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Evaluation of tumor necrosis factor alpha and interleukine-11 in a sample of aborted women infected with human Cytomegalovirus

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Abstract---This study aimed to evaluate the immunological role of TNF-alpha and interleukine-11 for a sample of women infected with HCMV. 65 blood samples were collected from aborted women and 15 blood samples were collected from healthy non-aborted women (as a control group) during the period from 6 April to 12 June from reviews Al-Zahra teaching hospital and Al-Manathira general hospital in Najaf governorate. HCMV IgM, IgG antibody tests were performed by using Enzyme-Linked Immunosorbent Assay (ELISA- Human, Germany). The results showed that the prevalence of IgG and IgM immunoglobulins against HCMV in pregnant women with miscarriages according to the statistical analysis that there is a high significantly difference with a level $\leq P 0.05$ in IgG and IgM concentration within different age groups of aborted women compared to the control treatment group of women. The samples under study were also tested to measure the level of TNF- α and IL-11 cytokines by using a quantitative technique the enzyme-linked immunosorbent assay as well, the results showed that there that there is a hight significant in the concentration of TNF- α protein in aborted women, which reached 8.24 ± 1.58 (pg/ml)., and this was significant at $P \leq 0.003$ compared with the control group 5.51 ± 2.96 (pg/ml).while IL-11 showed an increase in the level of its concentration in aborted women reached to 14.25 ± 2.9 (pg/ml), and this was significant at $P \leq 0.05$ compared with the control group at 11.25 ± 4.1 (pg/ml) respectively.

Keywords---Cytomegalovirus, IgM, IgG immunoglobulin, TNF- α , IL-11.

Introduction

Abortion is defined as the termination of a pregnancy by removing or rejecting the fetus from the uterus before it is able to live. There are two types of abortions that result in this outcome: spontaneous or induced miscarriage. Medical and surgical methods are also available for abortions in both the first and second trimesters (Lim and Singh, 2014). Genetics, immunologic factors, placental abnormality, endocrine disorder, nutritional, environmental factors, and infection with microorganisms such as *Toxoplasma gondii*, Cytomegalovirus, syphilis, rubella, herpes, and maternal disease such as diabetes mellitus, thyroid disease (Tang and Quenby, 2010). Women of reproductive age are frequently infected with HCMV (which is more common in pregnant women than in non-pregnant women, since the virus is more prevalent in pregnant women in industrialized nations, approximately (3.42-3.68) % (Enders *et al.*, 2012), The reason for this could be due to uninfected women's readiness to be infected with the virus at the start of pregnancy, as pregnancy is often associated with immunosuppression (which increases the risk of infection) and is responsible for more than 70% of miscarriages and causes of Congenital infection (Usta *et al.*, 2016), the risk of infection to the fetus increases if occurrence of the primary infection within the first trimester of pregnancy (Faiza *et al.*, 2013).

Because the HCMV virus has a significant affinity for cervical mucosa (the mucous membrane of the cervix), it can cause chronic and recurrent infection in the mother, leading to repeated miscarriages during pregnancy. (Yamamoto-Tabata *et al.*, 2014), the virus can reach the placenta after infection and the syndrome of the mother through the cervix or the transmission of blood, which results in insufficiency of blood vessels, fetal infection and tissue damage and breakdown (Nigro, 2013). TNF- α is mainly produced by T lymphocytes, natural killer cells and activated macrophages (Atzeni and Sarzi-Puttini, 2013) that plays a critical role in defending intracellular organisms against invasion (Brown *et al.*, 2015), and its role with HCMV infection accrue through the infection of villous cytotrophoblasts that cause a rapid loss of neighboring trophoblasts by mediated apoptosis and cell loss (Chan *et al.*, 2012). While IL-11 cytokine is hematopoietic cytokine which was originally identified as a factor produced by primate stromal cell (Bing *et al.*, 2015), its role accrues by support the formation of primitive hematopoietic and lymphohematopoietic progenitor colonies from bone marrow, to promote erythroid burst formation and to stimulate both early and late stages of megakaryocyte proliferation and differentiation (Samuel, 1995). Interleukin-11 is a multifunctional cytokine, and widely expressed in various tissues, including the brain, gut, and liver (Sugiura *et al.*, 2011). Previous investigations shown that IL-11 is involved in the development of several malignant tumors, including Hepatocellular carcinoma (HCC) (Sugiura *et al.*, 2013).

