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Evaluation of Cytomegalovirus Seroprevalence in Pregnant Women: A Multicenter Study

Gebe Kadınlardaki CMV Seroprvalansının Değerlendirilmesi: Çok Merkezli Bir Çalışma

Sefa Sayar et al. Cytomegalovirus in Pregnant Women

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Abstract
Introduction: Cytomegalovirus (CMV) infection during pregnancy poses a significant risk of congenital infection, particularly in seronegative women. This study aimed to assess CMV seroprevalence among pregnant women and evaluate the incidence of primary CMV infections during pregnancy.
Materials and Methods: This retrospective multicenter study included pregnant women aged ≥18 year who were hospitalized between January 2018 and December 2022. Demographic data - including maternal age, gravidity, and educational and occupational status - along with CMV serological results, gestational age at CMV diagnosis, and fetal ultrasonographic (USG) findings were collected and analyzed. In cases with positive CMV immunoglobulin M (IgM) and IgG, CMV-IgG avidity values, amniotic fluid CMV-DNA polymerase chain reaction results, and fetal USG findings were recorded to assess the likelihood of primary infection.
Results: Among 16,761 pregnant women, 261 (1.6%) tested positive for CMV-IgM. Of these, 126 (48.3%) underwent CMV-IgG avidity testing, and three cases demonstrated low avidity, indicating recent primary infection. Ultrasonographic abnormalities in these three fetuses included hydrops fetalis, polyhydramnios, skin edema, and hyperechogenic bowel. Additionally, five patients with high CMV-IgG levels underwent IgG avidity testing; fetal USG findings in these cases revealed intrauterine growth restriction, oligohydramnios, and cranial abnormalities.
Conclusion: Primary CMV infection during pregnancy is associated with adverse outcomes such as fetal anomalies, spontaneous abortion, and preterm birth. Preventive strategies, including educating CMV-seronegative women about transmission routes and routine assessment of CMV-IgG avidity and fetal USG findings, are essential for early diagnosis and improved perinatal outcomes.
Keywords: Abortion, congenital infection, cytomegalovirus, fetal abnormalities, pregnancy, seroprevalence

Öz
Giriş: Seronegatif kadınlarda sitomegalovirüs (CMV) enfeksiyonuna bağlı konjenital enfeksiyon riski çok yüksektir. Bu çalışmada gebelerde CMV seropozitivite prevalansı araştırılmıştır ve gebelikte primer CMV enfeksiyonu oranları değerlendirilmiştir.

Gereç ve Yöntem: Çalışma çok merkezli planlanmış olup; retrospektif dizayndadır. Ocak 2018 ile Aralık 2022 tarihleri arasında takip edilen 18 yaş ve üzeri kadınlar dahil edilmiştir. Hastaların CMV açısından tetkik edildiği yaş, gebelik sayısı, eğitim ve mesleki durumu, CMV seropozitifliği, gebelik yaşı ve fetal ultrasonografi (USG) sonuçları geriye dönük olarak incelendi. Sitomegalovirüs IgM ve IgG pozitifliği olan olgularda CMV-DNA polimeraz zincir reaksiyonu sonuçları ve fetal USG bulguları ile birlikte CMV-IgG avidite değerleri kaydedildi.
Bulgular: 16.761 gebenin CMV-IgM ve IgG tetkikleri birlikte mevcuttu. Toplam 261 (%1,6) gebenin CMV-IgM testi pozitifti. Yüz yirmi altısında (%48,3) CMV-IgG avidite test sonucu görüldü ve bunların üçü düşük avidite indeksine sahipti. Primer CMV enfeksiyonu saptanan üç fetüsün USG bulgularında hidropik değişiklikler, polihidramnios, deri ödemi ve hiperekojenik bağırsak saptandı. Sitomegalovirüs-IgG değerleri yüksek olan beş olguya CMV-IgG avidite testleri de yapıldı. Bu olguların fetal USG bulgularında intrauterin gelişme geriliği, oligohidramnios ve kraniyal anomaliler mevcuttu.
Sonuç: Primer CMV enfeksiyonu fetal anomaliler, düşük, erken doğum gibi olumsuz gebelik sonuçlarına neden olabileceğinden, CMV seronegatif gebelerin CMV bulaşma yolları hakkında bilgilendirilmesi öncelikli olarak ele alınmalıdır. Sitomegalovirüs-IgG avidite ve fetal USG değerlendirmelerine dikkat edilmelidir.
Anahtar Kelimeler: Abortus, konjenital enfeksiyon, sitomegalovirüs, fetal anormallikler, gebelik, seroprevalans

