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Screening Cytomegalovirus Infections in First Trimester of Gestation among High Prevalence Population

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Abstract

Introduction: Cytomegalovirus (CMV) is known as a major cause of congenital viral infection in humans. The aim of this study was to evaluate the rate of CMV infection and identify risk factors for infection by screening pregnant women in high prevalence population.

Methods: A retrospective study was conducted between January 2014 and December 2014 in women presenting for their first antenatal visit (between 6-12 weeks of gestation). All women were tested for IgG and IgM antibodies. Subsequently, avidity test was used to discriminate between primary or non-primary CMV infection. They were followed until delivery and newborns were examined by a pediatrician.

Results: A total of 3212 pregnant women were screened during the study period. The rate of seropositivity and seronegativity were found as 97.9% and 2.1% respectively. The prevalence of maternal CMV infection was found as 1.1% (34 women). Among these women, the rate of primary and recurrent CMV infection were found to be 0.3% (8 women) and 0.8% (26 women) respectively. Pregnants with primary CMV infection were referred to perinatal care unit. Pregnants with recurrent infection were followed by ultrasonography for the presence of fetal abnormalities. None of the women who completed follow-up until delivery showed gross evidence of in utero CMV transmission. Isolated IgM antibody positivity was not detected in any women.

Conclusion: Seroprevalence of CMV infection is very high in our region during the pregnancy. Although, there was no difference in terms of birth weight and gestational age at delivery, detection of primary CMV infection is associated with higher rate of spontaneous abortion.

Keywords: Cytomegalovirus, Congenital infection, IgG antibody.

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Introduction

The IgG antibodies, the only type of antibody that can cross the placenta, provide passive immunization in the fetus throughout the pregnancy. However, the IgG2 subclass antibodies cannot pass through the placenta and merge capsular/polysaccharide antigen which create IgG2 response; therefore, some infections related to these antigens may persist and can lead to serious intrauterine infection (1–3).

Cytomegalovirus (CMV), which is a member of human herpesvirus, is the most common causative viral agent of intrauterine infection worldwide (4). Previous studies reported that approximately 0.7% of live-born neonates are infected with CMV (5) and that 15%–20% of these infected children developed symptoms ranging from sensorineural hearing lost to multiple organ failure even fetal and neonatal death (6).

Congenital CMV infection manifest as a primary infection, non-primary infection with a new strain of CMV, or reactivation of a latent infection (7). The most severe cases of congenital CMV infection are those with consequences of primary infection during pregnancy (8,9) . The objective of the prenatal care is accurate diagnosis of primary infection and assessment of the risk of fetal transmission (10,11).

Diagnosis of primary maternal CMV infection depends on detection of virus-specific Immunoglobulin G (IgG) antibody in the blood of a pregnant woman who was previously seronegative, or on detection of specific Immunoglobulin M (IgM) antibody associated with low IgG avidity (12). IgM antibody is present 4 to 8 weeks following the primary infection and can persist for years. Nevertheless, false-positive results can occur due to cross-reactivity with other diseases, such as autoimmune disorders

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or other viral infections. The value and the over implementation of screening in all pregnant women for CMV infection are still under debate in many countries of the world (13). However, data regarding the prevalence of maternal CMV infection is quite insufficient in Turkey.

The aim of this study was to evaluate the rate of CMV infection and identify risk factors for infection by screening pregnant women in high prevalence population.

Materials and Method

This study was approved by the Institutional Review Board of Balikesir University. Participants were recruited from Balikesir Ataturk State Hospital between January 2014 and December 2014. Pretest counseling was given to all participants by the physician and 5 ml blood was collected from antecubital vein. A total of 3212 pregnant women have been tested for CMV IgG and IgM in the first trimester of pregnancy. All women were followed until delivery. To assess the neonatal CMV infection, newborns were examined by experienced pediatricians. This study demonstrates a rural population from the Aegean Territory of Turkey. The clinical characteristic's including, age and pregnancy outcomes were entered into a database.

A standardized protocol was used for screening of CMV infection. Serum samples of all women were tested for the presence of IgG and IgM antibodies against CMV. Enzyme linked fluorescent assay (VIDAS, Biomerieux, France) was used to measure antibody titers. Those with high IgG and IgM levels were tested by IgG avidity test to confirm or exclude acute infection. According to manufacturer's instructions, IgG levels greater than 6 IU/ml for CMV were noted as positive. A value of IgM greater than 0.9 IU/ml for CMV was considered as positive. Determination of the avidity of IgG was also performed by using VIDAS (Biomerieux, France) for CMV. Avidity index greater than 0.8 for CMV was considered as high avidity and whereas an index less than 0.2 for CMV was considered as low avidity.

