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Original Article

Seroepidemiology of Cytomegalovirus Infection during Pregnancy in Gonabad, East of Iran: A Cross-Sectional Study

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ABSTRACT

Background: Cytomegalovirus (CMV) is the most common cause of congenital infection, with increased morbidity and mortality at birth. The risk of intrauterine infection largely depends on the time of maternal infection during pregnancy. Currently, no national screening test for CMV infection is available during pregnancy in Iran. The aim of this study was to determine the seroprevalence of CMV infection in pregnant women in the east region of Iran.

Methods: In this descriptive study, conducted from February to April 2011, 240 serum samples were collected from pregnant women in the third trimester to measure CMV-specific immunoglobulin G (CMV-IgG) and CMV- specific immunoglobulin M (CMV-IgM) markers using ELISA test. IgG avidity test was used for all patients whom were positive CMV-IgM and positive CMV-IgG to distinguish primary and recurrent CMV infection. All positive CMV-IgM of pregnant women were monitored until birth.

Results: The majority of women (72.1%) were positive CMV-IgG in pregnancy. The rate of positive CMV-IgM, primary and recurrent infection was 2.5%, 0.83%, and 1.67% respectively. There was significant relation between history of abortion (P=0.013) and residential place (P=0.017) with IgG seropositive rate. Two subjects with positive CMV-IgM were faced with preterm labor and low birth weight.

Conclusion: The findings of our study indicated high prevalence rate of CMV seropositivity in this part of eastern region of Iran. A national screening of CMV-IgM serological is suggested for pregnant women who are at risk of CMV infection.

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Introduction

Cytomegalovirus (CMV) is a species of virus that belongs to the viral family known as herpes viruses[1,2]. CMV is found throughout all geographic locations and socioeconomic groups, but is more widespread in developing countries and in communities with lower socioeconomic status[1-4]. Global prevalence of CMV infection is reported approximately 40%-80%, but it has been estimated to vary from about 45% in developed countries and to 100% in developing countries[1,5-7]. Seroprevalence of the infection is also age dependent[1,3,8,9].

Usually, there are no clinical symptoms for CMV during primary infection and reactivation[1,2,5-10], but infected individuals may shed the virus via body fluids such as saliva, blood, cervical secretion, semen and urine[2,5,8]. CMV is transmitted by close non sexual contact, sexual activities, utero-placental transmission, breast-feeding, blood transfusion and organ transplantation[1,3,5-10]. CMV infection is typically unnoticed in healthy people, but can be life-threatening for the immunocompromised individuals and new born infants[1,3-5,10].

CMV is the most common of congenital infection and is most likely to occur following a primary infection in the mother during pregnancy[2,10-12]. However, maternal CMV reactivation or re-infection with different CMV strain may also lead to fetal infection[3,5].

It has been reported that primary infection occurs in 0.15% to 2.0% of all pregnancies and may be transmitted to the fetus in up to 40% of cases.[4,5] In addition, 10% of the symptomatic newborns at birth and 10% to 15% of asymptomatic newborns are infected with congenital CMV infection. The latter group will eventually show some developmental disorders over time[4,10,13,14].

It has also been reported that each year in the United States, 40,000 children are born with congenital CMV infection causing 400 deaths and leaving approximately 8000 children with permanent disabilities such as hearing or vision loss and mental retardation[5].

CMV infection can occur at any time during pregnancy and seroconversion does not protect against re-infection or reactivation[15-17]. The risk of intrauterine infection largely depends on the time of maternal infection during pregnancy. It is less common during first trimester but increases during pregnancy and reaches highest in the third trimester[10,18]. Some previous studies reported that CMV infection may lead to abortion and stillbirth in pregnancy[19,20].

Necessity of diagnostic tests at all stages of gestation has always been a debate due to the insufficient evidence of congenital abnormalities in re-infection. Thus, CMV infection diagnostic test has not been considered in the routine prenatal tests yet[10,11,21]. Currently, no national screening test for CMV infection is available at all stages of pregnancy in Iran.

Considering the importance of intrauterine CMV infection transmission and its complications, it seems necessary to investigate the prevalence of CMV infection during pregnancy. Furthermore, a few studies have investigated the prevalence of this infection among pregnant women in Iran. The aim of this study was to determine seroprevalence of CMV infection in pregnant population in the east region of Iran. The effects of age, residential region, history of abortion, parity, education, and socioeconomic status on CMV infection have also been investigated.

