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Full Length Research Paper

Screening of cytomegalovirus seroprevalence among pregnant women in Ankara, Turkey: A controversy in prenatal care

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Cytomegalovirus (CMV) seropositivity is common among pregnant women. CMV is the most common of the teratogenic viruses and is a leading cause of neurological impairment in newborns, especially sensorineural deafness. The aim of this study was to determine the seroprevalence of CMV among pregnant women in a tertiary maternity hospital setting in Ankara, Turkey. The study was conducted on 11,360 pregnant women in the first trimester admitted to Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey, between the years 2008 to 2010. Of the 11360 women, 11189 (98.5%) and 35 (0.3%) were seropositive for ImmunoglobulinG (IgG) and ImmunoglobulinM (IgM) anti-CMV antibodies, respectively. Evaluations of age-specific subgroups indicated high CMV seropositivity rates for all age groups. CMV seropositivity is common among pregnant women. Widespread population screening may aid in preventing congenital infections by this agent. Seroprevalence studies are needed to assess the burden of infection, to identify groups at special risk and to aid in the design of future preventive measures and vaccine strategies.

Key words: Cytomegalovirus (CMV), seroprevelance, pregnancy, avidity.

INTRODUCTION

Cytomegalovirus (CMV) is an enveloped deoxyribonucleic acid (DNA) virus from the Herpesviridae family and may remain latent in the host cell. It has double-stranded, linear DNA and cosahedral symmetry, it replicates within the nucleus of infected cells. Multinucleated giant syncytial cells with intranuclear inclusion bodies can develop during the latent state. CMV is so-named because infected cells become swollen (cytomegalic) (Glanwin and Trattler, 1996). The complexity present in the CMV genome allows for both persistent and latent infections. Recurrent infection can occur after reactivation of a latent virus or super infection with a new strain (Bernstein, 2007). The seroprevalence of CMV is dependent on multiple factors, including socioeconomic status, age and occupation (Betts, 1983). Seropositivity correlates with increasing parity, abnormal Pap smear, lower socio economic level, older age, trichomonas infection, number of sex partners and immune system status (Chandler et al., 1985). In the United States, 0.2 to 2.2% of all newborns are infected in utero and 6 to 60% of infants become infected within the

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first 6 months from intrapartum and breast-feeding exposure (Stagno et al., 1977). CMV is not highly contagious and close personal contact is required for infection to occur. The incubation period of the virus ranges from 28 to 60 days. There are four infectious stages: asymptomatic infection, congenital disease, infectious mononucleosis-like syndrome and reactivation. Although most CMV infections are asymptomatic, CMV is the most common viral cause of congenital birth defects and mental retardation in newborns (Glanwin and Trattler, 1996; Stagno et al., 1981; Weller and Hanshaw, 1964; Gaytant et al., 2005; Istas et al., 1995). Infection with the virus also causes microcephaly, deafness, seizures and multiple other birth defects.

The virus can remain latent in the body after primary infection; thus, fetuses can be infected by the reactivation of the virus during pregnancy. Maternal CMV infection is typically diagnosed with serological testing. It can also be diagnosed by culture or Polymerase Chain Reaction (PCR) of infected blood and other body fluids. Fetal infection can be documented by culture and PCR of amniotic fluid. After 21 weeks, PCR testing reaches a sensitivity of 100%. Despite this sensitivity, CMV detection in the amniotic fluid does not predict the severity of fetal infection. An ultrasonographic follow-up can detect fetal impairment to a certain extent. If a fetus presents as normal in serial ultrasound examinations, the risk of clinical symptoms of congenital CMV infection in the infected fetus is approximately 10% (Bernstein, 2007). Perinatal CMV infection can occur in utero, intrapartum and with breast-feeding.

A maternal primary CMV infection results in the congenital infection of 30 to 40% infants. Fortunately, recurrent CMV infection causes less than 1% of perinatal infections and serious sequelae are much less common following recurrent infection (Fowler et al., 1992; Stagno et al., 1982). Although the risk of CMV transmission is highest during the third trimester, infected fetuses suffer severe sequelae most commonly in the first trimester. The vast majority of the congenitally infected infants, 85 to 90%, are clinically asymptomatic and 5 to 10% of these will later suffer developmental impairments, especially hearing loss. At birth, the clinical findings of symptomatic infants can present as jaundice, petechiae,

thrombocytopenia, hepatosplenomegaly, hepatitis, growth restriction, chorioretinitis, deafness, microcephaly, cerebral calcification, mental retardation, nonimmune hydrops and/or early death. The direct detection of the virus or viral nucleic acids in the urine of newborns during the first 2 weeks of their life is the best diagnostic method. A recent study indicated that CMV-specific hyperimmune globulin decreased the incidence of congenital CMV infection and the number of symptomatic infants (Nigro et al., 2005). In this study, our aim was the detection of CMV seropositivity among pregnant women who were screened in our hospital between the years 2008 to 2010. Seroprevalence studies of CMV in Turkey are needed to assess the burden of infection, to identify groups at special risk and to aid in the design of future preventive measures and vaccine strategies.

