the above reservations, changes were made to the research protocols. In a subsequent study conducted by Kagan et al., patients were administered HIG at doses of 200 IU/kg every two weeks. Interestingly, in this case, a significant improvement in outcomes was observed among the women and fetuses studied. (37, 38)
In 2018, a study was conducted comparing the effectiveness of HIG depending on the treatment regimen used. The experiment was carried out retrospectively, in vitro, using amniotic fluid positive for the presence of CMV. The material was collected from pregnant women over the years 2007-2017. The participants were divided into three study groups: the first group consisted of women who did not receive HIG treatment, the second group included women treated with HIG but under a different regimen than 200 IU/kg every two weeks, and the third group comprised women treated with HIG at the regimen of 200 IU/kg every two weeks. The amniotic fluid was analyzed using real-time PCR and short-term (18-hour) micro-cultures to obtain information on the quantitative and qualitative assessment of the presence of cytomegalovirus material.

The study results showed a reduced median number of copies of HCMV DNA among women treated with the 200 IU HIG/kg every two weeks regimen compared to untreated women ($p = 0.037$; Mann-Whitney U test). Similar observations were made in the case of micro-cultures and the median number of cells expressing IE1 ($p = 0.025$; Mann-Whitney U test). The author of the study emphasizes that a small group of women participated in the experiment, thus further analysis on a larger sample is necessary. (39)

In 2021, the first open-label, multicenter, randomized Phase III study was conducted involving seronegative pregnant women regarding cytomegalovirus. Participants were divided into two groups: one group was monitored for seroconversion, and if positive results were obtained, they were treated with HIG (200 IU/kg every two weeks), while the second group served as a control and received routine prenatal care. The treatment was primarily administered to women in the second and third trimesters of pregnancy. In a prospective analysis of the results, a reduction in cases of congenital CMV was observed among women receiving HIG therapy; however, this change was statistically insignificant. Additionally, studies conducted on the seventh day of life of infants showed an increased rate of complications from congenital CMV in children of untreated mothers. (40)

The next study in response to the change in treatment protocols for pregnant women using HIG is the work by Schirwani-Hartl N et al. from 2023. It compares a 4-week treatment regimen of hyperimmunoglobulin with a 2-week administration frequency. The pregnant participants received drug therapy in the first and early second trimesters of pregnancy. The study results did not demonstrate an advantage of using HIG every 2 weeks. Vertical transmission remained at similar levels as in the absence of treatment, which may suggest a lack of efficacy of hyperimmunoglobulins. However, in studies on newborns, a reduction in severe cases of congenital cytomegaly was observed, especially in those treated with the 2-week regimen. This may suggest a decrease in the severity of cCMV progression. The authors of the study point out certain limitations of the analysis due to factors such as a small sample size, varying group sizes, lack of a control group, and changes in the treatment protocol during the analysis. (41)

An important aspect to mention is the safety of using hyperimmunoglobulins during pregnancy. There are reports that therapy carries the risk of intrauterine growth restriction, prematurity, and preeclampsia. (35) However, there are studies that contradict the associations between the use of hyperimmunoglobulins and the aforementioned conditions. (30, 37, 40)

3. Primary Prevention

The most effective method of protecting the fetus and newborn from cCMV infection is primary prevention. Educating and raising awareness among expectant mothers about the risks that cytomegalovirus poses to their children is crucial. Understanding how to protect themselves from the virus yields the best results later in pregnancy.

The main reservoir of CMV is primarily young children. Women in the periconceptional period and during pregnancy are advised to maintain good hygiene practices and avoid contact with the bodily fluids of young children. (14, 17)

Conclusions

The viral disease of cytomegaly undoubtedly poses a serious threat to fetuses. Diagnostic methods allow for the rapid identification of women at risk for primary infection. The introduction of widespread screening tests for cytomegaly would enable more efficient and quicker detection of exposed fetuses, thereby accelerating the initiation of treatment. The current state of knowledge does not allow for a definitive treatment protocol for pregnant women with cytomegaly. It seems that currently, the only confirmed method for treating children and fetuses is the use of antiviral medications. Hyperimmunoglobulins, despite the hope they offered in initial studies, still do not guarantee effectiveness in treating cCMV.

Author's contributions:

Conceptualization, Katarzyna Grego, Mateusz Grego and Łukasz Stojak; Methodology, Dariusz Popiela and Karina Urbańska; software, Mateusz Baczewski and Filip Kwiatkowski; check, Mateusz Grego, Katarzyna Grego and Łukasz Stojak; formal analysis, Witold Czyż; investigation, Karina Urbańska; resources, Dariusz Popiela; data curation, Witold Czyż; writing - rough preparation, Katarzyna Grego; writing - review and editing, Mateusz Grego; visualization, Łukasz Stojak; supervision, Katarzyna Grego; project administration, Dariusz Popiela and Filip Kwiatkowski; receiving funding, not-applicable.

All authors have read and agreed with the published version of the manuscript.

Funding Statement:

Not applicable.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflict of interest statement:

Authors have declared no conflict of interests.

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