Methods

This cross-sectional study was conducted on pregnant women undergoing routine prenatal care in health service centers related to Gonabad University of Medical Sciences from February to April 2011. For the random selection of subjects, the probably sampling method has been applied. At first, a comprehensive list of all centers was provided (12 centers). Then the number of subjects selected from each center was proportional to the number of pregnant women referred to the centers. In each center, the subjects were randomly selected.

The sample size of our study has been determined based on reports of previous studies of prevalence of CMV during pregnancy [7-14]. All 240 selected subjects were in the third trimester of pregnancy. They were informed about the aims of the study. Informed written consent was also obtained from all women. In order to increase the quality of data collection, the questionnaires were completed by trained interviewers. The study was approved by the Ethical Review Committee of Islamic Azad University, Gonabad Branch, Gonabad, Iran.

The blood samples collected from all subjects were sent to Jahad Daneshgahi Laboratory of Gonabad. All blood samples were centrifuged at 3000 g for 5 min. Then, the serum collected and stored in -20 ^{0}C. Titer of CMV-specific immunoglobulin G (IgG) and CMV-specific immunoglobulin M (IgM) was measured using ELISA technique. To distinguish

primary and recurrent CMV infection, IgG avidity assay (CMV IgG avidity EIA; Radim, Rome, Italy) was used for all patients whose IgM was positive. According to the manufacture's instructions, the results of IgG and IgM serology assays were reported in terms of positive, negative, or equivocal. Women with equivocal serology results or positive CMV IgM were screened three weeks later to confirm the serological status of CMV infection. The second result was considered as the final result.

All women with positive CMV IgM were followed up by an obstetric specialist until end of pregnancy. A random equal number of negative CMV IgM mothers were also followed up as a control group.

Data were collected on standardized forms and encoded for computer analysis by SPSS 16 statistical software for Windows. Cross- tabulation, Chi-squared test, and odds ratio test were used to examine the relationship between variables using a 0.05 confidence interval as measure of association.

Results

The mean age of participants was 28.72 yr [95% CI: 23.27, 34.17]. The majority of subjects (63.7%) were less than 30 yr. The mean gestational age was 32.43 weeks [95% CI: 29.87, 34.99]. The mean gravidity was 2.07 [95% CI: 1.03, 3.11]. Almost 68% of cases were multiparous and approximately 43% of subjects were experiencing their second pregnancy. About 66% of the subjects and 80% of their husbands were educated for less than 12 years. Nearly 73% of participants were living in urban area. The rate previous abortion and stillbirth were 22.1% and 5.8% respectively.

CMV seroprevalence rate was 72.1%. Among 240 tested women, 167 (69.6%) had a past CMV infection and 67 (27.9%) had never been infected with CMV. The remaining 6 (2.5%) women were positive CMV-IgM. In the latter group, four women (1.67%) had recurrent CMV infection (positive CMV-IgM with high IgG avidity) and two (0.83%) women had primary CMV infection (positive CMV-IgM with low IgG avidity) (Figure 1).

There was no significant difference between the mean age of subjects with IgG seropositive and subjects with seronegative. The subjects were divided in two age groups (<30 years and ≥30 years) to evaluate correlation between age and CMV seropositivity. There was no significant difference between the age groups (Table 1).

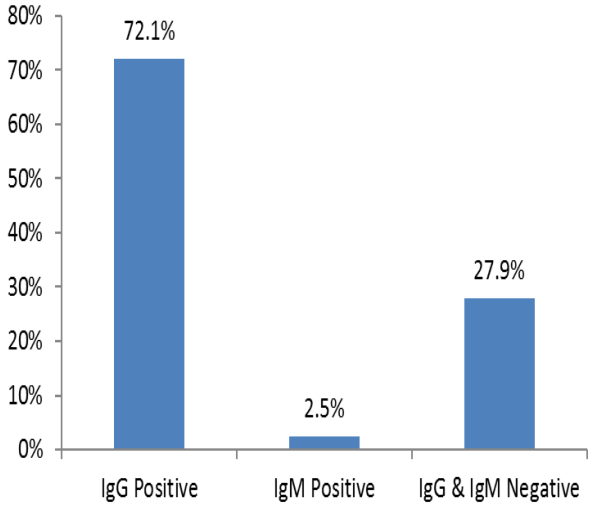

Figure 1: Frequency of seroprevalece of cytomegalovirus infection in pregnant women population in the eastern region of Iran during February to April 2011

There was significant relationship between the residential region and IgG seropositive rate (*P*= 0.017). The rate of infection was higher in pregnant women who lived in rural areas (Table 1).

