Human Cytomegalovirus in pregnancy

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Abstract:

Human cytomegalovirus (HCMV) has been described as an important etiological agent of intrauterine infection in pregnant women which may lead to some serious results such as miscarriage, stillbirth, cerebellar malformation, fetus developmental retardation, In the present study from the December 2011 to April 2012 in Kirkuk province we examined 110 serum samples from pregnant women and 80 non pregnant as control group for the presence of IgM and IgG antibodies against HCMV by standard enzyme linked immunoassay (ELISA) technique. The results was 65(59%) of the cases were seropositive for HCMV-IgG and 6(5.46%) cases were seropositive for HCMV-IgM and 12(10.9%) cases were seropositive for both HCMV-IgG and HCMV-IgM at the same time . Other women (controls) they were lower rates for seropositive HCMV antibodies. The highest rate of IgG was found in rural area while IgM found in urban area. There was an increasing trend in IgM positivity rate with age in pregnant women between 24-29 years. The IgG seroprevalance rate highest in second trimester of pregnancy while the maximum rate of abortion (73.07%) was found in the first trimester of pregnancy. High seropositive rates for HCMV in pregnant women indicate that most of the women were exposed to these viruses before child-bearing age as well as during the pregnancy.

Introduction :

Human Cytomegalovirus (HCMV) belongs to the herpes virus family (herpesviridae).It is the prototypical virus of the subfamily beta-herpesvirinae[(1)]. The virion of HCMV consists of a100 nm diameter icosahedral nucleocapsid containing a 230-kbp, double stranded linear DNA genome surrounded by a proteinaceous layer defined as the tegument or matrix, which, in turn, is enclosed by a lipid bilayer containing a large number of viral glycoproteins. The mature virion particle is 150–200 nm in diameter [(2)].

The HCMV is a widespread pathogen responsible for generally asymptomatic and persistent infections in healthy people, It is found in both the developed industrial societies and in isolated aboriginal groups. Following infection, it is excreted in body fluids (urine, saliva, tears, semen, milk, and cervical secretions) for months to years[(3)].

Infection is usually mild and subclinical. The unsuspecting host is thus able to spread the virus both vertically and horizontally. Virus can appear following primary infection, reinfection, or reactivation. About 10% of infants are infected by the age of 6 months, following transmission from their mothers via the placenta, during delivery, and by breast feeding [(4,5)] Transplacental infection can occur both in women infected for the first time during pregnancy and those infected long before conception (recurrent infection). Primary infection during pregnancy as a source of fetal infection was suggested by the observation that transplacental transmission ranges from 20% to 40% when primary infection varies from 0.7% to 4.1% [(6)]. In the case of recurrent infections, high rates of congenital infections are observed in populations with higher rates of maternal seropositivity, suggesting that most congenital infections are caused by reactivation of latent virus [(7,8)].

Cytotrophoblasts form a barrier between the maternal and fetal circulation, but readily allow HCMV replication in vitro, suggesting that the fetus is infected hematogen-ously [(9,10)] . The HCMV infection is asymptomatic in healthy individuals but causes serious morbidity and permanent sequelae in infants infected before birth [(2,11)]. Prenatal infections occur in 2% of births, and the risk of permanent sequelae, including neuronal defects and hearing loss, increases with a primary maternal infection. Early in gestation, HCMV can infect the uterus, replicating in the vascular endothelium, the glandular epithelium, and decidual cells [(12)] HCMV also replicates in placental cytotrophoblasts and dysregulates their functioning prior to their reaching the fetus [(9)]. Innate cellular and adaptive immune responses protect the placenta from HCMV infection in seropositive women with healthy, uncomplicated pregnancies [(12)]. Decidual granular leukocytes include macrophages, dendritic cells, and natural killer cells that populate the pregnant uterus [(13)]. In the decidua, these innate immune cells colonize in islands where HCMV-infected cells are present [(12)].

