CASE REPORT

Case report of severe cytomegalovirus infection in pregnancy: prevention and treatment options

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Submitted: 12 November 2025
Revised: 26 December 2025
Accepted: 29 December 2025
Online First: 31 December 2025
Published: 31 March 2026

Check for updates

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Summary

Introduction: Human cytomegalovirus (CMV) is the leading cause of congenital infection worldwide. It can be the cause of serious clinical manifestations, leading to permanent disability in infected children. Unlike most other TORCH infections, both primary and non-primary CMV infection can affect fetus.

Case Report: We present a case of congenital CMV infection that was diagnosed after the onset of severe fetal anomalies in the third trimester. The patient was referred to our hospital in 35. weeks of pregnancy complicated by severe intrauterine growth restriction and fetal brain anomalies seen on the ultrasound and magnetic resonance imaging (MRI): simplified gyration and a highly suspected band heterotopia (differential diagnosis: lissencephaly), dilated temporal and occipital horns of lateral ventricles with intraventricular septations, vermian hypoplasia, zones of t2 hyperintense lesions. Serology testing revealed positive results for CMV-specific IgM antibodies and a positive result for CMV-specific IgG antibodies with high avidity (91,7%). After performing the amniocentesis (PCR), we got positive result for CMV. The patient was informed about the poor prognosis of the congenital CMV infection with those findings on the fetal brain. She opted for the termination of pregnancy.

Conclusion: Given that this is the most common congenital infection, it is necessary to continually raise awareness among pregnant women about primary prevention methods. In the meantime, efforts should focus on research aimed at timely detection and treatment, to prevent severe forms of congenital infection.

Keywords: congenital infection, cytomegalovirus, screening, antiviral therapy

Cite this article as: Uljarevic J, Stankovic M, Drobnjak S, Tosovic G, Karadzov Orlic N. Case report of severe cytomegalovirus infection in pregnancy: prevention and treatment options; Medicinska istraživanja 2026; 59(1):67-72; DOI: 10.5937/medi0-62736

INTRODUCTION

Human cytomegalovirus (CMV) is the most common cause of congenital infection worldwide. The majority of infected children are asymptomatic, but some may develop serious clinical manifestations such as: neurodevelopmental delays, vision impairment, intellectual disability, and other systemic findings (1). The most common long-term health problem is non-genetic sensorineural hearing loss (SNHL) (1). Although the seriousness of this congenital infection has been recognized for a long time, little progress has been made in preventing it.

One reason is that maternal infection is most often asymptomatic. In addition, unlike other TORCH infections, both primary and non-primary infections can harm the fetus (2). Since infection can occur at any time before or during pregnancy, universal screening has not been introduced anywhere. As a result, timely diagnosis is often missed. Without early diagnosis of maternal infection, it is difficult to discuss the effectiveness of agents for the prevention of congenital infection.

The aim of this report is to present a case of cytomegalovirus infection diagnosed in 35 weeks of pregnancy.

CASE REPORT

A 27-year-old woman, gravida 2 para 1, was referred to our hospital with a pregnancy complicated by severe intrauterine growth restriction and fetal brain anomalies seen on the ultrasound and magnetic resonance imaging (MRI). She was 35 weeks pregnant. That was her second pregnancy. The first pregnancy was uneventful. She reported the history of chronic hypertension and was taking antihypertensive therapy.

The transabdominal ultrasound confirmed symmetrical intrauterine growth restriction. The estimated fetal weight was 1660g (less than 1%). The amniotic fluid index was within normal ranges. Doppler assessment of the placental and fetal circulation showed normal values. Ultrasound revealed the presence of mild ventriculomegaly, with dilated occipital and temporal horns of the lateral ventricles with normal frontal horns. Other fetal anatomy was normal **(Figure 1)**.