MedCalc Statistical Software Program version 15.8 (MedCalc Software bvba, Ostend, Belgium) was carried out. One-way analysis of variance (ANOVA), the log-transform method with Scheffe multiple comparison tests, the Kruskal-Wallis test, the Mann-Whitney test, and the x^2 test were used as appropriate. A *p*-value <0.05 was accepted as statistically significant.

Results

A total of 3212 pregnant women were screened for CMV infection. The mean ± SD age was 26.9 ± 5.8 and that of parity was 0.8 ± 0.8. Demographic characteristics of women were presented in Table 1.

Table 1. Characteristics of study participants (N = 3212).

Characteristics	Value
Maternal age (years)	26.97 ± 5.59
Parity (no.)	0.86 ± 0.82
Miscarriage Rate (%)	7,25
Infant birth weight (g)	3,235 ± 556
İnfant birth height (cm)	49,98 ± 2,53
Gestational age at delivery (weeks)	39,6 ± 0,97
Apgar score, 1 min	8.51 ± 1.25
Apgar score, 5 min	9.36 ± 1.74

According to serological status of the CMV infection, 3111 women had CMV IgM (-) with IgG (+), 34 women had CMV IgM (+) with IgG (+), 67 women had CMV IgM (-) with IgG (-) and there were no pregnant women screened for CMV infections with isolated IgM antibody positivity (Table 2).

Table 2. Maternal CMV seroprevalence.

CMV serology	Number of patients (%)
CMV IgM (-) IgG (+)	3111 (96,9)
CMV IgM (-) IgG (-)	67 (2,1)
CMV IgM (+) IgG (+)	34 (1,1)
CMV IgM (+) IgG (-)	-

As shown in table 3, the majority of the participants were between 20-24 or 25-29 years of age (29.23% and 31.16%, respectively). Parity was 0 in 1,065 (33.16%) and 1 in 1,725 (53.70%) patients. Overall 3145 (97.9 %) women were positive for anti-CMV IgG in the first trimester of the gestation and seropositivity of CMV IgG appeared to be increased with age and parity. However, analysis of x^2 test revealed that differences for age and parity did not reach statistical significance (p=0,05 and p=0,07 respectively). (Table 4,5).

Thirty-four (1.1%) women were positive or equivocal for CMV IgM with IgG in the study. High avidity was detected in 26 women, which excluded primary infection and avidity index was low or borderline in 8 women (5 with low and 3 with borderline), with IgG and IgM antibodies positive against CMV (Table 6).

Table 3. Maternal age group and parity.

		Parity				
Age group(Y)	**Total(n)**	**0**	**1**	**2**	**3**	**≥4**
<20	260	116	135	6	3	0
20-24	939	356	488	76	16	3
25-29	1001	319	540	96	44	2
30-34	650	181	365	55	37	12
35-39	311	80	172	24	30	5
≥40	51	13	25	2	5	6
Total	3212	1065	1725	259	135	28

Table 4. Maternal age group and cytomegalovirus IgG seropositivity.

Age group (Y)	**Maternal cytomegalovirus IgG seropositivity (%)**
<20	96,5
20-24	97,8
25-29	97,9
30-34	98,2
35-39	98,7
≥40	100

Table 5. Maternal parity and cytomegalovirus IgG seropositivity.

Parity	**Maternal cytomegalovirus IgG seropositivity (%)**
0	97,3
1	98,1
2	98,5
3	98,5
≥4	100

Table 6. Outcome of pregnancies by types of CMV infection.

	Primary infection (%) n=8	**Non-primary infection (%) n=26**	**P value**
Miscarriage rate (%)	62,50	7,69	0,004
Live Birth (%)	37,50	92,31	0,004
Gestational age at delivery(week)	38,4 ± 1,2	39,1 ± 1,5	0,657
Infant weight (week)	3573 ± 651	3215 ± 339	0,142

Comparing the non-primary infection, women with primary CMV infection had significantly higher miscarriage rate than those with non-primary infection (Table 6). In 5 of 8 women with primary infection the pregnancies resulted in spontaneous abortion at first trimester or early second trimester before the detailed ultrasonographic examination. Primary infections were resulted in a 62.5% miscarriage rates before the first 20 weeks of gestation, while after 20 weeks of gestation all pregnancies were full term. However, infant birth weight and gestational age at the delivery were similar between primary and non-primary infection groups. The median gestational age was 9 weeks (6–12 weeks), and the median number of pregnancies was 1 (range 1–10). All pregnant women, underwent a detailed sonographic examination at 18-22th week of gestation by obstetricians. No abnormal sonographic finding implicating any of the congenital infections screened was detected. Data regarding the first examinations of all neonates were obtained and no clinical symptoms or laboratory results of the infections were reported. Sixty-seven women (2.1%) were negative for CMV IgG antibody in the first trimester and susceptible to acute infection during pregnancy.

Discussion

Seroprevalence of CMV infection is very high in Aegean region of Turkey during the pregnancy and detection of primary CMV infection is associated with higher rate of spontaneous abortion.

