Elevated Serum TNF – α and Decreased IL-6 levels in Iraqi Women with First Trimester Missed and Threatened Miscarriage Compared to Healthy Pregnancy

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ABSTRACT

Objective: *To measure serum tumor necrosis factor- alpha (TNF-α) and interleukin-6(IL-6) in Iraqi women with first trimester missed and threatened miscarriage and compare their levels with those of normal pregnancy.* ***Methods:*** *A case control study was conducted from November 2009 to March 2010 at Obstetric and Gynecology Department of Al-Yarmouk Teaching Hospital, Baghdad, Iraq. Samples were obtained from 62 pregnant women in the first trimester: eighteen women with threatened miscarriage (group A), 22 with missed miscarriage (group B), 22 apparently healthy pregnant (group C) (positive controls) matched in age and body mass index (BMI) and 23 non-pregnant women (group D) (negative controls). The concentrations of serum TNF-α and IL-6 were determined by an enzyme immunometric assay (EIA).* ***Results:*** *Serum TNF-α levels in group B showed a highly significant increase compared to group A and D (17.68±2.90 pg/ml., 9.75±1.66 pg/ml. and. 4.41±1.23 pg/ml., p=0.039 and p=0.0001 respectively). A significant decrease in mean serum IL-6 in group B compared to group C (3.73±0.65 pg/ml. versus 6.99±1.02 pg/ml., p=0.014). No significant correlation was found between serum levels of TNF-α and IL-6 in all subjects.* ***Conclusion:*** *TNF-α might play an important role in the process of missed and threatened miscarriage and IL-6 may be an important factor for healthy pregnancy.*

Key Words: *Cytokines, TNF-α, IL-6, Missed Miscarriage, Threatened Miscarriage.*

INTRODUCTION

Cytokines are low molecular weight extracellular signaling proteins secreted by immune and inflammatory cell population, as well as growth factors, oncogenes, chemokines, and other soluble factors, which affect growth, differentiation, and viability of cells [1]. The effect of cytokines is generally paracrine: the action is restricted to the cell in their close proximity. They may also act in autocrine: the cytokine acts on the cell that secretes it, or an endocrine: the cytokine diffuses to distant regions of the body through blood or plasma to affect different tissues [2]. Cytokines, originally known as immuno-regulatory proteins, may affect the neuro-endocrine events of reproduction, ovarian /testis function, endometrium, developing embryo, placenta and parturition [3].

The differences in cytokines produced by these cells lead to differences in immune function. Th1-type cytokines, especially IFN- and TNF- (interferons and tumor necrosis factors), have been demonstrated to impair embryo development and trophoblast growth in vitro, and to mediate abortion in mice [4]. The cytokines (IFN-α and TNF-α) are involved in apoptosis of trophoblast cells, they can also inhibit outgrowth. On the other hand, Th2-type cytokines, IL-4, IL-6 and IL-10, are found in the deciduas during normal pregnancy [4]

Tumor necrosis factor (TNF, cachexin or cachectin and formally known as **tumor necrosis factor-alpha**) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. It was first isolated by **Carswell et al.** in 1975 [5].

TNF is primarily produced as a 212 – amino acid – long type II transmembrane protein arranged in stable homotrimers [6]. From that membrane-integrated form, the soluble homotrimeric cytokine (sTNF) is released via proteolytic cleavage by the metalloprotease TNF-alpha converting enzyme (TACE) [7]. The soluble 51 kDa trimeric sTNF tends to dissociate at concentrations below the nanomolar range, thereby losing its bioactivity. TNF-alpha contains a single disulfide bond that can be destroyed without altering the biological activity of the factor. Mutations reduce the cytotoxic activity of the factor almost completely [8]. Two receptors TNF-R1 of 55-60 kDa and TNF-R2 of 75-80 kDa have been described [9].

The primary role of TNF is in the regulation of immune cells, most organs of the body appear to be affected by TNF-α .Cytokine serves a variety of functions, many of which are not yet fully understood. It possesses both growth stimulating properties and growth inhibitory processes, and it appears to have self regulatory properties as well, also able to induce apoptotic cell death, to induce inflammation, and to inhibit tumorigenesis and viral replication [10]. Dysregulation and, in particular, overproduction of TNF have been implicated in a variety of human diseases, as well as cancer [5]. The synthesis of TNF-alpha is induced by many different stimuli including interferons, interleukin-2 (IL2), substance P, tachykinins, bradykinin, immune complexes, inhibitors of cyclooxygenase and PAF (platelet activating factor). The production of TNF is inhibited by: IL6 (Interleukin-6), TGF-beta (Transforming growth factor beta), vitamin D3, prostaglandin E2, dexamethasone, CsA (Cyclosporin A: an immunosuppressant drug), and antagonists of PAF (platelet activating factor)[10].