MRI examination of the fetal brain indicated smaller diameters of the cerebral hemispheres for the gestational age, with simplified gyration and a highly suspected band heterotopia (differential diagnosis: lissencephaly). Ventriculomegaly was described as mild, with dilated

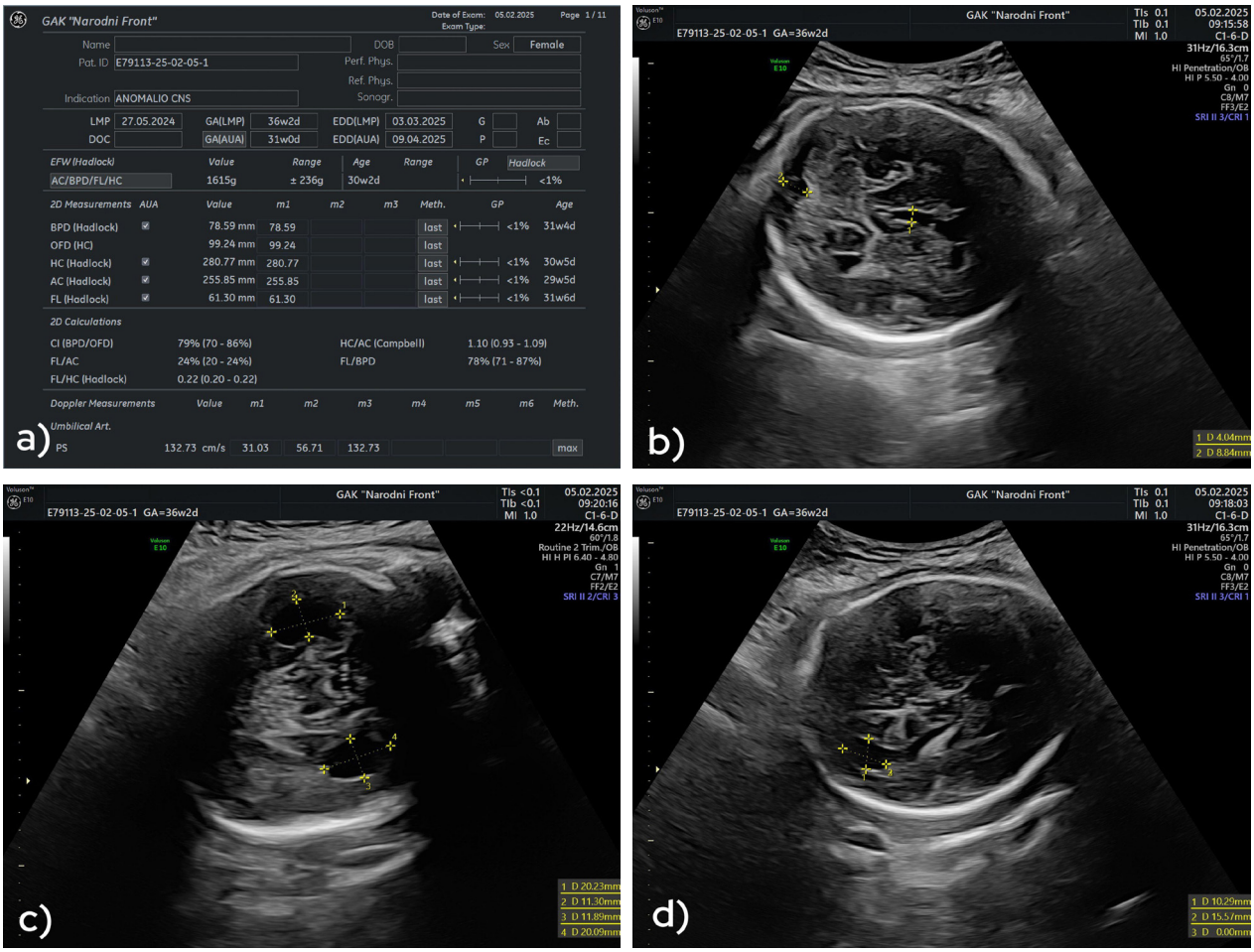

Figure 1. Sonographic features: a) intrauterine growth restriction; b) mild ventriculomegaly; c) dilated temporal horns of lateral ventricles; d) intraventricular septations in occipital horns of lateral ventricles.