Materials and Methods

The study samples were collected from Al-Zahra teaching hospital and Al-Manathira general hospital during the period from 6 April to 12 June. Samples were collected by drawing venous blood as (5 ml) were drawn from the blood by using medical plastic syringes, the drawn blood was placed in tubes that do not contain an anticoagulant substance, in which blood is placed and left (30)

minutes at room temperature for coagulation, then the sera are separated by centrifuge for 5 minutes at a rate of (3000 cycles/min), and the serum was divided into equal amounts (250 µl) in small tubes and kept at a temperature (-20 C) until use. 65 blood samples were collected from repeated miscarried women and 15 samples of healthy women were used as a control group and within the age range between (18-40) years. IgM, IgG antibody tests for HCMV using ELISA technology (Germany, Human - ELISA) and interleukins as well, according to the instructions the manufacture company.

Results

The diagnosis of HCMV (serological) was made by detecting antibodies Anti-viral (IgG, IgM) by using enzyme-linked immunosorbent assay (ELISA) technique .The results presented in the (table.1) were obtained, as the results of the statistical analysis for the level of concentrations immunoglobulins (IgG, IgM) were obtained as specifics for the virus, in the sera of aborted women shown that there is a high significantly difference with a level $\leq P 0.05$ in IgG concentration within different age groups of aborted women compared to the control treatment group of women. Also there is a very significant difference with a level of $P \leq 0.05$ between CMV immunoglobulin (IgM) concentration measured in aborted women sera and Control group and that is explained in (Table.1).

Table 1: Presence of specific immunoglobulin (IgG and IgM) in sera of studying groups according to ELISA test

Indicators	Abortion (No. = 65)		Control (No. = 15)		T test	P-value (Sig.)
	Mean	SD	Mean	SD		
IgG(U/ml)	55.62	33.1	35.89	14.97	3.5	0.001(HS)
IgM(U/ml)	0.76	0.38	0.60	0.08	3.05	0.003(HS)

SD: Standard Deviation, S: Significant at P-value <0.05

While the level of TNF- α cytokines in the sera of the study groups showed that there was a high significant concentration in its level among aborted women and that explained in Table.2.

Table 2: TNF- α cytokine concentration levels in the sera of the study groups

Patient group	TNF- α cytokine concentration by (Pico km/ml) (average $\pm$ standard deviation)	Morale level P-value
Aborted women	8.24 $\pm$ 1.58	P <0.003
Control	5.51 $\pm$ 2.6	

In addition to that the result of statical analysis for IL-11 showed that there is an increase in the level of concentration interleukin (IL-11) in aborted women and that explained in Table.3.

Table 3: IL-11 cytokine concentration levels in the sera of the study groups

Patient group	IL-11 cytokine concentration by (Pico km/ml) (average $\pm$ standard deviation)	Morale level P-value
Aborted women	14.25 $\pm$ 2.9	P <0.05
Control	11.25 $\pm$ 4.1	