Introduction

Cytomegalovirus (CMV) is a common viral pathogen that can cause congenital infection when transmitted during pregnancy. *In utero* transmission may result in intrauterine growth restriction, developmental delays, and long-term neurological sequelae in the fetus[1,2]. Although CMV can be transmitted at any stage of pregnancy, the risk of fetal infection is highest during the first half[2]. In addition to vertical transmission, CMV can also be acquired postnatally through exposure to infected oral secretions, urine, or other body fluids[3,4].

Globally, the estimated CMV seroprevalence in the general population is approximately 83%, with Europe reporting the lowest regional rate at 66%. Among women of reproductive age, seroprevalence rates are reported to be 86%, increasing to 97% in Türkiye. Cytomegalovirus is the most common congenital viral infection, with a prevalence during pregnancy ranging from 0.48% to 1.3%[5,6].

While the majority (about 90%) of infants with congenital CMV infection are asymptomatic at birth, approximately 10% present with clinical signs such as petechiae, jaundice, hepatosplenomegaly, intrauterine growth restriction, and microcephaly[7,8]. Recent advances in prenatal screening and imaging technologies have significantly enhanced the early detection of fetal anomalies, even in cases where serological markers may not yet be evident. Detailed fetal ultrasonography (USG) has become instrumental in identifying structural abnormalities associated with congenital infections.

Although several regional studies in Türkiye have assessed CMV seroprevalence in pregnant women, comprehensive nationwide data remain limited. This multicenter study aimed to evaluate CMV seropositivity among pregnant women and to determine the prevalence of primary CMV infections during pregnancy.

Materials and Methods

This nationwide, multicenter, retrospective, descriptive study included pregnant women aged ≥18 year who were admitted for routine obstetric follow-up between January 1, 2018, and December 31, 2022. Data were collected from multiple centers across various regions of Türkiye, including Bursa, İstanbul, Ankara, Çanakkale, Manisa, Kayseri, Konya, Kırıkkale, Trabzon, Van, and Şanlıurfa.

The following demographic and clinical variables were retrospectively reviewed from hospital records: maternal age, number of pregnancies and living children, educational and occupational status, gestational week at CMV screening, hepatitis B and C serology, human immunodeficiency virus (HIV) serology, fetal USG findings, and CMV-IgM and IgG levels. Participants were categorized based on nationality, occupation, gestational age at testing, gravidity, and maternal age. Due to incomplete data, serological findings for hepatitis B, hepatitis C (HCV), and HIV were reported only for patients with available results.

Laboratory Testing for CMV Seropositivity and Diagnosis of Primary CMV Infection

Cytomegalovirus serological testing was performed using commercial platforms from Roche (Mannheim, Germany), Abbott (Ireland, USA), and bioMérieux (Marcy-l'Etoile, France), depending on the facility (Table 1). Given the variability in testing equipment across centers, a standardized sample-to-control index (S/C) cutoff value of 1.0 was used to define positivity for both CMV-IgM and IgG antibodies when the same assay technology was applied. For one center that used arbitrary units (AU/mL) rather than the S/C index, results were recorded as positive or negative according to the center's established cutoffs and included accordingly.

For patients with simultaneous CMV-IgM and IgG positivity - indicative of potential primary CMV infection - we further analyzed CMV-IgG avidity values, CMV-DNA polymerase chain reaction (PCR) results from biological fluids (e.g., urine or amniotic fluid), and fetal USG findings.

Study Population

Of the initial 17,059 pregnant women screened for CMV serology, 298 were excluded due to incomplete or inconclusive data: one had isolated CMV-IgM positivity, 175 had only CMV-IgG positivity, 121 had intermediate CMV-IgM levels without confirmatory IgM or IgG avidity testing, and one had an intermediate CMV-IgG level without control or avidity data (Figure 1). After exclusions, 16,761 women with complete CMV-IgM and IgG results were included in the final analysis of seroprevalence.

For subgroup analyses evaluating associations between CMV seropositivity and maternal characteristics (age, gravidity, gestational week at testing, and number of living children), only participants with complete datasets were considered. This subset comprised 4,022 women (Table 3).

