

## Human Cytomegalovirus IgG and IgM Seropositivity among Pregnant Women in Sulaimani City and Their Relations to the Abortion Rates

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**Abstract:** This study was aimed to investigate the percentage rates of Cytomegalovirus IgG and IgM seropositivity and their relations to abortion among 185 tested women in Sulaimani city (Iraq) using ELISA technique. The studied cases were included 35 with abortion history, 120 pregnant and 30 controls. The majority of tested women were positive for IgG (90.2%) regardless to the tested groups, the percentage of CMV-IgM positive without IgG was (9.18 %), whereas (7.02 %) were negative for both IgG and IgM. Statistical analysis showed significant relation between CMV-IgM seropositivity and abortion ( $p = 0.048$ ), whereas no significant relations were found between abortion and CMV-IgG seropositivity ( $p = 0.512$ ). Significant relations were found between CMV-IgG and IgM seropositivity and changes in some haematological parameters included total white blood cells ( $p = 0.000$ ) for all three tested groups, significant differences were found for platelets between both pregnant women with and without abortion and controls ( $p = 0.0206$  and  $0.0308$ ) respectively. Effects of residency, socioeconomic conditions and previous history of blood transfusion on CMV-IgG and IgM seropositivity were studied and no significant effects were found regarding the tested women groups ( $p > 0.05$ ). No significant effects of CMV-IgG and IgM seropositivity were found on Haematocrit, Lymphocyte, Monocyte and granulocyte counts ( $p > 0.05$ ) for each regarding all three tested women groups.

**Keywords:** CMV-IgG, CMV-IgM, HCMV, pregnancy

### INTRODUCTION

Human Cytomegalovirus (HCMV) is a ubiquitous human beta herpesvirus type 5 belongs to the herpesvirus family (Haaheim *et al.*, 2002; Strauss and Strauss, 2002). Compared to other human herpesviruses, it is the largest, with a genome of ~235 kb encoding ~165 genes (Davison *et al.*, 2003). The virion (200-300 nm) (Mocarski *et al.*, 2007) consists of a double-stranded linear DNA core in an icosahedral nucleocapsid, enveloped by a proteinaceous matrix (Chen *et al.*, 1999), which are enclosed in a lipid bilayer envelope that is derived from the nuclear membrane of infected cell and contains viral glycoproteins (Brooks *et al.*, 2007; Greenwood *et al.*, 2007). Initial infection with HCMV commonly occurs during childhood and depending on geographic location and socioeconomic group, (35-90%) of population have antibody against the virus by adulthood (Harvey *et al.*, 2007).

The virus is highly species-specific and only human strains are known to produce human disease, the virus is ubiquitous and is transmitted horizontally, vertically and via infected blood transfusions, also the virus can be transmitted via saliva, sexual contact, placental transfer, breastfeeding, in addition to blood transfusion, solid-organ and hematopoietic stem cell transplantation (Sia and Patel, 2000). The

seroprevalence of HCMV in the human population ranges between 30-90% in developed countries, with increasing prevalence in parallel to the age (Staras *et al.*, 2006). CMV persists in a latent form after primary infections and reactivation may occur years later, particularly under such conditions including immunosuppression (Prosch *et al.*, 2003). During latent infection, the HCMV genome is estimated to be carried in between 0.004% and 0.01% of mononuclear cells from granulocyte colony-stimulating factor-mobilized peripheral blood or bone marrow, with approximately 2 to 13 genome copies per infected cell (Slobedman and Mocarski, 1999).

Congenital HCMV infection causes severe morbidity and mortality in newborns and is the leading infectious cause of deafness and a large contributor of neurodevelopmental abnormalities in children (Fowler and Boppana, 2006; Ross *et al.*, 2006). The frequency of congenital HCMV infection resulting from primary maternal infection contracted during pregnancy or from the reactivation of HCMV in a seropositive mother during pregnancy is about 0.64% of live births; however, the incidence can vary considerably among different study populations (Kenneson and Cannon, 2007). The risk of primary infection in a sero-negative mother is 1-4%, which carries a 30 to 40% risk of congenital infection (Stagno *et al.*, 1986; Kenneson and Cannon,

2007). The risk and severity of HCMV disease are greatest if primary infection in a sero-negative mother occurs during the first trimester (Pass *et al.*, 2006). The reactivation of an HCMV infection during pregnancy can still cause symptomatic congenital infection; however, the risk is lower, as preexisting maternal HCMV antibodies have a protective role against intrauterine transmission (Stagno *et al.*, 1982; Fowler *et al.*, 1992).

