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Cytomegalovirus infection in pregnancy: exploring screening strategies, prevalence rates, and impact on newborns in Turkey

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Abstract

Objective: Cytomegalovirus (CMV) infection during pregnancy can lead to congenital infection, with transmission rates varying depending on the trimester and whether it is a primary or recurrent infection. Early recognition and diagnosis of congenital CMV infections are crucial as it can prevent long-term complications such as sensorineural hearing loss. The aim of our study was to determine the seroprevalence of CMV infection and assess the neonatal outcomes in seropositive individuals.

Methods: A retrospective study was conducted at a tertiary center between January 2012 and January 2021, where screening for CMV immunoglobulin G (IgG) - IgM antibodies was performed on 11,609 pregnant women. Of these, 189 pregnant women who met the study criteria and had positive results for both IgM and IgG tests were included in the study.

Results: This study analyzed the seroprevalence of CMV in 11,609 pregnant women and found that 99.2% were positive for CMV IgG antibodies. Neurological anomalies were the most common (15%) fetal anomalies observed in the study, followed by urogenital and cardiovascular anomalies. The anomalies were most commonly observed in the group where seropositivity was detected in the second trimester, followed by the first trimester.

Conclusion: The study found that primary CMV infection during pregnancy can lead to long-term effects, and the central nervous system is the most commonly affected system, with approximately 20% of newborns with congenital infections exhibiting neurological sequelae.

Keywords: Amniocentesis, anomalies, cytomegalovirus, sensorineural hearing loss

Introduction

Cytomegalovirus (CMV), a member of the Herpesviridae family, can remain viable in the human body for a prolonged period and exclusively infects humans. [1] It can cause lytic or latent infections by replicating rapidly within cells. [1,2] The virus has the ability to compromise immunity through various mechanisms, such as evading CD8 and CD4 lymphocytes or inhibiting antibody production. [3] Following the recognition of specific antigens on MHC-I molecules, cytotoxic CD8 T lymphocytes (the classical killer cells of the immune system) become activated. These activated CD8 T cells secrete cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor (TNF) and utilize enzymes like perforin and granzyme to kill target cells. On the other hand, CD4 T cells are generally not cytotoxic and instead support the aggregation and activation of other cell types such as macrophages, B cells, dendritic cells, and other T cells. [4]

CMV causes severe diseases, including CMV pneumonia, in immunocompromised patients due to virus reactivation. [5]

CMV infection can occur during pregnancy through primary or secondary infection, and transmission to the fetus can happen through various routes, including transplacental, during childbirth, or through breastfeeding and close contact. [1,3]

In seropositive women, reactivation of CMV presents a lower risk of fetal infection, with an approximate rate of 1.2%, [6] compared to the higher transmission rate of 32% observed during primary infection. [1] Transmissi-

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on can occur during pregnancy or the preconception. [7] Vertical transmission rates were 26% in the first trimester, 28% in the second trimester, and 65% in the third trimester. [8,9] Infection during the first trimester can lead to a greater number of fetal complications, emphasizing the importance of determining the trimester in which the infection is acquired. [10]

The immunoglobulin G (IgG) avidity test is a diagnostic tool that can be utilized to more accurately detect primary infection compared to relying solely on IgM. A low IgG avidity result serves as an indicator of a recent infection experienced within the preceding 3 months. [11] This is because IgM positivity can persist for an extended period after acute infections and can also be positive in cases of secondary infections. [12–14] Studies have demonstrated that high IgG avidity indicates the infection has been present for more than 6 months, whereas low IgG avidity suggests recent infection. [1]

In the United States, the seroprevalence of CMV is approximately 50%, whereas in Turkey, it is significantly higher, with rates of 97.3% in the Black Sea region and 99.5% in Istanbul [15,16]. Young age and parity increase the risk of primary infection during pregnancy, with a 5.9% annual risk observed in seronegative women in the United States. [1]

It has been observed that the seroprevalence of congenital CMV infection is approximately 0.4-1%, and it increases proportionally with maternal infection. [1] Moreover, factors such as socioeconomic level and preterm birth also influence the incidence of congenital CMV infection. [1]

While the majority of newborns with congenital CMV infections are asymptomatic, 10-15% of cases can exhibit symptoms such as thrombocytopenia, hepatosplenomegaly, and psychomotor and neurodevelopmental delay. [10,17] Sensorineural hearing loss (SNHL) can occur in 20% of infected newborns, including those who are asymptomatic. [1] Early identification of congenital infections is essential to prevent long-term complications such as SNHL.

