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Original Article

Results of Routine Antenatal Screening for Cytomegalovirus at a Tertiary Center

Tersiyer Bir Merkezde Rutin Antenatal Sitomegalovirüs Taraması Sonuçları

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ABSTRACT

Objective: Cytomegalovirus (CMV) is the most common viral infection. In this study, we discussed the results of pregnant women who underwent antenatal CMV screening in a tertiary center and the value of CMV antenatal screening.

Methods: For this retrospective study, the data of pregnant patients with antenatal CMV screening test results between 2019 and 2022 were obtained from hospital records. CMV immunoglobulin M (IgM), CMV IgG, anti-IgG avidity test results, amniocentesis, CMV polymerase chain reaction (PCR), and the outcome of the babies were recorded.

Results: A total of 31,912 CMV IgM and 26,969 CMV IgG tests were performed. CMV IgG seropositivity was observed in 78.99% of pregnant women, and 0.09% of the pregnant women were confirmed to have a positive CMV IgM test result. Pregnant women with positive IgM accompanying low avidity were referred to perinatology clinics for detailed ultrasonography and amniocentesis. Only 3 of the 44 pregnant women who underwent amniocentesis were confirmed to have positive CMV PCR testing.

Conclusions: CMV screening should be preserved for pregnant women with ultrasonographic findings at high risk of congenital CMV infection.

Keywords: Cytomegalovirus, antenatal screening, pregnancy, prevalence, fetal infection

ÖZ

Amaç: Sitomegalovirüs (CMV), en sık viral enfeksiyondur. Bu çalışmada tersiyer bir merkezde antenatal CMV taraması yaptıran gebelerin sonuçlarını ve antenatal CMV taramasının değerini tartışmayı amaçladık.

Yöntemler: Bu retrospektif çalışma için 2019-2022 yılları arasında antenatal dönemde CMV tarama testi sonuçları olan gebelerin verileri hastane kayıtlarından elde edildi. CMV immünoglobulin M (IgM), CMV IgG, anti-IgG avidite, amniyosentez, CMV polimeraz zincirleme reaksiyonu (PZR) test sonuçları ve bebeklerin yenidoğan dönemindeki sonuçları kaydedildi.

Bulgular: Toplam 31.912 CMV IgM ve 26.969 CMV IgG testi yapılmıştı. Gebelerin %78,99'unda CMV IgG seropozitifliği görülmüş ve %0,09'unun CMV IgM test sonucunun pozitif olduğu doğrulanmıştır. Düşük aviditeye eşlik eden IgM pozitifliği olan gebeler ayrıntılı ultrasonografi ve amniyosentez için perinatoloji kliniğine yönlendirildi. Amniyosentez yapılan 44 gebeden sadece 3'ünün CMV PZR testinin pozitif olduğu doğrulandı.

Sonuçlar: Konjenital CMV enfeksiyonu açısından yüksek riskli ultrasonografik bulguları olan gebelerde CMV taraması uygulanmalıdır.

Anahtar kelimeler: Sitomegalovirüs, antenatal tarama, gebelik, prevelans, fetal enfeksiyon

INTRODUCTION

Cytomegalovirus (CMV) is a DNA virus from the herpesvirus family and is the most common congenital viral infection. The seroprevalence of CMV was reported to be the highest in the Eastern Mediterranean region at 90%, with a global seroprevalence of 83%[1,2]. The prevalence of active CMV infection during pregnancy was reported to be between 0.3% and 2.4%[3]. During pregnancy, whereas transplantal transmission of the virus spread was reported to be between 24% and 75% with the first infection of pregnant women, it was reported to be between 1% and 2.2% with non-primary infections[4]. Additionally, while the rate of maternal-fetal transmission is low in the first trimester, the rate of transmission to the fetus increases with advancing

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gestational age[5]. Conversely, infection at the early weeks of gestation was more often associated with long-term sequelae of CMV such as sensorineural hearing loss and mental retardation[6,7].

CMV, similar to other herpes viruses, remains latent after the primary infection and can reactivate. It is also possible to be infected with another viral strains[8]. Therefore, it is not easy to diagnose. The maternal diagnosis of suspected primary CMV infection is seroconversion. However, in cases where documented seroconversion is absent, the presence of anti-CMV immunoglobulin G (IgG) and anti-CMV IgM may represent primary infection, reactivation, reinfection, or latent disease. In these cases, the anti-CMV IgG avidity test is the most reliable test to demonstrate acute or recent infection. Maternal CMV infection during pregnancy can be diagnosed by the detection of IgG positivity in pregnant women known to be seronegative before or with low IgG avidity accompanying IgM positivity. The secondary infection can be considered in the increase in IgG antibody titers[9]. Prenatally, amniocentesis is performed for diagnosis.

It has been shown that seroconversion decreases with preventative approaches such as personal hygiene education during pregnancy[10,11]. It has been studied whether the use of hyperimmunoglobulins and valacyclovir for treating CMV reduces congenital infections[12,13]. Although there is no vaccine found yet, vaccine studies are still ongoing[14]. However, routine CMV screening is still a debated topic and is not recommended by some guidelines[15-17]. It is even thought that routine screening leads to unnecessary interventions[18]. In this study, we aimed to discuss the results of pregnant women who underwent antenatal CMV screening in a refereed hospital in Turkey and the value of CMV antenatal screening.