Discussion

Our findings showed that there was a higher frequency of HCMV infection in urban than rural areas, as shown in (Table.1) by the concentration of IgM and IgG, and that the concentration rate of globulin was increasing with the progression of age, this increase may reflect the accumulation of chronic infection with age (Gonzalez-Quintela, *et al.*,2008), the measurement of immune globulin (IgG) for the HCMV virus is useful for detecting recurrent infections since it is created during the initial infection and its concentration level starts to grow with time, indicating a chronic infection. (Abdul wahab, 2012), and this result is in agreement with the findings of the researcher AL-Khilkhali (2014) in Iraq, that found a substantial association between (IgG) immune globulin content in the serum measured in unit (aU/mL) and age groups, and that highly significant difference with a level of $P \leq 0.05$ between CMV immunoglobulin (IgG) concentration measured in aborted women sera (55.62 $\pm$ 33.1) aU/mL and Control group (35.89 $\pm$ 14.97) aU/mL indicates the presence of recent infections with the virus in women who have aborted. Also there is a very significant difference with a level of $P \leq 0.05$ between CMV immunoglobulin (IgM) concentration measured in aborted women sera (0.76 $\pm$ 0.38) aU/mL, and Control group (0.60 $\pm$ 0.08) aU/mL, and this result agreed with what was mentioned by (Usta *et al.*, 2016) in his study, which included pregnant women in the Aegean region of turkey, which showed the high rates of virus spread during the first trimester of pregnancy, the explanation for this might be ascribed to the fact that HCMV infection is a common infection in pregnancy, and pregnancy is a state of suppression, therefore immunosuppression increases the chance of infection. Kenneson and Cannon (2007), the first three months of pregnancy are extremely crucial, as they are marked by numerous immunological changes and physiological modifications to fulfill the demands of the fetus as well as mother health needs. (Jiang *et al.*,2012), when the initial infection occurs, immunoglobulin (IgM) arises, which is a sign of a recent or acute infection, but it vanishes after a period of time. as little as a couple of weeks (Goodrich *et al.*, 2004), IgM can also occur as a result of secondary infection, reactivation of an earlier infection, or interactions with some viral illnesses, although it might also be owing to the causes listed above (Benoist *et al.*, 2013). But in the Table-2 there is high significant in the concentration of TNF- α protein in aborted women and these results were found in agreement with the findings of the researchers (Stuart *et al.*, 2012), in their study that was conducted in Australia / Sydney, as the virus causes a defect in the regulation of cellular motility during pregnancy, which leads to changes within the immune environment of the placenta (Haider and Knofler, 2009), it was also found that the increase in the concentration of TNF- α is related to the risk for developing obstetric complications, particularly recurrent fetal loss, gestational diabetes mellitus, hypertensive syndromes, and fetal growth

restriction. The human immune system is unable to clear HCMV infection and latency, but mounts a spirited immune-defense including of TNF- α targeting multiple immune-evasion genes encoded by this dsDNA β -herpes especially (HCMV) virus (Chaudhuri *et al.*, 2009), in addition to the magnitude of cellular immune response devoted to HCMV may cause premature immune senescence, and the high frequencies of cytolytic T cells may aggravate vascular pathologies, However, uncontrolled HCMV viremia and life threatening symptoms, which occur readily after immunosuppression and in the immature host clearly indicate the essential role of immunity in maintaining asymptomatic co-existence with HCMV (Berman *et al.*, 2005). As shown by the current study that there is an increase in the level of concentration Interleukin (IL-11) in aborted women compared with the control group and here it is necessary to refer to the findings of Alarifi *et al* (2020) in their study conducted in Saudi Arabia, through which they showed that the levels of IL-10 was higher in HCMV-infected women compared to control, the reason for the presence of a significant difference to the stimulus of the inflammatory response represented by an increase in the level of IL-11 in abortion women infected with HCMV, then become production of pro-inflammatory cytokines from the virus, which causes many damages include cytopathic effect and poor growth of the placenta and fetus, as well as the syncytiotrophoblasts are more susceptible to apoptosis and therefore such effects lead to pre-eclampsia or spontaneous abortion or premature birth, which is one of the characteristics of viral infection. (Hamilton *et al.*, 2012), also IL-11 mediate of acute pro-inflammatory responses during HCMV infection by bind to distinct receptors and play roles not only in inflammation, but also in the regulation of apoptosis (Fu *et al.*, 2017). Many viral proteins that block IL-11 activity also suppress the expression of IL-1 and IL-6 such as IE1, IE2, pp71, and UL26, further impairing the initial inflammatory response, the reason for the presence of a significant difference in the levels of interleukin concentration is the virus has many immunomodulating properties Immunomodulatory the response of the host to a viral infection (Chu,2013).

Conclusions

According to the small population, there was high prevalence of IgG and IgM HCMV. Among pregnant women in Najaf province also there is a high significant effect of TNF- α and IL-11 cytokines in the serum of aborted women that infected with the virus.

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