Interleukin- 6 is a pleiotropic cytokine that regulates immune reaction, hematopoiesis, and differentiation of the nervous system. IL-6-type cytokines form a subfamily of the helix bundle cytokines. All IL-6-type cytokines comprise four long α-helices termed A, B, C and D, which are arranged in a way that leads to an up-up-down-down topology [11].

It acts as both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation. IL-6 promotes inflammatory events through the expansion and activation of T cells, differentiation of B cells and the induction of acute-phase reactants by hepatocytes. In contrast, IL-6 also performs a protective role during disease and counteracts the manifestation of certain inflammatory responses [12].This is paralleled by studies showing that IL-6 down-regulates pro-inflammatory cytokine expression while simultaneously inducing the expression of IL-1 receptor antagonist and the soluble p55 tumor necrosis factor α (TNF-α) receptor [13]. Thus, IL-6 acts not only as a pro- but also as an anti-inflammatory cytokine, and as a result serves a pivotal role during disease. IL-6 is also a "myokine," a cytokine produced from muscle, and is elevated in response to muscle contraction [14].

Aim of work : To asses the role of cytokines in early pregnancy by comparing serum TNF-α and IL-6 levels between women with missed, threatened miscarriage and healthy pregnant.

METHODS

Subjects:

Four groups of women were recruited, all women were attended to Obstetric and Gynecology Department and Primary Health Care Outpatient during the period from November -2009 to March -2010 from Al-Yarmouk Teaching Hospital/ Baghdad/ Iraq. Eighteen women with threatened miscarriage (group A) as defined by the presence of vaginal bleeding (light), closed cervical os, and viable fetus detected by ultrasonographic examination, 22 with missed miscarriage (group B) as defined death of the fetus and retained in the uterus, two ultrasound were taken with two weeks apart showing non viable fetus, the patients were admitted to the hospital for further management, 22 apparently healthy pregnant (group C)(positive controls) and 23 non-pregnant women (group D) were included as negative controls, matched in age and BMI. The gestational age of groups A, B and C, based on ultrasound measurements, ranged between the 7^{th} and 13^{th} weeks. Exclusion criteria were as followed: 1) Subject′s age >35 years old, 2). Previous history of infertility, 3) Previous history of 2 successive miscarriages, 4) History of autoimmune or endocrine diseases (diabetes mellitus, polycystic ovarian syndrome), 5) Remarkable previous medical, surgical and gynecological history. Ten milliliters of fasting venous blood were taken from each individual at time 8:00-10:00 a.m. Samples collected in plain polyethylene tube, allowed to clot at room temperature for thirty minutes, and then the sample was centrifuged at 2000 x g for 10 minutes.

Serum TNF-α was estimated by an enzyme immunometric assay (EIA) for the quantitative determination of human TNF-α in biological fluids using TNF-α kit produced by DGR(Germany) [15], while serum IL-6 was estimated by an enzyme

immunoassay for the in vitro determination of IL-6 in serum using IL-6 kit (Immunotech-France) [16].

Data were analyzed by unpaired student "t" test using statistical Package for Social Sciences (SPSS Inc, Chicage, IL, USA) Version14, quality χ^2 test, and simple correlation with regression equation, taking $p \leq 0.05$ as the lowest limit of significance.

RESULTS

Median age was similar among all the studied groups (**Table 1)**: 25.17±1.00 (range 20-33) years in group A (threatened miscarriage), 26.45±1.07 (range 20-35) years in group B (missed miscarriage), 26.14±1.00 (range 20-35) years in group C (healthy pregnant), and 26.04±0.91 (range 20-35) years in group D (healthy non-pregnant), (p = 0.120). Similarly, median gestational age was similar in the studied groups: 9.50±0.41 (range 7-12) weeks in group A, 9.18±0.28 (range 7-12) weeks in group B, and 9.55±0.44 (range 7-13) weeks in group C. The mean body mass index (BMI) for all groups show no significant difference, were within the range of overweight: 27.67±1.11 (kg/m²) (range 18.6-35.0) in group A, 27.77±0.98 (kg/m²) (range18.8-35.0) in group B, 28.10±1.17(kg/m²) (range 18.9-39.0) in group C, and 26.55±0.92(kg/m²) (range 19.5-34.5) in group D.