CMV seropositivity was also analyzed with respect to gravidity. No statistically significant difference was found between primigravid and multiparous women (Table 1). A significant relationship was found between history of abortion and IgG seropositive prevalence; OR= 2.72 [95% CI: 1.20, 6.14].

Two positive CMV-IgM women with primary infection faced with premature rupture of membrane and preterm labor. There was also a case of low birth weight in one of positive CMV-IgM women with recurrent infection. All of newborns with positive CMV-IgM mothers were referred to neonatal specialist in order to be assessed for CMV infection and hearing complications.

Table 1: Distribution of CMV seroprevalence by characteristics of the subjects

Variables	All subjects Number (%)	IgG^+, IgM^+ Number (%)	IgG^+, IgM^- Number (%)	IgG^-, IgM^- Number (%)	*P* value
Mean age (year)	28.72	23	28.04	27.28	0.326
Age (year)					0.242
<30	153 (63.7)	6 (3.4)	101 (68.7)	46 (31.3)	
≥30	87 (36. 2)	2 (3.2)	66 (75.6)	21 (24.1)	
Residential region					0.017
Urban	176 (73.3)	6 (3.4)	114 (67.1)	56 (32.9)	
Rural	64 (26.7)	0 (0.0)	53 (82.8)	11 (17.2)	
Previous abortion					0.013
No	187 (77.9)	6 (3.2)	122 (67.4)	59 (32.6)	
Yes	53 (22.1)	0 (0.0)	45 (84.9)	8 (15.1)	
Gravidity					0.643
Primigravid	77 (32.1)	4 (5.2)	50 (68.5)	23 (31.5)	
Multiparous	163 (67.9)	2 (1.2)	117 (72.7)	44 (27.3)	
Education					0.118
Primary school	19 (7.9)	0 (0.0)	14 (73.3)	5 (26.3)	
Secondary/High School	79 (32.9)	3 (3.8)	57 (75.0)	19 (25.0)	
Diploma	80 (33.3)	1 (1.3)	51 (64.6)	28 (35.4)	
Academic	62 (25.8)	2 (3.2)	45 (75.0)	15 (25.0)	

Discussion

In this study, it has been shown that the rate of CMV seroprevalence in pregnant women was 72.1%. This is partly similar to the result of the other studies performed in the south and west parts of Iran[11,23-26]. These studies showed that CMV IgG seroprevalence was about 85% to 98% in pregnant women population. This difference is probably due to different demographic characteristics of population study and geographic conditions. Other similar studies in other countries reported the prevalence of CMV infections to be 56.9% in Sydney Australia, 98.7% in Denizil state of Turkey, 87.0% in Singapore, 46.8% in France, 54.4% in the United Kingdom, 56.3% in Finland, 60.0% in the United State, 78.0% in Russia, 84.0% in Spain, 92.1% in Saudi Arabia, 95.6% in China and 100% in Thailand[7, 8,10,11,13,14,27,28]. It seems that seroprevalence of CMV infection in Iran is similar to other developing communities and is slightly higher than developed communities are.

A test result of positive CMV-IgG indicates that the subject has previously been infected. After CMV infection, IgG remains in the body forever and protects considerably against the next infections. In other words, a negative result of CMV-IgG test means that the subject has not been infected with CMV. Considering the high frequency of positive CMV-IgG[9,11,12]. This assay has a little value for diagnosis of the current CMV infection. However, it may be helpful to diagnose negative CMV-IgG cases.

IgG avidity test has been recently used to distinguish primary and recurrent infection by measuring the binding affinity of IgG antibodies[10,11]. At the beginning of the infection, low avidity IgG is formed and then its avidity increases gradually[10,11]. In this study, the rate of positive CMV-IgM, primary and recurrent infections were 2.5%, 0.83% and 1.67% respectively. Another similar study in the south part of Iran has reported the rate of positive CMV-IgM, primary and recurrent infection 33%, 0.74% and 32.24% respectively[24]. This rate of secondary infection is much higher than that of our study. Another similar study in south part of Iran has reported the rate of positive CMV-IgM in pregnant women was 4.35% which 34.4% of whom had primary infection[26]. In

south part of Iran the rate of primary CMV infection is reported as 5.2% in women hospitalized for spontaneous abortion[11]. The rate of positive CMV-IgM in pregnant women was 5.5% in Australia which 1.2% of it had primary infection[10]. In Turkey, the rate of positive CMV-IgM is reported 1.2%[13]. The rate of primary CMV infection in pregnant women has been reported in the range of 1% to 4%[10, 11,26].