If extra-cerebral or intracerebral findings, such as ventriculomegaly, periventricular calcification, and parenchymal calcification, are identified during ultrasound examination, fetal infection is suspected. [15,18] In cases where these findings suggestive of fetal infection or maternal infection are detected, amniocentesis is recommended to detect viral DNA for the diagnosis of fetal infection. [17]

To achieve more accurate results, there should be a time interval of at least 6-8 weeks between maternal infection and amniocentesis. This is because it takes this duration for the virus to reach the fetal bloodstream, replicate in the fetal kidneys, and be released into the amniotic fluid. [17] Generally, conducting polymerase-chain-reaction (PCR) tests through amniocentesis after 21 weeks of gestation leads to favorable outcomes in terms of fetal health. [19]

The high seroprevalence of CMV infection globally, combined with the absence of effective treatment, raises the question of the necessity of screening. In our study, our objective was to explore the seroprevalence of CMV infection and evaluate the neonatal outcomes among seropositive individuals.

Methods

Our study was conducted retrospectively from January 2012 to January 2021 at the Department of Obstetrics and Gynecology, Health Sciences University Tepecik Training and Research Hospital. The study included a cohort of 11,609 pregnant women who underwent CMV IgG-IgM antibody screening. A total of 189 pregnant women, who met the study criteria and tested positive for both IgM and IgG, were included in the analysis.

The inclusion criteria for the study were as follows: live, singleton, intrauterine pregnancies ranging from 5 to 40 weeks of gestation. Exclusion criteria encompassed individuals under 18 years of age or over 45 years of age, those with solely IgM or IgG test results, pregnancies less than 5 weeks or exceeding 40 weeks, fetal anomalies, extrauterine or multiple pregnancies, and fetuses lacking visible cardiac activity.

The patients who tested positive for IgM were advised to undergo CMV IgG avidity testing. Antibody titration was performed using the chemiluminescent immunoassay method with the Abbott Architect Plus I2000 SR device. Screening commenced during the routine prenatal examinations of the first trimester upon the detection of fetal heart activity.

Translation: CMV IgG levels exceeding 0.6 IU/mL were deemed positive. Individuals with CMV IgM levels surpassing 22 AU/mL were classified as positive, whereas those with levels ranging from 18-22 AU/mL were categorized as grayzone.

We conducted a retrospective review of medical records from our hospital database, which encompassed patient histories, ultrasound findings, and serologic screening tests for acute infection. Newborn outcomes were also extracted from the hospital database. The study received approval from the ethical committee under the reference number 2021/04-03.

Based on the information obtained from the study, our

research implemented a follow-up protocol to monitor the infected children. Considering the challenges posed by the possibility of late-onset hearing loss, progression, improvement, and fluctuation of hearing thresholds, previous studies have recognized the difficulty in predicting outcomes and standardizing the follow-up process. Consequently, in accordance with the recommended guidelines, we conducted follow-up examinations up to the age of 4-6 years, as late-onset sensorineural hearing loss (SNHL) typically manifests within the first 2 years of life. [1] Our follow-up methodology adhered to the standards outlined in the relevant scientific literature to ensure comprehensive monitoring of the patients' condition. [1]

A phase II multicenter open-label study demonstrated that high-dose valaciclovir (8 g/day) administered to pregnant women with an infected fetus from the second trimester until delivery resulted in a significantly higher proportion of asymptomatic neonates (82%) compared to an untreated historical cohort (43%). However, due to concerns regarding medication side effects and low patient compliance with the treatment dose, particularly among those with low socioeconomic status, the recommended high-dose valaciclovir treatment was not implemented according to the study's findings. [1] CMV vaccines, despite undergoing preclinical studies, have not yet been released on the market.