Detection of HCMV specific antibodies is the most common approach used to identify HCMV infected individuals (Prince and Leber, 2002). Many types of assays are available for the determination of the anti-HCMV antibody titer in serum with different degrees of sensitivity; the most widely used procedure is the ELISA, for which there are various commercial products. HCMV immunoglobulin M (IgM) detection is a very sensitive marker for primary infection and can be detected for many months following primary infection and may also be produced following reinfection or reactivation. Likewise, detection of increasing HCMV IgG levels over time is an unreliable approach for distinguishing primary from non-primary HCMV infection, since most seropositive patients showed high IgG levels in the first serum sample collected for testing (Prince and Leber, 2002).

The aim of the current study is to investigate cytomegalovirus IgG and IgM seropositivity among pregnant women in Sulaimani city (Iraqi Kurdistan region) in addition to studying the relations between positive results an abortion rates.

## METHODOLOGY

Blood samples (185 samples) were collected during September to December, 2010 from 155 pregnant women aged (17-45 years) in 5-40 week of gestational age from Sulaimani Maternity Hospital in addition to 30 samples from immunocompetent non-pregnant women aged (17-45 years) as controls. Screening of the collected sera for CMV-IgG and IgM antibodies were done by Enzyme-Linked Immunosorbent Assay (ELISA) (BioCheck, Inc 323 Vintage Park Drive Foster City, CA 94404) as well as complete blood count were performed by automated full blood counter using Automated Hematology Analyzer.

Purified CMV antigen is coated on the surface of micro-wells. Diluted patient serum was added to the wells. All unbound materials are washed away. HRP-conjugate was added. Excess HRP-conjugate was washed off and a solution of TMB Reagent was added. The enzyme conjugate catalytic reaction was stopped at a specific time. The intensity of the color generated was proportional to the amount of IgM or IgG specific antibody in the sample. The results were read by a micro-well reader compared in a parallel manner with calibrator and controls.

**Calculation of result:** The mean of duplicate calibrator value  $X_c$  was calculated; The mean of duplicate positive control ( $X_p$ ), negative control ( $X_n$ ) and patient samples ( $X_s$ ) also were calculated; The CMV IgM or IgG index of each determination was calculated by dividing the mean values of each sample ( $X$ ) by calibrator mean value,  $X_c$ .

**Quality control:** The following criteria were used for the positive reactions of each test and sample depending on the kit supplied company: The optical density value of the reagent blank against air from a micro-well reader was less than 0.250; meaning that the Cut-off value was above 0.250.

### Interpretation:

**Negative:** According to the supplied company instructions:

- CMV IgM and IgG index less than 0.90 is a negative result for IgM and IgG (<1.2 IU/mL) antibodies against CMV.
- CMV IgM and IgG index between 0.91-0.99 is equivocal and the samples should be retested.
- CMV IgM and index of 1.0 or greater is positive for IgM antibody to CMV.
- CMV IgG index of 1.00 and greater (or IU value greater than 1.2) is a sero-positive and indicates prior exposure to the CMV virus (>1.2 IU/mL).

**Haematological tests:** Each sample was tested for haematocrit (Hct), total and differential white blood cell count and platelet count using automated Hematology Analyzer (MEK-6410/6420).

## RESULTS

The current study performed in Sulaimni city for detecting of HCMV IgG and IgM antibodies in 185 women including, 120 asymptomatic pregnant women, 35 women who were identified with spontaneous abortion by gynecologist during the study period who were referred to Sulaimani Maternity Hospital curettage department and control group consisted of 30 immunocomptent non pregnant women.

Out of 185 tested women, it was noticed that 167 (90.2%) and 17 (9.18%) women regardless to their groups were positive for IgG and IgM, respectively. Among pregnant women who were suffered from abortion (35 cases), only seven of them (20%) showed IgM positive results, while 30 of them (85.7%) were seropositive for IgG (Table 1). Among pregnant women with no abortion history (120 cases), only 8 (6.7%) showed seropositivity for IgM, whereas 109 of them (90.8%) were positive for IgG, while the rest (2.5%) were negative. Among the control group (30 cases) only 2 (6.7%) showed seropositivity for IgM, whereas 28 (93.3%) of them were