Virological and molecular detection of HCMV and serological demon-stration of a specific immune response are used for diagnosis, although acute infection is usually diagnosed through detection of the virus in body fluids such as urine, saliva, vaginal secretions, amniotic fluid, and blood, [(3)].infection during pregnancy is a major task of the diagnostic virology laboratory[(14)]. The detection of HCMV and their components' in the body fluids, following primary or recurrent infections. Moreover, HCMV-infected cells can be identified in biopsy samples (e.g., liver, lungs), showing ‘‘owl’s eye’’ inclusions or, more efficiently, by immunohisto-chemistry , in situ PCR, or nucleic acid hybridization. Electron micros-copy is employed to detect the virus in the urine from congenitally or prenatally infected infants .The most widely used assays for detection and quantitation of HCMV load in blood include tests for viremia, antigenemia, and DNAemia. [(3,15)]

Serological determination of a past or recent HCMV infection by detection of virus-specific IgG or IgM antibodies. Occurrence of a primary infection is conventionally deduced from seroconversion from IgG negative to IgG positive in the interval between two serological assays. A specific IgM response may be serologic evidence of a recent primary infection. Interpretation of a positive IgM assay in pregnant women is assisted by determination of the avidity of HCMV-specific IgG, since low-avidity IgG is produced early in infection and high avidity IgG is a marker of past or recurrent infection. Detection of anti-HCMV IgG antibodies is a useful way of documenting a past infection, and they are also a marker of potential infectivity, since reactivation of a latent infection may occur [(3)].

Despite advances in the diagnosis of maternal-fetal HCMV infection, effective therapy remains unavailable. Pregnancy termination is often offered as an option when affected or infected fetuses are identified by ultrasonography or amniocentesis, respectively. Several drugs are now available for the treatment of HCMV disease. Maternal HCMV infections may be treated with one or other of two drugs: ganciclovir or foscarnet[(16)].

The morbidity and mortality associated with congenital HCMV infection underscores the need for a vaccine with which to prevent HCMV infection. Promising advances have been made in vaccine development, and a number of vaccines are currently being tested. [(17)] . Possible approaches to preventing congenital HCMV infections include changes in hygienic behavior for seronegative pregnant women, administration of HCMV hyperimmune globulin (HIG) to pregnant women with a primary infection, and vaccines administered to girls or women well before pregnancy [(18)]. Because of no data is available about HCMV in pregnancy in Kirkuk province ,this study conducted to evaluate the seroplrevalence of HCMV in pregnancy .

Materials and Methods :

During December 2011 to April 2012 Peripheral venous blood (5 ml) was aspirated from 110 pregnant women (18 to 40 years old) and 80 non pregnant women control group (18 to 40 years old) that belonged to Different geographical regions in Kirkuk province was presented in Kirkuk general hospital and primary health care centers of Dubiz health care sector, then clear serum separated from blood samples. HCMV serology test was done using a standard enzyme-linked immunoassay ELISA to determine HCMV IgM and IgG antibodies (Bio Check, Foster City). Testing was performed strictly according to the manufacturer's instructions. The results were then interpreted on the basis of antibodies as seropositive, and seronegative ,Then results submitted to determine the relation of the HCMV antibodies positive IgM or/and IgG and negative for both antibodies with gestational age of pregnancy, abortion ,residency and age,.

Results:

All 110 pregnant women and 80 non pregnant women control group were tested for HCMV specific antibodies and they were classified according to the presence or absence of CMV-IgM and CMV-IgG antibodies to the following groups :

1. CMV-IgM (-) and CMV-IgG (+) .
2. CMV-IgM (+) and CMV-IgG (-).
3. CMV-IgM (+) and CMV-IgG (+).
4- CMV-IgM (-) and CMV-IgG (-) .

The results for 110 pregnant women were CMV-IgM (-) and CMV-IgG (+) 65 (59.09%) , CMV-IgM (+) and CMV-IgG (-) 6(5.46%), CMV-IgM (+) and CMV-IgG (+) 12(10.9%) and CMV-IgM (-) and CMV-IgG (-) 27(24.55%). Results for 80 non pregnant control group were 35(43.75%), 4(5%) , 3(3.75%) and 38(47.5%) respectively as ordered in pregnant group (Table 1). Residency distribution of IgG seropositive positive were from the total HCMV-IgG 65 seropositive pregnant women was 44(76.70%) found in rural area and 21(23.30%) found in urban, while the residency distribution of HCMV-IgM seropositive in pregnant women was 4(66.67%) in urban from the total 6 HCMV-IgM seropositive, also the highest rate of seropositive for both HCMV-IgM and HCMV-IgG at the same time found in urban area (Table 2). According to the age groups the Maximum IgM seroprevalence rate occurred in women between 24-29 years old, the highest rate of IgG seroprevalence occurred in women between 30-35 years old follow by 24-29 years old (Table 3) .The prevalence of seropositive HCMV IgM was high in the first trimester of pregnancy while the seropositive HCMV IgG high in the second trimester (Table 4).the relation of HCMV infection with the number and gestational age of abortion in our study was recorded in the (Table 5) and (Table 6) respectively.