Based on sonographic measurements of intrauterine growth retardation (IUGR), fetal biparietal diameter, head circumference, abdominal circumference, and femur length, EFW was defined as below the 3rd percentile, accompanied by diastolic end-flow loss observed during Doppler examination. Additionally, the EFW percentile was determined according to the 'International estimated fetal weight standards of the INTERGROWTH-21st Project' study. [20]

The data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Chicago, IL, USA), as commonly used in social science research. One-way ANOVA test was employed for comparing continuous variables among more than two independent groups. The data were presented as mean ± standard deviation (median-range) and also reported as numbers with relevant percentages. Additionally, frequency distributions regarding demographic data were provided. A significance level of $p < 0.05$ was considered statistically significant for all statistical procedures.

Results

This study retrospectively analyzed the CMV IgM-IgG antibody screening results of 11,609 pregnant women between January 2012 and January 2021. Among them, 90 pregnant women tested negative for both IgM and IgG. Conversely, both IgM and IgG were detected in 209 pregnant women included in the study. After excluding 20 individuals who did not meet the research criteria, the study was conducted on 189 individuals (Figure 1).

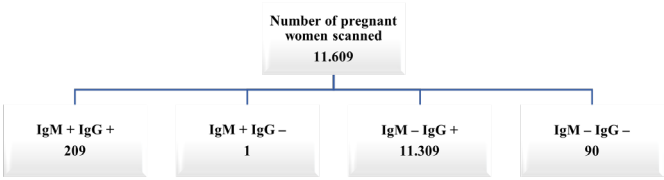

Fig. 1: Cytomegalovirus Immunoglobulin M (IgM) – IgG Results

The study revealed that 99.2% of the cases tested positive for IgG antibodies. Pregnant women who tested positive for IgM antibodies underwent avidity testing, which predominantly showed high avidity, except for one case with low avidity. It remained unclear whether the infections were primary or secondary.

The seropositive cases were more prevalent in the age group of 20-35, with a mean age of 27.74 (Figure 2).

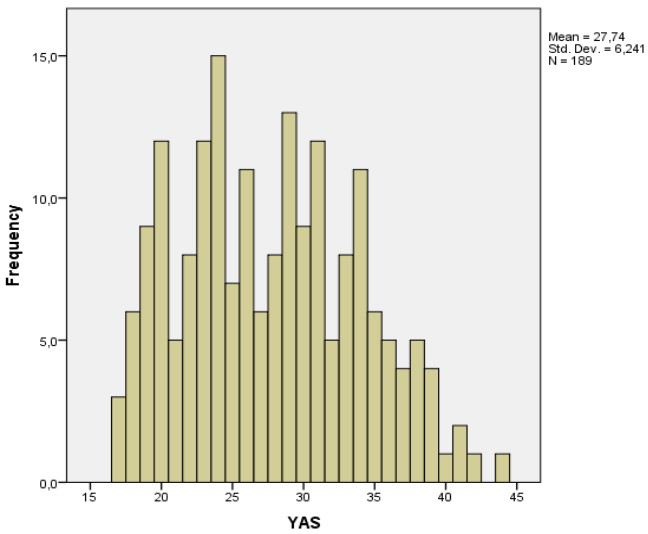

Fig. 2: Age Distribution in Seropositive Cases

CMV IgM and IgG positivity in pregnant women were categorized based on trimesters, and factors to be assessed were compared among the trimesters.

Among the 189 individuals who tested positive for both IgM and IgG, 43.9% were primigravida and 29.6% were multigravida.

In the study, it was observed that 42.16% of the 189 participants were in the first trimester, 42.70% were in the second trimester, and 15.14% were in the third trimester. More than 80% of seropositivity cases were observed in the first two trimesters (Figure 3).

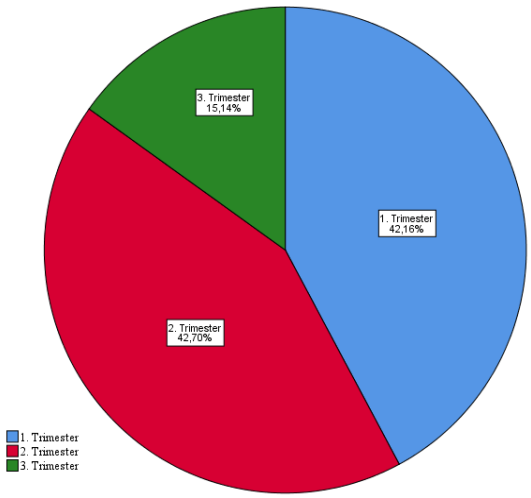

Fig. 3: Distribution of immunoglobulin M (IgM) and Ig G positivity by Trimesters

In the fetal anomaly screening results, 95 individuals did not undergo screening, and 52 individuals had normal results. The remaining individuals had anomalies related to the neurological (15%), urogenital (10%), cardiovascular (9%), gastrointestinal (8%), and maternoplacental (5%) systems (Table 1).