Table 1: Tested women and CMV results regarding both IgG and IgM

Tested women	CMV IgG*		CMV IgM**		No of cases
	Positive	Negative	Positive	Negative	
Abortion	30 (85.7%)	5 (14.3%)	7 (20%)	28 (80%)	35 (100%)
Pregnant	109 (90.8%)	11 (9.2%)	8 (6.6%)	112 (93.4%)	120 (100%)
Control	28 (93.3%)	2 (6.7%)	2 (6.6%)	28 (93.4%)	30 (100%)
Total	167 (90.2%)	18 (9.8%)	17 (9.18%)	168 (90.82%)	185 (100%)
p-value	0.512		0.048 *		

\*: Significant differences were found

Table 2: CMV IgG and IgM results among tested women groups

Tested groups	IgG+ve IgM+ve	IgG-ve IgM+ve	IgG+ve IgM -ve	IgG-ve IgM-ve	Total
Abortion	3(8.57%)	4 (11.43%)	27 (77.15%)	1 (2.85%)	35
Pregnant	7(5.83%)	1 (0.83%)	102 (85%)	10 (8.34%)	120
Control	2(6.7%)	0 (0%)	26 (86.7%)	2(6.6%)	30
Total	12	5	155	13	185

Table 3: Blood transfusing among CMV IgG and IgM positive and negative tested women

Tested women		CMV IgG		CMV IgM		Total
		Positive	Negative	Positive	Negative	
Blood transfusion	Yes	12 (80%)	3 (20%)	1 (6.7%)	14 (93.3)	15 (100%)
	No	155 (91%)	15 (9%)	16 (9.4%)	154 (90.6%)	170 (100%)
Total		167	18	17	168	185
p-value		0.161		0.724		

Table 4: CMV IgG and IgM seropositivity among tested women in regard to their living status

Tested women		CMV IgG		CMV IgM		Total
		Positive	Negative	Positive	Negative	
Living status	Good	56 (91.8%)	5(8.2%)	4 (6.6%)	57 (93.4)	61(100)
	Medium	103 (90.4%)	11(9.6)	12 (10.5%)	102 (89.5%)	114(100)
	Bad	8 (80%)	2 (20%)	1 (10%)	9 (90%)	10(100)
Total		167	18	17	168	185
p- value		0.505		0.684		

CMV-IgG positive (Table 1). Statistical analysis showed that there were significant relation between the ratio of abortion and CMV-IgM seropositivity ( $p = 0.048$ ), while CMV-IgG seropositivity showed no significant relation with abortion percentages ( $p = 0.512$ ).

The results of CMV- IgG and IgM were clarified in (Table 2), in which 12 women showed seropositivity for both CMV-IgG and IgM, whereas 13 showed negative results for both CMV-IgG and IgM. The highest percentage was for women who were CMV-IgG positive with IgM negative (155 tested women), moreover only 5 cases showed CMV-IgM positive without IgG and the vast majority was within women who were suffered from abortion (Table 2).

After studying the effects of the blood transfusion on the rates of CMV seropositivity (both CMV-IgG and IgM), it was revealed that the process of blood transfusion have no significant effect on both CMV-IgG and IgM seropositivity ( $p = 0.161$  and  $0.724$ ) respectively (Table 3).

**CMV infections and its relation to socioeconomic status:** Out of 61 women with a good economic status 56 (91.8%) were CMV-IgG positive, while only 4 (6.6%) of them were CMV-IgM. Regarding intermediate socioeconomic status, 103 (90.4%) women

were CMV-IgG positive, while only 12 (10.5%) showed CMV-IgM positive results.

Among women with bad socioeconomic status, 8 (80%) were CMV-IgG positive while only one (10%) showed positive CMV-IgM result (Table 4). Statistical analyses indicated that there were no significant differences among the three tested groups regarding the IgG and IgM seropositivity ( $p = 0.504$  and  $0.648$  respectively), meaning that the socioeconomic conditions have no any relation with CMV infection.

**Effect of residence on CMV IgG and IgM seropositivity:** CMV IgG and IgM seropositivity among tested women according to their residence area was clarified in (Table 5). From 132 women from urban residency, 120 (91%) were positive for CMV-IgG antibodies and 11 (8%) were positive for CMV-IgM antibodies. From 53 women from rural residency 47(89%) were positive for CMV-IgG antibodies and 6 (11%) were positive for CMV-IgM antibodies (Table 5).

Statistical analyses indicated that there were no significant differences among two tested groups regarding the IgG and IgM seropositivity ( $p = 0.643$  and  $0.524$ ). respectively clarifying that the living places have no any significant effects on the sero positivity of cytomegalovirus.