Table 1 : Seroprevalence of HCMV Antibodies in Pregnant Women and Control Group by ELISA .

HCMV-Antibodies Type	Pregnant		Control	
	NO.	%	NO.	%
IgM (-) and IgG (+)	65	59	35	43.75
IgM(+) and IgG (-)	6	5.46	4	5
IgM(+) and IgG (+)	12	10.9	3	3.75
IgM (-) and IgG (-)	27	24.54	38	47.50
Total	110	100	80	100

Table 2 :Residency Distribution of HCMV Antibodies in Pregnant Women.

AREAS	HCMV Antibodies seropositive					
	IgM(+) and IgG (-)		IgM (-) and IgG (+)		IgM(+) and IgG (+)	
	NO.	%	NO.	%	NO.	%
Urban	4	66.6	21	32.30	7	58.33
Rural	2	33.4	44	67.70	5	41.67
Total	6	100	65	100	12	100

Table 3 :Relation of HCMV Antibodies to Age Groups of Pregnant Women.

Age groups (Years)	HCMV Antibodies seropositive					
	IgM(+) and IgG (-)		IgM (-) and IgG (+)		IgM(+) and IgG (+)	
	NO.	%	NO.	%	NO.	%
18-23	2	33.33	15	23.07	4	33.33
24-29	3	50	17	26.15	5	41.66
30-35	1	16.67	23	35.38	2	16.67
36-40	0	0	10	15.39	1	8.34
Total	6	100	65	100	12	100

Table 4 :Relation of HCMV Antibodies with Gestational Time of Pregnancy.

HCMV Antibodies seropositive	Gestational time of pregnancy						Total	
	1st trimester		2nd trimester		3rd trimester			
	NO.	%	NO.	%	NO.	%	NO.	%
IgM(+) and IgG (-)	3	50	2	33.4	1	16.6	6	100
IgM (-) and IgG (+)	25	38.46	28	43.07	12	18.47	65	100
IgM(+) and IgG (+)	6	50	5	41.7	1	8.3	12	100
Total							83	100

Table 5 :Relation of HCMV Infection with History of Abortion in Pregnant Women.

Total Seropositive pregnant women	History of abortion							
	No abortion		One time		Two time		Three or more	
	NO.	%	NO.	%	NO.	%	NO.	%
83	57	68.7	10	12.04	9	10.83	7	8.43

Table 6 :Relation of Abortions Due to HCMV Infection with Gestational Time of Pregnancy .

ABORTIONS (TOTAL)		Gestational time of pregnancy					
		1st trimester		2nd trimester		3rd trimester	
		NO.	%	NO.	%	NO.	%
NO.	%						
26	100	19	73.07	6	23.07	1	3.86

Discussion :

The prevalence of HCMV antibodies during pregnancy is variable in the world IgG prevalence is between 40% to 100% depending on the variability of viral accessibility and its circulation rate in the community[19]. As previously mentioned, our study indicated that the total HCMV-IgG seroprevalence rate was 69.99 % that close to world IgG prevalence that reported. In contrast, the total HCMV-IgM seroprevalence rate 16.36% is high in relation to that reported in developed countries (3%-10%) .These findings indicated CMV infections are highly associated with poor hygienic conditions, communal life style, and close contact with day care units [20] theses factors interpret the different distribution of seropreval-ence of IgM and IgG in relation to urban and rural area with regard to primary , past, recurrent and reinfection that influenced hygienic and communal life in both areas. According to previous studies it is estimated that up to 1% of fetuses in pregnant women had been infected by HCMV via intrauterine infections, of whom 30% subsequently developed into con- genital diseases. As previously described, several epidemiological factors including age, parity numbers, number of gestations, geographical distribution, socioeco-