The IgG antibodies, the only type of antibody that can cross the placenta, provides passive immunization in the fetus throughout pregnancy. However, the IgG2 subclass pass through the placenta and some infection agents related to IgG2 response can cause intrauterine infections in the fetus (1–3).

CMV is one of the most common causative viral agent that can cause intrauterine infection (4). Congenital CMV infection can be due to a primary infection, non-primary infection with a new strain of CMV, or with reactivation of a latent CMV infection (7). The most severe cases of congenital CMV infection are the consequence of primary infection during pregnancy (8,9). The objective of the prenatal care is the accurate identification of primary infection and accurate evaluation of the risk of fetal transmission (10,11).

In the present study, a total of 3212 pregnant women were screened for CMV infection and the results revealed a CMV IgG seropositivity rate of 97.9% among pregnant women in Turkey. This result is in accordance with reports from Turkey (14,15), in which the CMV seropositivity rate was ranging from 84.5% to 97.3%. However, In a study performed among Turkish women living in an urban area, The

prevalence of seropositivity was found 84.1%, which is lower than those reported in other parts of Turkey (16). A major factor contributing to this decline may be the decreased risk of CMV infection because of improved life standards in urban Turkish population.

Our findings showed that the seropositivity of CMV IgG was not associated with increased age or parity. On the contrary, reports from developed countries revealed that the prevalence of CMV IgG seropositivity appeared to increase with both age and parity. Furthermore, parity was found to be an independent determinant of CMV IgG seropositivity for each previous delivery (17). This difference may be caused by CMV IgG seroprevalance rate and that almost every person contaminated with CMV in early childhood in our country.

Also, 67 women (2.1%) were negative for CMV IgG antibody in the first trimester and deemed to be susceptible to acute infection during pregnancy. However, there was no seroconversion for CMV antibody in these patients during pregnancy. In previous reports, the seroconversion rate for CMV IgG antibody during pregnancy was found as 0.37%. Our results are not compatible with this finding due to both high IgG seropositivity and restricted individual enrollment to the study.

34 (1.1%) women had positive or equivocal test results for CMV IgM with IgG in the current study. High avidity was detected in 26 women, which excluded the presence of primary infection. The 8 women whose avidity index was low or borderline (5 with low and 3 with borderline test results), had positive anti-CMV IgG and IgM antibodies were considered to have primary infection. Pregnancies with primary infection had significantly higher miscarriage rate than for those with non-primary infection. Primary infections in the first 20 gestational weeks was associated with a high (62.5%) miscarriage rate. However, all pregnants with CMV infections after 20 weeks of gestation had live births. There was no significant differences between primary and non-primary CMV infection groups in terms of infant birth weight and gestational age at the delivery.

Currently, there are conflicting results regarding the association between maternal CMV infection and spontaneous abortion. In several case reports were suggested that CMV infection may cause of fetal death (18,19). Few studies have been conducted to evaluate the association between maternal CMV infection and spontaneous abortion. Their results indicated that maternal CMV infection can cause miscarriage and fetal death (20–23). However, in some reports suggest that viral replication in genital tract is associated with fetal transmission and early fetal death (23). Regarding the association between CMV IgG antibody positivity and recurrent abortions, there are few studies have been conducted to evaluate the association between early fetal loss with or without CMV IgG antibody positivity. One of them compared the results of 309 women with or without CMV IgG antibody positivity and found that CMV IgG antibody was not association with spontaneous recurrent abortions (24).

In our study we found that there was no difference between the groups in terms of birth weight. Contrary to our results, previous studies, showed that maternal CMV infection has been associated with low birth weight (25).

The value and the over implementation of screening in all pregnant women for CMV infection are still under debate in many countries of the world (13). However, data lacks regarding the maternal CMV infection in our country. The objective of the prenatal care is the accurate diagnosis of primary infection and evaluation of the risk of fetal transmission. (10,11). We assessed IgG and IgM antibodies in pregnant women applying to the hospital in the first trimester. Thus, only women with elevated IgM antibody titers together with high IgG titers were further evaluated with avidity test to diagnose or exclude primary infection. This study may help clinicians to evaluate pregnant women who live in a population with high prevalence of CMV IgG.

Serological assessment for CMV may be considered for all women during pregnancy or in the presence of sonographic findings such as intrauterine growth retardation, microcephaly, ventriculomegaly, periventricular calcifications and echogenic bowel (26). However, sonographic findings often imply poor prognosis, but their absence does not rule out health problems following birth. In our study, we did not observe any abnormality suggestive of acute CMV infection on ultrasound in pregnant women with seropositive test for CMV.

In conclusion, seroprevalence of CMV infection is very high in Aegean region of Turkey during the pregnancy. Although, there was no association between CMV infection and birth weight and gestational age at delivery, detection of primary CMV infection is associated with higher rate of spontaneous abortion.

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