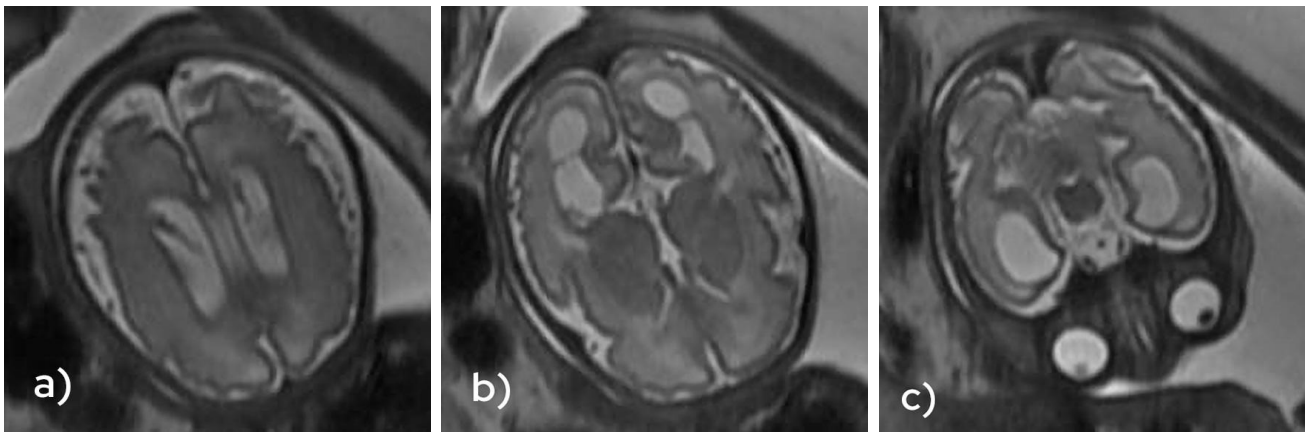

Figure 2. MRI of fetal brain: a) simplified gyral pattern with mild ventriculomegaly, b) dilated occipital horns of lateral ventricles with intraventricular septations, c) dilated temporal horns of lateral ventricles with white matter rarefaction

temporal horns of lateral ventricles, diameters 12mm on the left side and 11mm on the right side with white matter rarefaction, especially on the left side. Occipital horns were dilatated with intraventricular septations. Vermian hypoplasia was described. There were zones of t2 hyperintense lesions, predominantly in temporal lobes. Those changes were described as suspicious for sequelae of an infectious or metabolic disorder **(Figure 2)**.

The tests for blood count, blood group and biochemistry showed results within the reference range. Screening for preeclampsia showed low risk (sFlt-1/PlGF rat 28,88%).

The results of TORCH test were: no detected Toxoplasmosis specific IgM or IgG antibodies; no detected Rubella specific IgM antibodies, positive result for Rubella specific IgG antibodies; positive result for CMV specific IgM antibodies and positive result for CMV specific IgG antibodies with high avidity (91,7%) **(Table 1)**.

Table 1. Serology for cytomegalovirus (CMV) infection

	Result	Ref values	Unit of measurement
CMV IgM	1.12	Non-reactive <0.85 Reactive >1.00	Index
CMV IgG	1102.4	Non-reactive <6.0 Reactive >6.0	U/ml
CMV Av	91.7	Low avidity <50.0 Grey zone 50.0-59.9 High avidity >60.0	%

Given the ultrasound-diagnosed severe intrauterine growth restriction, the presence of CNS anomalies, as well as suspicious CMV serology, it was decided to perform a diagnostic amniocentesis. The result of diagnostic quantitative fluorescent-polymerase chain reaction (QF-PCR) was normal (rsa(X,13,18,21)x2). The microarray test showed a normal molecular karyotype (arr(X,1-22) x2). Polymerase chain reaction (PCR) for CMV diagnosis infection was positive (92750 copies/mL).

The diagnosis was congenital cytomegalovirus infection with a severely symptomatic fetus. The patient was informed at the Fetal Anomalies Committee about the poor prognosis of the congenital CMV infection, especially with those findings on the fetal brain. She opted for the termination of pregnancy.

The fetus and placenta were sent to an autopsy. An autopsy confirmed ventriculomegaly and histological analysis revealed small foci of mineralization in the periventricular white matter, suggesting damage to the brain parenchyma, most likely of infectious origin.