Table 1: Characteristics of miscarriage groups and normal pregnant and non-pregnant women

Parameters	*(Group A)*	*(Group B)*	*(Group C)*	*(Group D)*
Number of women	18	22	22	23
Age (years)	25.17±1.00	26.45±1.07	26.14±1.00	26.04±0.91
Gestational age(week)	9.50±0.41	9.18±0.28	9.55±0.44	----------
BMI, Kg/m2	27.67±1.11	27.77±0.98	28.10±1.17	26.55±0.92

Serum TNF-α concentrations were detectable in 77.8 % of the sera in women with threatened miscarriage, 86.4 % in women with missed miscarriage, 81.8 % in healthy pregnant, and 73.9 % in healthy non-pregnant women, while serum IL-6 concentrations were detectable in 77.8 % of the sera in women with threatened miscarriage, 72.7 % in women with missed miscarriage, 86.4 % in healthy pregnant, and 43.5 % in healthy non-pregnant women. **Table 2** showed the number and percentage of detectable and undetectable TNF-α and IL-6 in sera of women in this study.

Table 2 Number and percentage of detectable TNF-α and IL-6 in sera

Groups	*Total Number*	*TNF-α (pg/ml)*		*IL-6 (pg/ml)*	
		Detected	**Undetected**	**Detected**	**Undetected**
Threatened miscarriage	18	(14) 77.8 %	(4) 22.2 %	(14) 77.8 %	(4) 22.2 %
Missed miscarriage	22	(19) 86.4 %	(3) 13.6 %	(16) 72.7 %	(6) 27.3 %
Healthy pregnant	22	(18) 81.8 %	(4) 18.2 %	(19) 86.4 %	(3) 13.6 %
Healthy non- pregnant	23	(17) 73.9 %	(6) 26.1 %	(10) 43.5 %	(13) 56.5 %

There were a significant higher TNF-α levels in women with missed miscarriage compared to women with threatened miscarriage and healthy non-pregnant women (17.68±2.90 pg/ml vs. 9.75±1.66 pg/ml and 17.68±2.90 pg/ml vs. 4.41±1.23 pg/ml, p=0.039 and p=0.0001 respectively). Mean serum TNF-α levels in women with missed miscarriage (17.68±2.90 pg/ml) were higher than that of healthy pregnant women (12.71±3.32 pg/ml). **Table 3** and **Figure 1** show the results of mean serum TNF-α level in the studied groups.

Table 3: Mean Serum TNF-α Levels for the Studied Groups.

Groups	*TNF-α (pg/ml)*		*P value in comparison to*		
	Mean±SEM	**Range**	**Missed miscarriage**	**Healthy pregnant**	**Healthy non-pregnant**
Threatened miscarriage (n=14)	9.75±1.66	(1.1-25.7)	0.039 (S)	0.472 (NS)	0.013 (S)
Missed miscarriage (n=19)	17.68±2.90	(8.3-64.1)		0.265 (NS)	0.0001 (S)
Healthy pregnant (n=18)	12.71±3.32	(2.4-63.4)			0.029 (S)
Healthy non-pregnantt (n=17)	4.41±1.23	(0.4-16.0)			

NS= non significant, S= significant

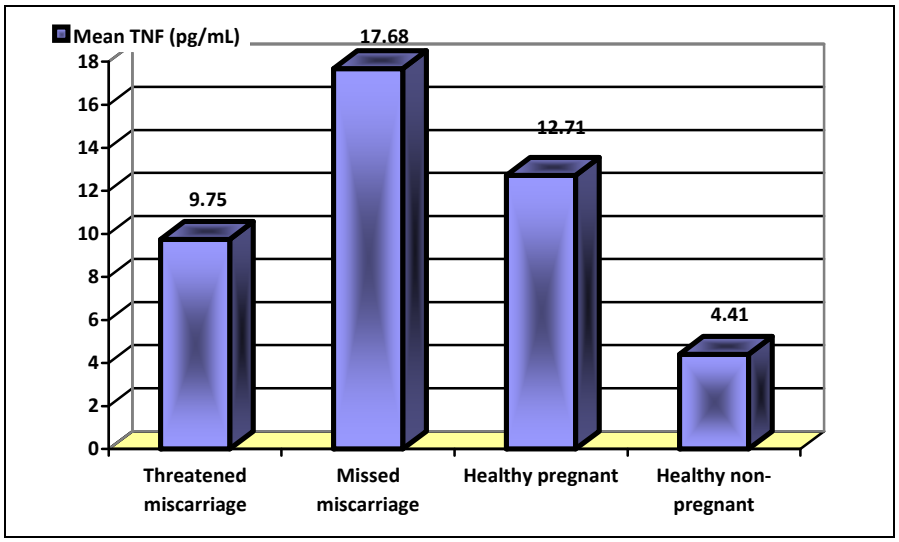

Figure 1: Means of serum TNF-α levels for the studied groups.