Ethical approval for the study was granted by the University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital Local Institutional Ethics Committee (decision no: 2011-KAEK25 2023/01-04, decision date: 25.01.2023).

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for the Social Sciences statistics for Windows, version 23.0 (IBM Corp., Armonk, New York). The distribution of continuous variables was assessed visually (histograms, probability plots) and analytically (Kolmogorov-Smirnov and Shapiro-Wilk tests). Normally distributed variables were reported as means with standard deviations, while non-normally distributed and discrete variables were presented as medians with interquartile ranges.

Comparisons between groups were performed using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed or categorical variables. A two-tailed p value <0.05 was considered statistically significant.

Results

General Characteristics of the Study Population

A total of 16,761 pregnant women were included in the study, of whom 8% (n=1,342) were immigrants. The mean age of the participants was 28.08±6.5 year. Serological testing for CMV was performed at a mean gestational age of 11.22±7.58 weeks.

Occupational data were available for 539 participants. Among these, 41.3% (n=223) were housewives, 31.1% (n=168) were employed in the private sector, 24.8% (n=134) were employed in the public sector, and 2.5% (n=14) were blue-collar workers (Table 2).

Serological testing for hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV antibodies was not available for all participants. Specifically, 4,598 women were tested for HBsAg, 4,601 for anti-HCV, and 4,234 for anti-HIV. The prevalence rates were as follows: HBsAg positivity, 1.69% (78/4,598); anti-HCV positivity, 0.15% (7/4,601); and anti-HIV positivity, 0% (0/4,234).

The prevalence of CMV-IgM positivity was 1.6% (n=261), while CMV-IgG positivity was observed in 99.6% of the participants.

Evaluation of Factors Associated with CMV-IgM Positivity

The association between CMV-IgM positivity and selected maternal factors was analyzed in a subgroup of 4,022 women for whom complete data were available on CMV-IgM/IgG levels, gestational age at testing, gravidity, and number of living children.

There was no statistically significant difference in the number of pregnancies between CMV-IgM-positive and CMV-IgM-negative women ($p>0.05$; Table 3). However, the gestational age at the time of CMV-IgM testing was significantly higher among IgM-positive women compared with the IgM-negative group ($p=0.002$). Additionally, the number of living children was significantly greater among CMV-IgM-positive women ($p=0.029$; Table 3).

CMV-IgG Avidity, Fetal Ultrasonographic Findings, and Pregnancy Outcomes in CMV-IgM-positive Women

Of the 261 CMV-IgM-positive women, 126 (48.3%) underwent CMV-IgG avidity testing. Among them, three women (2.4%) had a low CMV-IgG avidity index, suggesting primary CMV infection. These women were evaluated via fetal USG at a mean gestational age of 18 weeks (range: 16-20 weeks).

Ultrasonographic findings varied among the three women: one exhibited no abnormalities, one had findings of hydrops fetalis, polyhydramnios, and skin edema, and the third showed a hyperechoic bowel. Amniotic fluid analysis using CMV-DNA PCR was conducted in the first case, revealing a viral load of 2,214 IU/mL. This woman subsequently underwent pregnancy termination at 20 weeks. The remaining two women experienced preterm delivery at 27 weeks (Table 4).

Of the 126 women who underwent CMV-IgG avidity testing, 43 (34.1%) also had detailed fetal USG evaluations. Despite positive IgG avidity results, these women exhibited low avidity indices. Their mean gestational age at USG was 19.4 weeks (range: 10-23 weeks). Detected abnormalities included intrauterine growth restriction, oligohydramnios, and cranial malformations. These women either underwent amniocentesis or experienced spontaneous abortion, with a mean gestational age at intervention of 32.4 weeks (range: 12-40 weeks).

Among 35 women with no evidence of CMV infection, fetal USG revealed no abnormalities (median gestational age at examination: 18.9 weeks; range: 6-32 weeks). No further serological data were available for the remaining CMV-IgM-positive women who did not undergo additional testing.

Discussion

This cross-sectional study investigated the prevalence of primary CMV infection among pregnant women in Türkiye and evaluated the diagnostic and clinical characteristics of CMV infection during pregnancy. Cytomegalovirus infection is frequently underdiagnosed in women of reproductive age, despite its potential to cause severe fetal complications when acquired during gestation.