DISCUSSION

Congenital CMV infection affects 0.48% of all live-born infants in high-income countries and 1.42% in low- and middle-income countries and is responsible for significant morbidity, especially in infants who are symptomatic in the neonatal period (3). The rate of transmission to the fetus during primary CMV infections is 30%–40% and 1-2% during non-primary infection (1,3). The risk of sequelae is the greatest following maternal primary infection in the periconception period and first trimester (3,4).

Infected fetuses may be classified into one of three prognostic categories: asymptomatic, mild or moderately symptomatic and severely symptomatic. An asymptomatic fetus has no visible anomalies, has a risk of hearing loss, but generally has a good prognosis. A mild or moderately symptomatic fetus has anomalies like hyperechogenic bowel, mild ventriculomegaly, or isolated calcifications. The prognosis is uncertain and needs an ultrasound or MRI follow-up to define the prognosis. A severely symptomatic fetus has severe brain anomalies: microcephaly, ventriculomegaly, white matter anomalies and cavitations, intracerebral hemorrhage, and delayed cortical development. The prognosis is poor (3).

Maternal serology is used for the diagnosis of primary maternal infection: the appearance of CMV-specific IgG in a woman who was previously seronegative or by the detection of CMV IgM antibody with low IgG avidity. Diagnosis of non-primary CMV infection is not possible using serology (3).

In spite of the high morbidity that may follow the CMV infection, routine screening is not recommended

(5). Some guidelines recommend offering pre-pregnancy or early pregnancy screening for women who are at high risk of infection. Those are the women who have young children at home or who work in childcare, since children under three years old have prolonged viral shedding in their saliva and urine (2). One of the reasons for not screening is that we can't predict the risk of fetal infection, and when we prove fetal infection, we can't always predict the magnitude of fetal/neonatal impairment. Second, half of congenital CMV infections occur following non-primary infection, which means that routine screening would miss half of the cases (3,6). The next reason is that we still don't have approved therapy that can prevent congenital infection (2). Besides that, there is always a question of cost-effectiveness (7).

For the last few years, many clinical trials have been conducted to find a therapy for the secondary prevention of CMV congenital infection or at least serious postnatal sequelae. The older studies did not confirm the efficacy of the use of hyperimmune globulin in the prevention of congenital infection (8,9,10). New studies on the impact of high-dose valacyclovir on the outcomes of cytomegalovirus infection in pregnancy have promising results (11,12). The initiation of therapy soon after the diagnosis of maternal primary infection in the first trimester can lower the risk of vertical transmission (11). More evidence from larger randomised trials is needed to introduce this agent into clinical practice. If the efficacy of valacyclovir is proven, it will be necessary to revise the positions related to screening. Namely, most women have asymptomatic CMV infection, which means that the majority will not benefit from antiviral therapy.

Most current guidelines, including ours, agree not to screen for CMV infection, but there are some discordances on the terms of follow-up. Some recently updated guidelines recommend considering antiviral therapy at the time of maternal infection diagnosis. Following the diagnosis, serial ultrasound examinations should be performed, and fetal brain MRI should be considered in the third trimester. Amniocentesis (PCR) should be conducted at least 6–8 weeks after the diagnosis of maternal infection and no earlier than the 17th week of gestation, although most recommendations suggest performing it after the 21st week of gestation (13). While a negative amniocentesis result can't definitively rule out the presence of a congenital infection, it is indicative of almost no risk for serious neonatal injury (14,15).

The prognostic criteria are the other main focus of research. CMV viral load at second-trimester amniocentesis has low prognostic value, especially in the absence of visible anomalies (16,17). Other indicators, such as fetal thrombocytopenia or viral load, offer superior prognostic value, though they require invasive procedures that are not routinely advised (18). Despite certain limitations, ultrasound and MRI remain the most widely used tools for prognostic assessment (19,20,21). Cytomegalovirus (CMV) exhibits a pronounced neurotropic effect, with the potential to affect various brain cell types, particularly during the early stages of fetal development (19,22). The resulting cerebral anomalies are most often irreversible, which underscores their clinical significance. The involvement of the reticuloendothelial system, manifested as anemia, thrombocytopenia and hepatosplenomegaly, is of lesser significance, as these changes are often reversible (22). CMV has also been shown to affect cytotrophoblast differentiation and migration, leading to placental insufficiency and, in turn, fetal growth restriction (22). All of these effects should be taken into consideration during the follow-up period.