A significant decrease in mean serum IL-6 levels in women with missed miscarriage compared to healthy pregnant women (3.73±0.65 pg/ml vs. 6.99±1.02 pg/ml, p=0.014), but they showed no significant difference compared to healthy non-pregnant women (3.73±0.65 pg/ml vs. 3.56±0.92 pg/ml, p= 0.877), and there was a significant increase in mean serum IL-6 levels in healthy pregnant women compared to healthy non-pregnant women (6.99±1.02 pg/ml vs. 3.56±0.92 pg/ml, p=0.037). All the results of mean serum IL-6 levels in the studied groups were described in **Table 4** and **Figure 2.**

Table 4: Mean Serum IL-6 Levels for the Studied Groups.

Groups	***IL-6 (pg/ml)***		***P value in comparison to***		
	Mean±SEM	**Range**	**Missed miscarriage**	**Healthy pregnant**	**Healthy non-pregnant**
Threatened miscarriage (n=14)	5.35±0.78	(0.4-9.8)	0.119 (NS)	0.239 (NS)	0.153 (NS)
Missed miscarriage (n=16)	3.73±0.65	(0.4-9.1)		0.014 (S)	0.877 (NS)
Healthy Pregnant (n=19)	6.99±1.02	(0.4-16.2)			0.037 (S)
Healthy non-pregnant (n=10)	3.56±0.92	(0.4-8.2)			

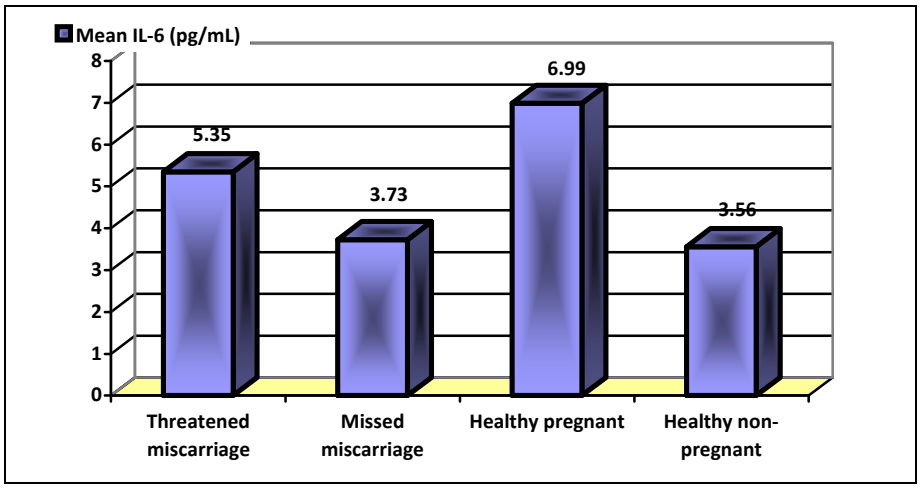

Figure 2: Means of serum IL-6 levels for the studied groups

Table 5: Correlation of Mean Serum TNF-α Levels with All Variables in this Study.

Variable		*TNF (pg/ml)*			
		Threatened miscarriage	**Missed miscarriage**	**Healthy pregnant**	**Healthy non-pregnant**
Age (years)	**r**	0.085	-0.077	0.168	0.361
	P	0.771	0.755	0.504	0.155
Gestational age (weeks)	**r**	0.138	0.154	-0.100	-
	P	0.637	0.529	0.694	-
Gravidity	**r**	0.399	-0.193	0.257	0.299
	P	0.158	0.429	0.303	0.243
Parity	**r**	0.435	-0.099	0.389	0.389
	P	0.120	0.686	0.111	0.123
Abortions	**r**	0.066	-0.268	-0.176	-0.051
	P	0.823	0.266	0.484	0.846
BMI (Kg/m2)	**r**	0.522	0.425	0.612*	0.577*
	P	0.056	0.070	0.007	0.015
IL-6 (pg/ml)	**r**	0.379	0.388	0.129	0.550
	P	0.225	0.170	0.633	0.201

* Correlation is significant at the 0.05 level.

Table 6: Correlation of Mean Serum IL-6 Levels with All Variables in this Study.