Table 5: CMV IgG and IgM seropositivity among tested women in regard to residency

Tested women		CMV IgG		CMV IgM		Total
		Positive	Negative	Positive	Negative	
Residence	Urban	120 (91%)	12 (9%)	11 (8%)	121 (92%)	132 (100%)
	Rural	47(89%)	6 (11%)	6 (11%)	47 (89%)	53 (100%)
Total		167	18	17	168	185
p-value		0.643		0.524		

Table 6: Different haematologic parameters from three tested women groups regarding CMV-IgG and IgM positive and negative results

Tested Women	Mean of Hematologic parameters *	IgG for CMV		IgM for CMV	
		Positive	Negative	Positive	Negative
Aborted	WBC (cells/mL)	9623	12120	9214	10171
	Platelets (10 <sup>3</sup> /mL)	290	256	296	283
	Hematocrit %	34	37	35	35
	Lymphocytes	23%	17%	20%	22%
	Monocytes %	3%	4%	3%	3%
	Granulocytes %	74%	80%	77%	75%
Pregnant	WBC (cells/mL)	9528	9800	10163	9510
	Platelets (10 <sup>3</sup> /mL)	269	234	231	269
	Hematocrit %	35	33	35	35
	Lymphocytes %	24%	22%	23%	24%
	Monocytes %	4%	5%	4%	4%
	Granulocytes %	72%	74%	73%	72%
Controls	WBC (cells/mL)	7 632	5750	7900	7479
	Platelets (10 <sup>3</sup> /mL)	276	181	207	278
	Hematocrit %	39	40	39	39
	Lymphocytes %	29%	36%	22%	30%
	Monocytes %	5%	6%	7%	5%
	Granulocytes %	65%	58%	71%	64%

**Haematologic results:** In the current study the complete blood counting which was performed by automated hematologic analyzer, was summarized in (Table 6), as the mean values regarding seropositivity for CMV-IgG and CMV-IgM antibodies among three tested women groups. Over all tested women, the ranges for total WBC count was 5750-12120 cells/mL, platelet count was 181000 and 296000/mL, hematocrit was 34-40, lymphocyte percentage was 17-36%, monocyte was 3-7% and granulocytes were 58-80% (Table 6).

After statistical analysis, it was noticed that total WBC count was significantly different among pregnant women with abortion and those without abortion as well as controls and between controls and pregnant women without abortion ( $p = 0.000$ ) for each respectively. Regarding platelets and CMV-IgG test, it was noticed that there was significant differences between both pregnant women with and without abortion and controls ( $p = 0.0206$  and  $0.0308$ ), respectively. No significant differences were observed between three tested groups regarding haematocrit, lymphocyte, monocyte and granulocyte ( $p$ -value) was higher than 0.05.

Among CMV-IgM positive and negative women, it was noticed that total WBC count was significantly different among pregnant women with abortion and those without abortion as well as controls ( $p = 0.000$ ) for each respectively. Regarding platelets and CMV-IgM test, it was noticed that there was a significant difference between pregnant women with abortion and controls only ( $p = 0.006$ ).

No significant differences were observed between three tested groups regarding platelets, haematocrit, lymphocyte, monocyte and granulocyte counting as indicated in which the  $p$ - values were higher than 0.05.

## DISCUSSION

CMV is the most common viral infection worldwide and among different age groups including both sexes, also its incidence has been estimated to be between 0.2-2.2% of all live births in different parts of the world (Ross *et al.*, 2006). The current study tried to determine the percentage rates of both CMV-IgG and IgM seropositivity among a group of women who were subgrouped into abortion, still pregnant and controls. The vast majority of CMV infection can be asymptomatic and the infected person may not suffer from the infection consequences, similar observations were observed by other researchers who noticed substantial prevalence of infection in the local population (Wreghitt *et al.*, 2003). Infection among pregnant women can cause risks for the fetus as reported by Enders and his colleagues in 2001 (Enders *et al.*, 2001), who reported that there is a risk for transmission of the virus to the fetus during the pregnancy.

The highest percentage rates of CMV-IgG seropositivity as observed in the current study may indicate the previous exposure of the tested women and now they are immune against CMV, especially when they were IgM-negative, these women as mentioned can

considered immune and their primary infection with CMV was assumed to have been taken place before the current pregnancy, similar conclusions were reported by other researches in 2006 who noticed that most of the tested women were had immune against primary CMV infection and these results suggested that latent CMV infection predisposes to adverse pregnancy outcomes (Tanaka *et al.*, 2006).