MATERIALS and METHODS

This retrospective study was approved by the Ankara City Hospital Institutional Review Board (no: E2/22/2319, date: 07.09.2022). The data of the patients between 2019 and 2022 were obtained from the hospital records. In our hospital, which is one of the largest tertiary centers in the country, CMV screening is routinely performed as a part of antenatal screening at the first admission to the hospital during pregnancy (first trimester) and is free of charge. As a routine procedure, all pregnant women were counseled about behavioral and hygienic measures and the likelihood of fetal infections. Informed consent was obtained from all pregnant individuals at the initial examination in our hospital as a routine procedure.

Patients with antenatal CMV screening test results, which were sent from the outpatient clinics, were the inclusion criteria. 31,912 CMV serum screening tests were determined during the study period.

LIAISON diagnostic system kits were used to test CMV IgM and CMV IgG from serum samples. The LIAISON assay uses chemiluminescent immunoassay technology for quantitative determination of specific antibodies to CMV in serum samples. VIDAS automated analyzer system was used to test the avidity. The VIDAS assay is an automated qualitative test for determination of anti-IgG avidity in human serum using enzyme-linked fluorescent assay technique. Avidity test results were divided into three groups: low, intermediate, and high avidity. Patients with an avidity index <0.40 were considered low avidity, while 0.40-0.65 was considered intermediate and ≥0.65 high avidity. Pregnant women with positive test results were re-evaluated and the tests were sent to the control.

In addition, pregnant women with positive IgM accompanying low avidity were referred to perinatology outpatient clinics for a detailed ultrasound examination, and amniocentesis was performed, CMV polymerase chain reaction (PCR) was sent to the reference molecular laboratory. Additionally, the age of the pregnant women was recorded.

Statistical Analysis

SPSS 20.0 statistical software (SPSS, Inc., Chicago, IL, USA) program was used to analyze the data. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test normality. Normally distributed data were presented as mean ± standard deviation. Non-normally distributed data were presented as median (minimum-maximum). Categorical data are presented as number (%). Mann-Whitney U test was used to compare the CMV IgM-positive and negative patient age.

RESULTS

Over 3 years of data were included in this study. A total of 26,969 CMV IgG tests were performed. CMV IgG seropositivity was observed in 21,305 pregnant women (78.99%). Additionally, of the 31,912 CMV IgM tests, 28 pregnant women were confirmed to have a positive CMV IgM test result (0.09%). The frequency of CMV IgG and CMV IgM distribution by years are shown in Table 1 and Table 2, respectively.

While the median age of the pregnant women who were CMV IgM positive was 26 (18-37), the median age of the pregnant women who were CMV IgM negative was 28 (16-44) (p=0.007).

There were 97 pregnant women with high avidity and 10 pregnant women with intermediate avidity. Ten pregnant women with intermediate avidity were reevaluated and all intermediate avidity test results were confirmed to have high avidity. Additionally, 46 pregnant women with positive IgM accompanying low avidity were referred to perinatology outpatient clinics for a detailed ultrasound examination and amniocentesis. Amniocentesis was performed on 44 of these pregnant women, and CMV PCR was sent to the molecular laboratory. Only three pregnant women were confirmed to have positive CMV PCR testing (Figure 1). None of the pregnant women received antiviral therapy.

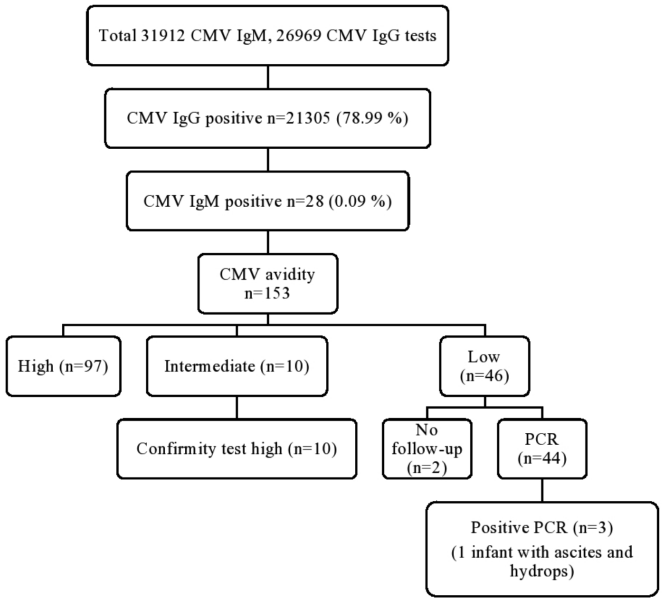

Figure 1. CMV screening flowchart.

CMV: Cytomegalovirus, IgG: Immunoglobulin G, IgM: Immunoglobulin M, PCR: Polymerase chain reaction

Table 1. CMV IgG seropositivity by years.