Globally, CMV seroprevalence among women of reproductive age is estimated at 86%. While this rate is approximately 70% in Europe, it reaches 92% in the Eastern Mediterranean region. In Türkiye, reported CMV seroprevalence among this population is as high as 96%[5]. Regional studies have reported similar rates, including 98.7-94.2% in Izmir, 98.8% in Rize, 98.7% in Denizli, 100% in Konya, and 96.4% in Çorum[9-14]. In our study, the CMV-IgG seropositivity rate was 99.6%, consistent with the high prevalence observed in previous Turkish studies.

Due to this widespread seropositivity, routine CMV screening during pregnancy is not currently recommended in many clinical guidelines[15]. However, targeted screening may be warranted in high-risk populations, particularly among pregnant women with frequent contact with young children, especially those under three year of age[16]. Young children can shed CMV asymptomatically, posing a risk of transmission to susceptible pregnant individuals[17]. Primary maternal infection during pregnancy can result in congenital CMV, which may manifest as fetal anomalies, intrauterine growth restriction, or fetal loss[1,18]. The risk of fetal transmission varies by trimester, with estimated rates of 30% in the first trimester and 47% in the third trimester[19].

In the present study, among 4,022 pregnant women with complete serologic data, CMV screening was more likely to be performed in later gestational weeks in those with CMV-IgM positivity. Additionally, CMV-IgM-positive women had significantly more children than CMV-IgM-negative women (Table 3). These findings highlight the importance of early CMV screening, particularly in multiparous women or those with regular exposure to young children.

Diagnosis of primary CMV infection relies on a combination of serological testing and detailed fetal USG[20]. Ultrasound findings such as periventricular echogenicity, ventriculomegaly, and intraparenchymal calcifications, as well as extracranial anomalies like echogenic bowel, cardiomegaly, hepatosplenomegaly, and pericardial effusion, can suggest congenital infection[21]. Feldman et al.[22] reported fetal echogenic bowel in nine of 17 cases, intrauterine growth restriction in four, and microcephaly in one. In our study, among 43 CMV-IgM-positive women who underwent fetal USG, 18.6% exhibited fetal anomalies, including cranial and extracranial abnormalities. The remaining 81.4% showed no abnormal findings on USG. Specific anomalies detected included hydrops fetalis, oligohydramnios, and intrauterine growth restriction. Although these women were diagnosed using serologic and USG findings, amniocentesis was not performed in most cases, limiting confirmation via CMV-DNA PCR.

In vitro studies have demonstrated that CMV can infect a variety of cell types, including epithelial cells, stromal cells, macrophages, and trophoblasts. Cytomegalovirus infection of trophoblasts induces inflammation and apoptosis, potentially impairing placental function and contributing to fetal complications[23]. Primary CMV infection during pregnancy has been associated with spontaneous abortion, preterm labor, and congenital anomalies[24]. Eletreby et al.[25] reported that among 201 pregnant women with CMV infection, 11% experienced preterm labor, and 3.77% had fetuses with congenital anomalies. In our study, of the eight women identified with primary CMV infection, one experienced pregnancy termination at 20 weeks, three had preterm deliveries, and the remaining three delivered at term. However, given the retrospective nature of the study and the inconsistent availability of advanced serologic and molecular testing across participating centers, it was not possible to evaluate all CMV-IgM-positive cases comprehensively. In particular, fetal USG and amniocentesis were not consistently performed, limiting our ability to accurately assess the incidence of primary CMV infection and its outcomes.

Our findings indicate that CMV seropositivity among pregnant women in Türkiye remains high, at 99.6%. Eight cases of congenital CMV infection were identified. Cytomegalovirus-IgM positivity was more common in women with more advanced gestational age and a higher number of children. Despite the high seroprevalence, early CMV screening during prenatal care, particularly in the first trimester, should be considered, especially for women at increased risk of exposure. Pregnant women with regular contact with infants should receive targeted screening and counseling to minimize transmission risk. Additionally, comprehensive diagnostic evaluation, including CMV-IgG avidity testing, fetal USG, and amniocentesis when appropriate, is critical for confirming congenital CMV infection and guiding clinical management.