Results obtained in the current study were agreed with observations recorded by Ali and his colleagues in 1992 in Mousil (Ali *et al.*, 1992) who noticed that the rates of CMV-IgG and IgM seropositivity among pregnant women were 90 and 2.5%, respectively while the percentage was lower among nonpregnant women which were 84 and 1%, respectively. Women with IgM seropositivity without positive IgG antibody were considered as acutely infected with CMV, although there was cross reactivity of about 3.3% for IgM positivity with other viral infectious including EBV, measles, herpes simplex varicella- zoster influenza vaccine as reported by Maine *et al.* (2000). As mentioned before these women who showed CMV-IgM positivity may be asymptomatic as pointed by other investigators (Wreghitt *et al.*, 2003). Other researchers recorded similar observations as in 2004 Lazzarotto and co-workers found that CMV-IgM can be found frequently in the serum of normal pregnant women without any influence on the pregnancy outcome, although our findings were disagreed with observations by Lazzarotto *et al.* (2004), regarded to normal pregnancy, because our findings revealed that CMV-IgM seropositivity was significantly related to abortion and the vast majority of pregnant women with IgM positive results were aborted. Different researchers indicated that primary CMV infections in any stages of pregnancy presents a risk for intrauterine infection from 30-50% but congenital infection in seropositive mothers is only from (0.2-1.5%) and that it needs more microbiological and histological confirmation (Stagno, 1990).

There were some tested women who showed both CMV-IgG and IgM positive results which were considered to be possibly infected with CMV during the current pregnancy or a chronic infection which can be confirmed by IgG avidity test because antibody binds to the antigen with less avidity during acute infection than chronic infection (Wreghitt *et al.*, 2003). Moreover some cases were negative for both CMV-IgG and IgM, Most of these participant groups were immune against CMV and CMV maternal seropositivity being associated with less severe fetal involvement and maternal immunity plays a protective role in this setting (Fowler *et al.*, 2003), or may be non-infected with CMV at all. Generally and in comparison with other studies, our findings regarding CMV-IgG were lower than results of other study done in China who recorded higher percentage and prevalence of CMV-IgG

seropositivity which was (95.67%) among pregnant women (Guo, 1992). Also other investigators reported higher percentages of CMV-IgM seropositivity in compare to our study as in a study in Kashmir in 2004 by a research team who done a serological survey and they showed that the prevalence of CMV-IgM antibodies among pregnant women was 15.98% (Lone *et al.*, 2004).

The current study also revealed that the process of blood transfusion have no significant effect on the rates of seropositivity for both CMV-IgG and IgM as clarified in results, although it was presumed that the virus exists in the blood of healthy donors in a latent state especially in monocytes (Söderberg-Nauclér *et al.*, 1997) and also it was noticed that CMV is reactivated following transfusion when these cells encounter an allogeneic stimulus (Roback, 2002). Socioeconomic conditions showed no significant effects on seropositivity of CMV- IgG and IgM in addition the residence which showed similar effects as in socioeconomic conditions, which was disagreed with observations reported by other researchers in Helsinki who noticed that social environment seemed to be the most powerful factor, predicting both CMvIgG and IgM seropositivity during pregnancy (Mustakangas *et al.*, 2000). CMV-IgG and IgM seropositivity showed significant effects on some haematologic parameters included total white blood cells which were in agreement with results recorded by Britt and Alford (1996) as well as with observations noticed by Wahab *et al.* (1998). Significant effects of CMv-IgG and IgM seropositivity on platelet counts in the current study was in agreement with conclusions reported by Nomura *et al.* (2005) who observed thrombocytopenia among early CMV infection.

This study also concluded that CMV seropositivity have no significant effect on some blood parameters included lymphocytes, monocytes, granulocytes and haematocrit, which were not in parallel with observations reported by different researchers, who reported lymphocytosis and Monocytosis (Britt and Alford, 1996; Wahab *et al.*, 1998).

## CONCLUSION

From this study the following points were concluded:

- Only CMV-IgM seropositivity showed significant relations with the abortion percentage among pregnant women.
- Total WBC counts, platelet counts were significantly different among CMV seropositive women with abortion history and those without abortion history and also with controls.
- CMV-IgG seropositivity, blood transfusion, living places socioeconomic conditions, haematocrit, lymphocyte, monocyte and granulocyte counts

showed no significant relations with the abortion percentages.

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