Years	Total test (n)	CMV IgG positive (n, %)
2019	2283	1553 (68.02%)
2020	6715	4724 (70.35%)
2021	11660	9437 (80.94%)
2022	6311	5591 (88.59%)
Total	26969	21305 (78.99%)

Values were presented as number (%). CMV: Cytomegalovirus, IgG: Immunoglobulin G

Table 2. CMV IgM seropositivity by years.

Years	Total test (n)	CMV IgM positive (n, %)
2019	2617	6 (0.02%)
2020	8266	7 (0.09%)
2021	13514	9 (0.07%)
2022	7515	6 (0.08%)
Total	31912	28 (0.09%)

Values were presented as number (%). CMV: Cytomegalovirus, IgM: Immunoglobulin M

In a fetus, there were findings of ascites and hydrops in the abdomen during the intrauterine period. For the other two fetuses of pregnant women who were confirmed to have positive PCR testing, no ultrasonographic finding that could be related to CMV was observed. In the neonatal period, CMV IgM positivity was detected and confirmed in these babies, and the babies passed the hearing test in the newborn period.

Pregnant women whose amniocentesis was performed before 21 weeks of gestation and less than 6 weeks from the estimated time of infection were offered to have a repeat amniocentesis, however, they did not accept.

DISCUSSION

CMV was reported to be at different frequencies in different countries around the world. CMV is the most common viral infection[1,2]. Although maternal CMV infection can be mildly symptomatic with flu-like symptoms, the fetal effects can be more devastating, especially if the infection occurs during the early weeks of gestation[6,7]. In the current study, CMV screening results over three years in one of the largest hospitals in Turkey were evaluated. CMV IgG seropositivity was observed in almost eighty percent of pregnant women. A total of 31,912 CMV IgM tests were performed. However, only 0.09% of the pregnant women were confirmed to have a positive CMV IgM test result. In our study, pregnant women with positive IgM accompanying low avidity were referred to perinatology clinics. Only 3 of the 44 pregnant women who underwent amniocentesis were confirmed to have positive CMV PCR testing.

The high rate of CMV IgG seropositivity found in our study is actually compatible with the literature[1,2]. However, the number and rate of CMV IgM-positive patients were found to be quite low. Sert et al.[3] evaluated the CMV screening results of a tertiary hospital between 2008 and 2017. Compared with this study, our results showed that IgG seropositivity in the Turkish pregnant women population has increased over the years, but CMV IgM positivity has decreased. The increased IgG seropositivity may be due to the increased number of refugees who can receive health services in our country. Additionally,

the rate of CMV primary infection and CMV IgM positivity during pregnancy may have decreased with the increased participation in the pregnancy training education school in our hospital and the routine infection precautions and hygiene education given to pregnant women. It is seen in the literature that the CMV rate was lower in patients who received hygiene education[10,11].

The number of pregnant women who underwent amniocentesis was quite high in our study. This finding brings back the debate about whether CMV screening should be performed routinely or does this increase unnecessary interventions and should be performed only when there are CMV-related ultrasonography findings. Unlike the routine protocol in our hospital, in some studies and guidelines, routine CMV screening is not recommended as no clear intervention has been found that was shown to change the course of the disease[15-17].

The most common ultrasonography findings of a CMV infection during fetal life were reported to be cerebral calcifications, microcephaly, echogenic bowel, fetal growth restriction, cerebral ventriculomegaly, ascites, pericardial effusion, subependymal cysts, hyperechogenic kidneys, hepatomegaly, placentomegaly/placental calcifications, hepatic calcifications, hydrops[19]. We think that the high number of amniocentesis in our study was because the procedure was free of charge and this right was granted to every patient with any of the ultrasonography findings. In the current study, one infant who was confirmed to be CMV positive was found to have ascites and hydrops during the fetal life and the neonatal period.

Our study occurred in one of the largest hospitals in Turkey with many patients. Therefore, it reflects the serological status of the Turkish population. However, the main limitation was the retrospective design of the study. Another limitation was that some patients were lost to follow up. The incomplete data of this research may lead to the lack of credibility of the results.

CONCLUSION

In conclusion, we found a high rate of CMV IgG positivity in our study. According to the results of this study, CMV screening should be preserved for pregnant women at high risk of congenital CMV infection. Ultrasonographic findings and patient history may be beneficial in the selection of appropriate cases.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ankara City Hospital Institutional Review Board (no: E2/22/2319, date: 07.09.2022).

Informed Consent: Informed consent was obtained from all pregnant individuals at the initial examination in our hospital as a routine procedure.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: I.O., S.S., E.T., Concept: D.T.E., I.O., A.G.B., E.G.Y., S.S., E.T., O.K., D.S., Design: D.T.E., I.O., A.G.B., E.G.Y., S.S., E.T., D.S., Data Collection and/or Processing: D.T.E., A.G.B., E.G.Y., S.S., A.T., Analysis and/or Interpretation: D.T.E., A.G.B., E.G.Y., S.S., A.T., Literature Search: D.T.E., I.O., E.T., O.K., A.T., D.S., Writing: D.T.E., E.T., O.K., A.T., D.S.

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