According to these results we can conclude that the prevalence of CMV is related to race, ethnicity, parity, age, sexual behaviors and occupational activities[1,2,6,10,11,13].

We did not find any relationship between age and CMV infection. In other similar studies no relationship was also found between age and CMV infection in pregnant women [10,11]. One reason is that most of the participants (63.3%) were less than 30 years old.

In the present study, the rate of CMV infection in pregnant women living in rural area was higher than those living in urban area were. In addition, the first group had lower education level than the latter group. Both factors may increase the risk of CMV infection among rural population.

Our study showed a significant relationship between history of abortion and prevalence of CMV infection. The rate of CMV infection in pregnant women with history of abortion was approximately twice as much as rate of infection among women who had no history of previous abortion. Other studies have also reported higher prevalence of CMV infection in women with spontaneous abortion [11,19,20,29]. Thus, it seems that CMV infection may play an important role in abortion.

Several studies have implied that transmission of CMV via the urine and saliva of children is a major cause of infection among childbearing women especially pregnant women. This increases the risk of spontaneous abortion and congenital abnormalities in fetus[5,6,10,11]. Therefore, it is important to understand that proper hygiene practices and behavioral changes are effective in CMV transmission[5]. As a result, all women of childbearing age, whether they are CMV seropositive or seronegative, are at risk of reinfection during pregnancy and thus they should be trained how to reduce the risk of infection. A national screening of CMV-IgM serological is suggested for pregnant women who are at risk of CMV infection.

In the present study, six positive CMV-IgM pregnant women were monitored until birth. Two of them faced with premature rupture of membrane and preterm labor. There was also a case of low birth weight in one of positive CMV-IgM women with recurrent infection. Due to the few numbers of positive CMV-IgM pregnant women, we could not conclude about the consequences of pregnancy. Further studies should follow up the women with primary and recurrent CMV infection in the third trimester of pregnancy.

Our study had a few limitations. First, we investigated the seroprevalence of CMV in third trimester of pregnancy. Because of our cross-sectional study, we do not have the data regarding the outcomes of pregnancy and well-being of newborns in all subjects. We also could not conclude that CMV infection increases the risk of abortion or not. Second, we followed up a small group of pregnant women with positive CMV-IgM assay until end of the pregnancy. Indeed, we could not also conclude about the consequences of their pregnancy.

Conclusion

The findings of our study indicated high prevalence of CMV seropositivity in a part of eastern region of Iran. Furthermore, the results showed that living in rural area, previous abortion are the major risk factors of CMV infection. Screening of CMV-IgM serological assay would also be an important diagnostic step for pregnant women.

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Conflict of interest statement

The authors have no conflict of interests to declare.