MATERIALS AND METHODS

Zekai Tahir Burak Women's Health Education and Research Hospital is a large tertiary referral center in Turkey. Approximately 16,000 pregnant women receive care at the hospital each year. Women are routinely screened for CMV infection during their first antenatal visits. We designed a retrospective study to include all pregnant women who received antenatal screening tests in our hospital from 2008 to 2010. Because we were especially concerned with congenital CMV infection, our study population consisted entirely of pregnant women. We classified the patients into four age groups: ≤20 years, 20 to 25 years, 26 to 35 years and >35 years. The distribution of CMV-specific antibodies was evaluated among these groups. The study was approved by the Research Committee of our hospital. In this study, 11,360 pregnant women applying for their first prenatal visit were enrolled. For the screening test, 8 to 10 ml of venous blood was taken from each woman under sterile conditions. Antibodies were investigated in sera by using a chemiluminescent immunoassay (CLIA) (LIAISON, DiaSorin S.p.A, Italy).

The cut-off value used for IgG was 0.6 IU/ml. The CMV IgG samples were considered negative when their absorbance was less than 0.4 IU/ml. Absorbance readings between 0.4 and 0.6 IU/ml were considered ambiguous. For CMV-specific IgM, the cut-off value was 30 AU/ml. IgM results between 15 to 30 AU/ml were consisted ambiguous and a result of less than 15 AU/ ml was considered negative. No patients were excluded from the study. If both CMV-specific IgG and IgM tests were positive, IgG avidity enzyme-linked immunosorbent assay testing was preformed (ELISA) (Chorus Diesse Diagnostica, Italy). Avidity was considered low if the test index was <0.2, moderate between 0.2 to 0.3 and high at ≥ 0.3. Low IgG avidity levels strongly suggest an infection contracted less than three months before, whereas a high avidity level tends to exclude this (Revello and Gerna, 1999). If the testing indi-cated that the patient was IgG negative but IgM positive, the patient was reevaluated after 2 to 3 weeks. If IgM positivity persisted without detection of IgG, the detected IgM were considered to be nonspecific antibodies. If tests for both IgM and IgG were positive after 2 to 3 weeks, we diagnosed these cases as acute prenatal CMV infection. In cases where both the IgG and IgM tests were negative, the tests were repeated at twelve-week intervals.

RESULTS AND DISCUSSION

A total of 11,360 pregnant women were screened for CMV infection in our hospital during the study period. The results of CMV IgG and IgM seropositivity testing for the whole study group are shown in Table 1. The mean age and gestational week of women was 28.2 years and 10.3 weeks, respectively. The patients were stratified into five groups by age. CMV seropositivity for each age group is shown in Table 2. Seropositivity was equally high in all age groups with levels of 98.6, 99, 97.8, 98.8 and 98.6% for patients aged ≤20 years, 20 to 25 years, 26 to 30 years, 31 to 35 years and >35 years, respectively. When the entire study population is considered, 11189 (98.5%) patients were seropositive for CMV. Only 171 (1.5%)

Table 1. Results of antenatal serologic screening for cytomegalovirus infection at Zekai Tahir Burak women's health hospital between 2008 to 2010.

Cytomegalovirus (CMV) n:11360			
Immunoglobulin G (IgG)		Immunoglobulin M (IgM)	
Positive	Negative	Positive	Negative
11189 (98.5%)	171 (1.5%)	35 (0.3%)	11325 (99.7%)

Table 2. Distribution of seropositivity of CMV infection by age of pregnant women.