Table 1: Fetal Anomaly Screening Ultrasonography Results and Distribution by Trimester

Parameters	1st trimester n/%	2nd trimester n/%	3rd trimester n/%	Total n/%
Normal	21 (41.2)	22 (43.1)	8 (15.7)	51 (100.00)
Patients without imaging	42 (45.2)	37 (39.8)	14 (15.1)	93 (100.00)
Patients with Pathology on Imaging	15 (36.6)	20 (48.8)	6 (14.6)	41(100.00)
Total	78 (42.2)	79 (42.7)	28 (15.1)	185 (100.00)

The most commonly observed anomalies in the study were pelvicaliectasis, hyperechogenic cardiac focus, fetal echogenic bowel, and choroid plexus cysts and unilateral ventriculomegaly (4 individuals each). Other anomalies included oligohydramnios, megacystis, meningomyelocele, limb shortening, cystic hygroma, transposition of the great arteries, holoprosencephaly, neural tube defect, suboptimal evaluation of the atrial septum secundum, aberrant right subclavian artery, absence of the gastric pouch, and heterogeneous appearance of the right cerebral hemisphere. These identified anomalies were coincidentally observed and no association with CMV could be determined.

Looking at systemic involvement, it was found that the most common involvement was neurological, with incidence rates of 11.5%, 5.1%, and 2% for each trimester, respectively. Cardiovascular and urogenital system involvement ranked second, with the same number of anomalies seen in each trimester, with incidence rates of 3.8%, 6.3%, and 3.6%. Gastrointestinal involvement was observed in 8 individuals (1.3%, 7.6%, and 3.6%, respectively), and placental insufficiency was observed in 5 individuals (2.6%, 2.5%, and 3.6%, respectively).

In this study, fetal anomaly screening ultrasound results were compared between trimesters in which CMV IgM and IgG were detected as positive. Pathological findings were most common in the second trimester group, followed by the first trimester group. Babies with normal birth weights accounted for over 80% of those who tested positive for both CMV IgM and IgG. Although there was a 12.7% incidence of low birth weight babies in the first-trimester seropositivity group, the mean birth weights did not significantly differ between the groups (p: 0.262) (table 2). In the second trimester, IUGR was observed in 7 out of the patients with CMV positivity (26.9%), while in the third trimester, IUGR was detected in 11 out of the patients with CMV positivity (47.8%). This difference was not statistically significant (p=0.15).

Table 2: The Relationship Between Trimesters Diagnosed by Pregnants and Birth Weight

Parameters	Number of patients n	Mean birth weight±standard deviation (gr)	p value
1st trimester	24	2.993.33±619.607	**0.262**
2nd trimester	27	3.262.78±609.580	
3rd trimester	20	3.130.10±486.299	
Total	71	3.134.32±584.410	

In this study, the majority (two-thirds) of positive cases with 1st APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score 4 6 were in the first trimester. However, there was no significant difference in mean 1-minute and 5-minute APGAR scores among trimesters (respectively; p: 0.831, p: 0.546). Health problems were

observed in 9% of the newborns, with 61.1% of sick newborns attributed to infections in the first trimester. Head circumference and length results were not statistically significant based on trimester of infection (respectively; p: 0.383, p: 0.184).

Of the newborns included in the study, 9.6% (n=18) were symptomatic. Only one of these newborns was found to have sensorineural hearing loss. During the follow-up period, termination was recommended for five individuals due to fetal anomaly indications. Additionally, one newborn had jaundice, one had isolated lower limb agenesis, one had delayed speech, one had cerebral palsy, one had dermatitis, one had spina bifida, one had anemia, one had wheezing, and one had transposition of the great arteries (Table 3). All the data presented in Table 3 pertains to observations made during the neonatal period.