In our case, the patient was admitted to our hospital in the third trimester of pregnancy with a severely symptomatic fetus. Based on the serologic findings and the time of diagnosis, we could not determine whether it was a primary or non-primary infection. Since there are no national recommendations for routine TORCH screening, the diagnosis was established following ultrasound abnormalities. Even if we knew about maternal acute infection, we could only closely monitor the pregnancy, since we do not have national recommendations on the prevention of the vertical transmission. Described central nervous system anomalies are the sign of poor prognosis, so the patient was counselled regarding the option of termination of pregnancy.

CONCLUSION

All pregnant women should be given information about CMV infection and its impact on the fetus and neonatus. They should be informed about the primary prevention measures. Research related to preventive therapy should be supported. National screening recommendations should be subject to ongoing evaluation as new evidence emerges, to ensure timely diagnosis and appropriate treatment.

Acknowledgements: N/A

Funding information: The authors declare that the study received no funding.

Conflict of interest: None to declare.

Author contribution: Conception or design of the work: NKO, JU; Acquisition: MS, SD; Analysis and interpretation of data: JU, NKO, GT; Preparing the draft of the manuscript: JU; Agreement to be accountable for all aspects of the work: JU, MS, SD, GT, NKO. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethical approval: Ethical approval to report this case was obtained from the Ethics Committee of the Ob/Gyn Clinic "Narodni front", No. 22009/2025/015075.

Informed consent: Written informed consent was obtained from the patient for the publication of her anonymized information in this article.

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PRIKAZ SLUČAJA TEŠKE KONGENITALNE INFEKCIJE CITOMEGALOVIRUSOM: PREVENCIJA I MOGUĆNOSTI LEČENJA

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Sažetak

Uvod: Humani citomegalovirus (CMV) je vodeći uzrok kongenitalnih infekcija širom sveta. Može dovesti do ozbiljnih kliničkih manifestacija koje vode trajnom invaliditetu inficirane dece. Za razliku od drugih izazivača kongenitalnih infekcija, fetalna CMV infekcija može biti posledica primarne infekcije u trudnoći, ali i reinfekcije.

Prikaz slucaja: Predstavljamo slučaj kongenitalne CMV infekcije koja je ustanovljena u trećem trimestru trudnoće, nakon pojave ozbiljnih fetalnih anomalija. Pacijentkinja je upućena na našu kliniku u 35. nedelji trudnoće komplikovane teškim zastojem u rastu ploda i anomalijama centralnog nervnog sistema, koje su viđene ultrazvučnim pregledom i magnetnom rezonancom: smanjena kortikalna girifikacija i visoko suspektna "*band* heterotopija" (diferencijalna dijagnoza: lizencefalija), dilatacija temporalnih i okcipitalnih rogova bočnih komora sa intraventrikularnim septama, hipoplazija vermisa, zone T2 hiperintenziteta. Serološkim testiranjem je ustanovljeno je postojanje pozitivnih IgM i pozitivnih IgG antitela za CMV sa visokim aviditetom (91,7%). Dijagnostičkom amniocentezom (PCR analiza) dobijen je pozitivan rezultat za CMV. Pacijentkinja je informisana o lošoj prognozi kongenitalne CMV infekcije, naročito u prisustvu opisanih anomalija centralnog nervnog sistema, nakon čega je zatražila prekid trudnoće.

Zaključak: S obzirom da se radi o najčešćoj kongenitalnoj infekciji, potrebno je raditi na informisanju trudnica o načinima primarne prevencije. Paralelno fokus istraživanja treba da bude na pronalaženju metoda pravovremene detekcije i lečenja infekcije, u cilju prevencije teških formi bolesti.

Ključne reči: kongenitalna infekcija, citomegalovirus, skrining, antivirusna terapija

Primljen: 12.11.2025. I **Revidiran:** 26.12.2025. I **Prihvaćen:** 29.12.2025. I **Online First:** 31.12.2025.

Medicinska istraživanja 2025