nomic provinceus, marital provinceus. Age is a determinant factor influencing HCMV seroprevalence .Data indicated that there was an increasing trend in IgG seropositivity rate with age that is in complete concordance with previous findings. Also age group 24-29 years old was determined as the major age group for the occurrence of HCMV primary infections. Further analysis revealed that most marriages (60%) occurred among the recent age group. According to other studies this data raises the probable role of sexual maturity as a determinative factor of HCMV infections. Despite the established implication of human HCMV in congenital infection, there are still conflicting reports regarding its association with spontaneous miscarriage., high prevalence of HCMV-IgG antibodies in women following spontaneous abortions. This suggests that abortion might result from fetal infection due to reactivation of chronic CMV infection during the course of pregnancy[21]. Regarding to HCMV with abortion in pregnancy it may related to many sites in the placenta the proposed as routes of HCMV infection in utero during the pregnancy, although there is different between the number of abortion and the gestational time of abortion that may result from the infection time previous or during the pregnancy and immunological state of the mother ,also relation of IgM and IgG prevalence and abortion with gestational time as in our study. A decreased in abortions in the second and third trimester might be an indication that anti-HCMV maternal immunity could prevent abortions due to HCMV infections, so HCMV-IgG circulating antibody is only considered significantly protective against abortion. Considering all the epidemiologic factors that may contribute to HCMV infection , we suggested roles of age, parity, geographical position and sexual maturity as the most probable associated factors, ,since there is no effective therapeutic and prophylactics strategies against HCMV infections, primary HCMV infections are very challenging health problem during pregnancy period. So more emphasis should be laid for women of childbearing age, including prospective screening program for HCMV infections before pregnancy, limited contact with HCMV infected children during pregnancy and responsible sexual practices. Also for reducing the chance of abortion implications an effective HCMV vaccination program should be concluded [22]. High seropositive rates for HCMV in pregnant women indicate that most of the women were exposed to these viruses before child-bearing age as well as during the pregnancy. The ability of HCMV to cause abortion more than one time may be due to the reactivation of latency or re infection.

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الفيروس المضخم للخلايا البشري في النساء الحوامل

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الملخص

يعد فيروس المضخم للخلايا البشري من أهم المسببات الفيروسية أثناء الحمل والتي قد تسبب إسقاط أو ولادة جنين ميت أو الشلل الدماغي أو تأخير نمو للجنين. شملت الدراسة 110 امرأة حامل و 80 امرأة غير حامل كمجموعة ضبط من تاريخ كانون الأول 2011 لغاية نيسان 2012 في مدينة كركوك .تم التحري عن الأجسام المضادة نوع(ام)و(جي) لفيروس المضخم للخلايا البشري في مصل تلك النساء الحوامل بطريقة فحص المترابط الأنزيمي المناعي. أظهرت النتائج أن 65 (59%) لديهن أجسام مضادة نوع (جي) و6(5.46%) لديهن أجسام مضادة نوع (ام) بينما 12 (10.9%) منهن لديهن النوعين (ام)و(جي) للفيروس المضخم للخلايا البشري في نفس الوقت .حيث كانت نسبة انتشار الأجسام لفيروس المضخم للخلايا البشرية اقل في مجموعة الضبط.وأظهرت النتائج أيضا إن نوع (جي)كانت أكثر في المناطق الريفية وان نوع (ام) كانت أكثر لدى نساء الحوامل من ساكنات المدن.حيث كانت نسبة انتشار الأجسام المضادة للفيروس المضخم للخلايا البشري أكثر في الأعمار 24–29 سنة من النساء الحوامل . وأظهرت الدراسة أن نسبة الأجسام المضادة نوع (جي) كانت أكثر في الأشهر الثلاثة الأولى من الحمل بينما كانت أكثر حالات الإسقاط لدى النساء الحوامل في الأشهر الثلاثة الثانية من الحمل والتي بلغت (73%). حيث أن النسبة العالية للإصابة بفيروس المضخم للخلايا البشري في النساء الحوامل ناتجة من الإصابة في مرحلة الإنجاب من العمر و أثناء الحمل.