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References

1. Landolfoa S, Garigliob M, Gribaudoa G, Lembo D. The human cytomegalovirus. *Pharmacol & Ther*. 2003;98(3):269-297.
2. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol*. 2007;17(4):253-276.
3. Revello MG, Campanini G, Piralla A et al. Molecular epidemiology of primary human cytomegalovirus infection in pregnant women and their families. *J Med Virol*. 2008;80(8):1415-1425.
4. Kim CS, Congenital and prenatal cytomegalovirus infection. *Korean J Pediatr*. 2010.53(1);14-20.
5. Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. *BMC Public Health*. 2005;5(1):70.
6. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. *J Clin Virol*. 2009;46:S6-S10.
7. Staras SAS, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. *Clin Infect Dis*. 2006;43(9):1143-1151.
8. Dollard SC, Staras SA, Amin MM, Schmid DS, Cannon MJ. National prevalence estimates for cytomegalovirus IgM and IgG avidity and association between high IgM antibody titer and low IgG avidity. *Clin Vaccine Immunol*. 2011;18(11):1895-1899.
9. Colugnati FA, Staras SA, Dollard SC, Cannon MJ. Incidence of cytomegalovirus infection among the general population and pregnant women in the United States. *BMC Infect Dis*. 2007;7(71).1471-2334.
10. Munro SC., Hall B, Whybin R et al. Diagnosis of and Screening for Cytomegalovirus Infection in Pregnant Women. J Clin Microbiol. 2005;43(9):4713-4718.
11. Sotoodeh A, Jamshidi M, Farjam MR et al. Cytomegalovirus Immunity in South of Iran. *Am J Infect Dis*. 2010;6(1):8-12.
12. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17(1):355-363.
13. Karabulut A, Polat Y, Turk M, Isikbalcl Y. Evaluation of rubella, Toxoplasma gondii, and cytomegalovirus seroprevalences among pregnant women in Denizli province. *Turk J Med Sci*. 2011;41(1):159-164.
14. Wong A, Tan KH, Tee CS, Yeo GS. Seroprevalence of cytomegalovirus, Toxoplasma, and Parvovirus in pregnancy. *Singapore Med J*. 2000;41(4):151-155.
15. Yamamoto AY, Mussi-Pinhata MM, Boppana SB et al. Human cytomegalovirus reinfection is associated with intrauterine transmission in a highly cytomegalovirus-immune maternal population. *Am J Obstet Gynecol*. 2010;202(3):297.e1-8.
16. Zalel Y, Gilboa Y, Berkenshtat M et al. Secondary cytomegalovirus infection can cause severe fetal sequelae despite maternal preconceptional immunity. *Ultra Obstet Gynecol*. 2008;31(4):417-420.
17. Ergun UG, Bakaris S, Ucmak H, Ozbek A. Fetal congenital cytomegalovirus infection following recurrent maternal infection after a 7-year interval. *Saudi Med J*. 2007;28(2):264-267.
18. Enders G, Bader U, Lindemann L, Schalasta G, Daiminger A. Prenatal Diagnosis of Congenital cytomegalovirus infection in 189 pregnancies with known outcomes. *Prenatal Diag*. 2003;21(5):362-377.
19. Iwasenko JM, Howard J, Arbuckle S et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. *Infect Dis*. 2011;203(11):1526-533.
20. Meng LL, Chen H, Tan JP et al. Evaluation of etiological characteristics of Chinese women with recurrent spontaneous abortions: a single-centre study. *Chinese Med J*. 2011;124(9):1310-1315.
21. Cahill AG, Odibo AO, Stamilio DM. Screening and treating for primary cytomegalovirus infection in pregnancy: where do we stand? A decision-analytic and economic analysis. *Am J Obstet Gynecol*. 2009;201(1):466.e1-7.
22. Revello MG, Gerna G. Diagnosis and management of Human Cytomegalovirus Infection in the mother, fetus and newborns infant. *Clin Microbiol Rev*. 2002;15(4):680-715.
23. Rajaii, M, Pourhassan A. Evaluation of immunity against CMV in Azarbaijan female population. *Iranian J Clin Infect Dis*. 2008;3(3):143-148.
24. Arabzadeh AM, Mosavat SA, Eftekhari N. Seroepidemiology of Human Cytomegalovirus in pregnant women and their in Keman City during 2005. *J Kerman Univ Med Sci*. 2007;14(4):279-288.
25. Siadati A, Noorbakhsh S, Ghazi F, Rimaz SH. Monavari MR, Cytomegalovirus infection in primiparous pregnant women and their neonates. *Acta Medica Iranica J*. 2002;4(3):136-139.
26. Tabatabaee M, Tayyebi D. Seroepidemiologic study of human cytomegalovirus in pregnant women in Valiasr Hospital of Kazeroon, Fars, Iran. *J Matern Fetal Neonatal Med*. 2009;22(6):517-521.

27. Picone O, Vauloup-Fellous C, Cordier AG et al. A 2-year study on cytomegalovirus infection during pregnancy in a French hospital. *BJOG*. 2009;116(6):818-823.
28. Alanen A, Kahala K, Vahlberg T, Koskela P, Vainionpää R. Seroprevalence, incidence of prenatal infections and reliability of maternal history of varicella zoster virus, cytomegalovirus, herpes simplex virus and parvovirus B19 infection in South-Western Finland. *BJOG*. 2005;112(1):50-56.
29. Saraswathy TS, Az-Ulhusna A, Asshikin RN, Suriani S, Zainah S. Seroprevalence of cytomegalovirus infection in pregnant women and associated role in obstetric complications: a preliminary study. *Southeast Asian J Trop Med Public Health*. 2011;42(2):320-322.