Cytomegalovirus (CMV) n:11360					
Age	Immunoglobulin G (IgG)		Immunoglobulin M (IgM)		Total
	Positive	Negative (%)	Positive (%)	Negative (%)	
≤20	515 (98.6)	7 (1.4)	-	522 (100)	522
21 to 25	2384 (99)	24(1)	8 (0.4)	2400 (99.6)	2408
26 to 30	3722 (97.8)	82(2.2)	11 (0.3)	3793 (99.7)	3804
31 to 35	2818 (98.8)	33 (1.2)	10 (0.4)	2841 (99.6)	2851
>35	1750 (98.6)	25 (1.4)	6 (0.3)	1769 (99.7)	1775
Total	11189 (98.5)	171 (1.5)	35 (0.3)	11325 (99.7)	11360

patients were found to be seronegative. 35 (0.3%) patients tested positive for IgM, and further evaluation documented that all of these patients were also positive for IgG. These patients were consulted and avidity testing was recommended. 17 patients agreed to have an avidity test. 16 patients had high avidity, while only one patient had low avidity. This single patient was counsel about the risks of congenital CMV infection and she decided to terminate her pregnancy. CMV causes infection worldwide and is frequently isolated in perinatal infections.

It is the most common viral cause of congenital birth defects and mental retardation (Glanwin and Trattler, 1996; Stagno et al., 1981; Weller and Hanshaw, 1964; Gaytant et al., 2005; Istas et al., 1995). The virus can cause severe short- and long-term neurologic impair-ment. Although CMV is common and causes severe damage to fetuses, only limited information is available about the incidence and natural history of this infection and routine antenatal screening is controversial. Some authors advocate routine screening in at-risk women and a closer surveillance of these cases. On the other hand, these screening tests are expensive and unreliable and the necessity of these tests is not always fully justified. Before deciding to utilize a screening test, it is necessary to determine the seroprevalence of the infection in the population of concern along with other relevant epide-miological factors. The prevalence of CMV depends on the different factors that were previously mentioned: age, parity, socioeconomic status and cultural differences. This paper is mainly focused on the seroprevalence of CMV rather than other factors. There are only limited studies on CMV seroprevalence in Turkey. We need larger, multicenter studies to more accurately reflect the population. Our institution is a referral center with a large number of deliveries. Patients from the whole Central Anatolia region are referred to our clinic.

In this study, we screened a very large number of cases representative of the population of Central Anatolia. The seropositivity of CMV varies across the world: 78% in Russian pregnant women, 87% in Singaporean pregnant women and 92.1% in Saudi Arabia pregnant women (Yavuz and Alaaddin, 2008). The prevalence in Turkey has been reported to be 84.3 to 98.5% among pregnant women (Tekerekoğlu et al., 2003; Satılmış et al., 2007; Yılmazer et al., 2004; Çakıcı et al., 1995; Duran e t al., 2002; Bakıcı et al., 2002). In Central Anatolia, the detected seropositivity for CMV IgG was 98.5%. The results of the present study are consistent with the CMV infection rates noted in the literature and the rates reported for pregnant Turkish women. A routine screening test is usually justified only for conditions with an expected high rate of infection, conditions that have a proven mode of prevention and conditions where the screening method is safe and inexpensive. At this time, routine screening for CMV is not recommended given the high seropositivity prevalence. Because there is no consistently effective treatment for congenital CMV infection available, the testing is clinically useless and expensive. However, Nigro et al. (2005) recently reported promising results concerning passive immunization against congenital CMV infection (Nigro et al., 2005). Previous immunization with CMV is not perfectly pro-tective against either reinfection or vertical transmission

of infection from mother to fetus.

A recent review of the literature indicated that the incidence of congenital CMV infection increases with increasing maternal CMV seroprevalence (Bakıcı et al., 2002). The positive correlation between higher maternal seroprevalence and high birth prevalence may seem paradoxical because this suggests that a smaller number of pregnant women are at risk for primary infection. However, in a high seroprevalence population, the number of pregnancies at risk for reactivation is also increased. In addition, the high seroprevalence may be due to a higher prevalence of risky behaviors in the population. In a high seroprevalence population, a pregnant woman has a higher likelihood of exposure to CMV-infected people. Thus, in a high risk population, seropositive women have a higher risk of reactivation and seronegative women have a higher risk of primary infection (Kenneson and Cannon, 2007). Preventive measures should be taken to decrease perinatal mortality and morbidity related to CMV infection and to ensure that women are not infected with CMV during pregnancy. Pregnant women should be consulted and encouraged to implement these preventive measures. Routine nationwide screenings for this condition should be considered, although serious cost-effectiveness issues need to be evaluated before the implementation of such screenings. In the Central Anatolia region, CMV seroprevalence is as high as 98.5%. Routine CMV screening in such a population is unnecessary, but there are exceptions. Pregnant women who had contact with a patient with a proven acute CMV infection, as well as patients with upper respiratory system infection-like symptoms, hepatomegaly, elevated liver enzymes, lymphadenopathy and immunocompro-mised statuses should all receive screening.

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