Study Limitations

This study had several limitations due to its retrospective and multicenter design. We were unable to obtain complete data from all participating centers, including information on participants' occupations, hepatitis B and C status, HIV serology, number of pregnancies, and gestational age. These data gaps hindered comprehensive statistical analysis. The use of different equipment across centers for serological testing introduced variability and may have affected the consistency of results. Additionally, some centers did not perform advanced serologic testing in CMV-IgM-positive cases. The number of patients who underwent fetal USG and amniocentesis was also limited in centers where advanced testing was available. These limitations reduced the study's ability to accurately determine the rate of primary CMV infection.

Conclusion

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Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital Local Institutional Ethics Committee (approval number: 2011-KAEK25 2023/01-04, dated: 25.01.2023).
Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.S.S., Concept: M.S.S., Y.Ç., N.Y., Design: All authors, Data Collection or Processing: All authors, Analysis or Interpretation: All authors, Literature Search: All authors, Writing: M.S.S., Y.Ç., N.Y.
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Table 1. Commercial ELISA devices used and CMV-IgM and IgG cutoff values

Commercial ELISA device	CMV-IgM-positive cutoff value	CMV-IgG-positive cutoff value
Abbott (Irland, USA)[a]	1	1

Roche (Mannheim, Germany)[a]	1	1
Roche (Mannheim, Germany; AU/mL)	<15	0-5
Biomerux (Marcy-l'Etoile, France)[a]	1	6
[a]S/C: Sample control index ratio, CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G		

Table 2. Characteristics of pregnant women with CMV serology testing	
Characteristic	Mean (±SD), n (%)
Total number of pregnant women	16,761 (100)
Nationality	
Turkish	15,419 (92)
Immigrant	1,342 (8)
Occupation (n=539)	
Housewife	223 (41.3)
Private sector employee	168 (31.1)
Public employee	134 (24.8)
General worker	14 (2.5)
Serological status of blood-borne infections	
HbsAg positivity (n=4,598)	78 (1.69)
Anti-HCV positivity (n=4,601)	7 (0.15)
Anti-HIV positivity (n=4,234)	0 (0)
CMV serological status	
CMV-IgM seropositivity	261 (1.6)
CMV-IgG seropositivity (including isolated IgG-positive and IgG/IgM co-positive cases)	16,701 (99.6)
CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G, SD: Standard deviation, HbsAg: Hepatitis B surface antigen, HCV: Hepatitis C, HIV: Human immunodeficiency virus	

Table 3. Factors associated with CMV-IgM positivity during pregnancy			
Factor	CMV-IgM-positive (n=115)	CMV-IgM-negative (n=3,907)	p value
Age (mean±SD)	29.05±5.83	28.93±5.62	0.813[a]
Week of pregnancy at examination [median (IQR)]	10 (4)	8 (6)	0.002[b]
Number of pregnancies [median (IQR)]	2 (2)	2 (2)	0.964[b]
Number of living children [median (IQR)]	1 (2)	1 (2)	0.029[b]
[a]t-test. [b]Mann-Whitney U test. CMV-IgM: Cytomegalovirus-immunoglobulin M, SD: Standard deviation, IQR: Interquartile range			

Table 4. CMV-IgG avidity, fetal ultrasonographic findings, and pregnancy outcomes in CMV-IgM-positive								
Case	Week of CMV testing	CMV-IgM	CMV-IgG	CMV-IgG avidity	Week of fetal USG	Fetal USG findings	Week of birth	Pregnancy outcome
1	12	Positive	Positive	Low	16	No pathological findings	20	Abortion
2	9	Positive	Positive	Low	18	Hydrops, polyhydroamnios, skin edema	27	Preterm labor
3	11	Positive	Positive	Low	20	Hyperechogenic bowel	27	Preterm labor
4	22	Positive	Positive	High	22	Microcephaly, cerebral hypoplasia	40	Term birth
5	23	Positive	Positive	High	23	Microcephaly, cerebral hypoplasia	38	Term birth
6	8	Positive	Positive	High	10	Intrauterine growth retardation	12	Abortion
7	7	Positive	Positive	High	20	Oligohydroamnios	38	Term birth
8	14	Positive	Positive	High	22	Intrauterine growth retardation	34	Preterm labor
CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G, USG: Ultrasonographic								

Figure 1. Number of pregnant evaluated in the study
*This group included in 201 patients with CMV-IgM and IgG co-positivity. CMV-IgM: Cytomegalovirus-immunoglobulin M, IgG: Immunoglobulin G