Table 3: Follow-up Results of Newborns of Cytomegalovirus Infected Mothers

Parametreler	Number of Newborns n	%
No information	89	47.1
Asymptomatic	82	43.3
Hearing loss	1	0.5
Abortion	3	1.6
Termination	5	2.6
Anemia	1	0.5
Transposition of the great arteries	1	0.5
Wheezing	1	0.5
Spina Bfida	1	0.5
Dermatitis	1	0.5
Cerebral palsy	1	0.5
Jaundice	1	0.5
Limb shortening	1	0.5
Speech disability	1	0.5
Total	189	100

Seventy-five of the infected mothers gave birth at our hospital. Of these, 30.7% delivered before 37 weeks and 66.7% delivered between weeks 37-41 of gestation.

Out of 80 individuals recommended for amniocentesis in the study, only 16 accepted. All those who accepted had negative CMV PCR results and only one person had Down syndrome. Postpartum results of six pregnant women who underwent amniocentesis were unavailable, but no problems were observed in the remaining cases. Among those who declined, three were found to have health problems. The investigation of CMV was not conducted in infants.

Discussion

CMV infection in infants is a significant public health concern, causing congenital infection and posing a serious risk of illness, particularly in pregnant women with impaired immune function and their fetuses. [1] This virus can be transmitted to the fetus through the transplacental route, leading to long-term effects and emphasizing the urgent need for screening and intervention. [1]

Our study had a larger sample size compared to other studies, [15,16,21] and our hospital is one of the major hospitals in Turkey, located in one of the three largest cities. It is a tertiary training and research hospital. The study's patient population is representative of the socioeconomic distribution in Turkey, making it a study that reflects the nationwide context. Furthermore, it can be described as a seroprevalence study that reflects the nationwide prevalence in Turkey.

The screening of CMV during pregnancy is currently a subject of debate. The objective of our study was to contribute to this ongoing discussion by analyzing the ultrasonography results, amniocentesis outcomes, and neonatal data gathered during the pregnancy monitoring of 189 women who tested positive for both CMV IgM and IgG.

The prevalence of CMV varies from region to region. The seroprevalence rates of countries range from 80% to 100%. [22] The seroprevalence worldwide is 83%, with rates of 90% in the Eastern Mediterranean and 66% in Europe. In Turkey, the prevalence is 96%, while in Ireland it is 39%, according to another study cited in the same article (Biron, 2006). Brazil (98%) and Sudan (97.8%) have similar rates to Turkey, while France (60%) and Finland (72%) show compatibility with other studies conducted in Europe. [1]

The regional study conducted in Turkey showed similar results, with CMV seroprevalence rates of 93.42% in Isparta (2017), 99.45% in Istanbul (2015), 98.90% in Izmir (2017), 98,2% in Kayseri (2018), [22] 91.54% in Zonguldak (2015), and 98.50% in Ankara (2011). [16]

We conducted a study between 2012 and 2021 to screen for CMV IgM and IgG in 11,609 pregnant women. The seroprevalence of anti-CMV IgG was calculated to be 99.2%, which was found to be similar to the average of Turkey, estimated at 97.7%. [16] Our study results are consistent with those reported in developing countries.

Our study found that having more than two births did not increase the risk of CMV infection, which is cont-

rary to what is reported in the literature. The average age of those who tested positive for both IgM and IgG was 27.74, which also differs from the literature.

The increased infection rate in these pregnancies is likely attributable to the fertility rate in İzmir, which was reported as 1.48 according to the TSI (Turkish Statistical Institute) 2019 data. The predominance of multigravida individuals among pregnant women who tested positive for both IgM and IgG antibodies in our study provides support to this finding.

Studies have shown that babies of pregnant women with primary CMV infection have a 10-15% chance of experiencing symptomatic congenital infection. [1]The central nervous system is the most commonly affected system, which is consistent with clinical research findings. [16] In a study conducted by Kalaycı et al., it was emphasized that CMV positivity was observed in ventriculomegaly cases at varying frequencies depending on the severity of ventriculomegaly. [23] Severe ventriculomegaly was not detected in this study. However, it is important to note that ventriculomegaly may be present in patients with CMV positivity. This finding emphasizes the need for careful evaluation of patients with CMV positivity, particularly those with ventriculomegaly, in order to facilitate appropriate clinical management.

In our study, cerebral palsy was detected in a pregnant woman. Although it is not possible to determine the exact causes of cerebral palsy in this case, asphyxia can be considered among the possible causes. Asphyxia can occur due to various reasons such as nulliparity, intrauterine growth restriction, prolonged second stage of labor, presence of meconium, or category II and III fetal heart rate monitoring tracings. [24]

In a study involving 13 pregnant women with positive serology, it was determined that active virus replication was present in three of them, and those with replication had a history of primary infection. The study also demonstrated that those without replication were experiencing recurrent infections. [16] The negative results of CMV PCR in amniotic fluid cultures in our study were attributed to recurrent infections.

The sensitivity of routine ultrasound in predicting neonatal symptoms is approximately 25%. [1] Although it is believed that the pathological findings detected on ultrasound, such as fetal echogenic bowel, IUGR, and intracranial abnormalities, [1] may be associated with CMV, the exact relationship could not be fully understood due to the insufficient number of patients undergoing amniocentesis.

Approximately 20% of newborns with congenital infections exhibit neurological sequelae. [16] Of the infected mothers whose newborn data we were able to obtain in our study, symptoms were not observed in 82 (43.3%), but health problems were observed in 18 (9%). The neonatal symptoms identified in our study were similar to those reported in the literature.

The probability of transmission is lower in the first trimester compared to other trimesters. However, if infection occurs during this period, it poses a higher risk for long-term fetal sequelae and symptomatic disease after birth compared to infections that occur in other trimesters. [10] In our study, we observed health problems in 11 (61.1%) newborns whose mothers had IgM positivity in the first trimester, consistent with the literature that suggests infections in the first trimester cause more sequelae. The higher prevalence of seropositivity in the first trimester is also consistent with previous research. Nonetheless, this may have led to a greater number of health problems in this trimester.

The average gestational age of our patients was 38 weeks, and 30.7% of them experienced preterm birth. In a study conducted by Numan, [15] the information regarding the increased risk of preterm birth due to CMV infection is controversial, as only one out of 13 infected mothers gave birth before 38 weeks. Hence, we cannot attribute the preterm birth of the patients in our study solely to CMV infection.

CMV is a major cause of nonhereditary adverse birth outcomes, including IUGR, stillbirth, and preterm delivery. While the exact mechanisms by which CMV leads to these adverse outcomes are not fully understood, studies have identified potential mechanisms such as impairment of trophoblast differentiation, dysregulation of signaling pathways, and cytokine changes in the placenta. [25] Although we detected IUGR associated with CMV, we did not find any statistically significant differences in terms of IUGR when we analyzed the data based on the trimesters in which seropositivity was detected.

The strengths of our study include the inclusion of a diverse patient group consisting of individuals reflecting the socio-economic distribution in Turkey, thereby representing the health status of various socio-economic groups. Additionally, another strong aspect of our study is the extensive screening of a large number of patients. However, there are weaknesses in our study, such as patients refusing treatment and the majority of patients rejecting diagnostic procedures, such as amniocentesis. Furthermore, the fact that many patients did not give birth at our hospital has created limitations in the data available for newborns, which is seen as a weakness. These factors indicate that the generalizability of our study results may

be limited in terms of overall validity.

Conclusion

CMV infection in infants can lead to congenital infection, posing a risk of illness. Pregnant women with impaired immune function are particularly vulnerable. Furthermore, CMV can be transmitted to the fetus through the transplacental route, highlighting the need for screening and intervention to prevent long-term effects.

It is important to be aware of the prevalence rates of CMV in your region. Conducting more seroprevalence studies in specific areas and at different times can fill gaps in the literature and aid in the development of prevention and treatment strategies. Implementing preventive measures is the most effective way to reduce infection rates, and increasing awareness through educational programs in healthcare centers can be beneficial. Screening for CMV during pregnancy is currently a topic of debate. Prospective and concurrent studies will be particularly useful in determining the best approach for screening and intervention.

To prevent the potential effects and neurological sequelae of congenital CMV infection in the fetus, careful evaluation, early diagnosis, and appropriate management of patients with CMV positivity are crucial.

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