Variable		*IL-6 (pg/ml)*			
		Threatened miscarriage	**Missed miscarriage**	**Healthy pregnant**	**Healthy non-pregnant**
Age (years)	**r**	-0.171	0.206	0.500*	0.140
	P	0.559	0.444	0.029	0.699
Gestational age (weeks)	**r**	-0.179	0.299	0.310	-
	P	0.540	0.261	0.196	-
Gravidity	**r**	0.196	0.083	-0.037	-0.011
	P	0.503	0.761	0.881	0.977
Parity	**r**	0.102	0.337	0.040	0.151
	P	0.730	0.202	0.872	0.677
Abortions	**r**	0.342	-0.520*	-0.226	-0.188
	P	0.231	0.039	0.353	0.603
BMI (Kg/m2)	**r**	0.340	0.636*	0.317	0.471
	P	0.235	0.008	0.186	0.170
TNF (pg/ml)	**r**	0.379	0.388	0.129	0.550
	P	0.225	0.170	0.633	0.201

- Correlation is significant at the 0.05 level.

Data showed that the BMI values were significantly positive correlated with serum TNF-α levels in the healthy control women whether pregnant (r=0.612, p=0.007) or non pregnant subjects (r=0.577, p=0.015), while in women with missed and threatened miscarriages showed significant positive correlation. No significant correlation was found between serum levels of TNF-α and Il-6 in all groups. Table 5 showed all the correlations of mean serum TNF-α levels with all the variables in the present study, while Table 6 showed correlations of mean serum IL-6 levels with the studied variables.

IL-6 showed no significant correlation with any of the investigated parameters except with the number of abortions and BMI of threatened miscarriage (r=0520, p=0.039, r=0.636, p=0.008 respectively).

DISCUSSION

Data of the current study demonstrate that serum TNF-α (T helper 1) levels are significantly higher, and serum IL-6 (T helper 2) levels are significantly lower in missed miscarriage group compared to healthy pregnant women of < 20 gestational weeks. **Arslan *et al* (2004)** suggested that the highest levels of TNF-alpha are found in pregnant women with a past history of habitual abortion and the lowest in healthy non pregnant [17]. Many previous studies suggested that an imbalance of TH1, TH2 cytokine pattern may be one of

the immunologic causes in unexplained infertility, and recurrent / miscarriage [18] [19]. Increased levels of Th1 cytokines appear to be critical in early pregnancy and were able to discriminate between pregnancies that continue and those that end in miscarriage [20]. However, another study could not confirm the previous finding of a Th1 biased cytokine profile in miscarriage patients, compared to a Th2 biased profile in normal pregnant women [21]. One study suggests that women with a history of recurrent miscarriage can have abnormal cytokine expression even when not pregnant; this may influence the potential for future successful immune modulatory therapy [22].

A previous study observed the opposite of these presented findings a low circulating levels of several cytokines— IL-1β, IL-4, IL-6, IFN-γ and TNF-α—and lack of consistent associations with miscarriage risk. A possible explanation for inconsistency in human studies may be related to timing of sample collection relative to the miscarriage. Since it involved analysis of serum samples collected at least 10 days prior to diagnosis of the miscarriage [23]. Other previous study [24] found IL-6 concentrations were lower in women with miscarriage than those undergoing normal delivery considering that IL-6 is a TH2 type cytokine and that normal pregnancy appears to be a TH2 biased condition, and the observation of elevated TNF-α concentrations even before the onset of pregnancy is indicative of immune dysregulation as a possible aetiological cause of miscarriage.

Contradictory data reported different functional gene polymorphisms of IL-6 to be well [25] or not [26] associated with the pathogenesis of miscarriage or even to decrease the risk for miscarriage [27]. Inadequate expression of IL-6 and IL-1α mRNAs in endometrial tissue may predispose to recurrent miscarriage through a perturbed maternal immune response, effects on decidual tissue remodeling and angiogenesis, or dysregulated trophoblast differentiation and invasion [28].

Others reported that no significant differences in circulating IL-6 levels were found for pregnant women at < 20 weeks of gestation with miscarriage, in comparison to nonpregnant women with a past history of habitual abortion as well as healthy nonpregnant women [21].

TNF-alpha is a proinflammatory, proapoptotic, and procoagulant and, thus, abortogenic, mainly Th1-type, cytokine. Its production is also partly under genetic control. Contradictory data reported that TNF-alpha functional gene polymorphisms were not correlated with recurrent spontaneous abortion (RSA) in Caucasians [29]. Other previous study showed a trend to be associated with RSA [30], or associated with an increased risk for RSA [31]. In pregnant women at < 20 weeks of gestational age and with a history of RSA, several reports agree that serum TNF-alpha levels were elevated in comparison to those of healthy pregnant women at the same gestational age [21,23]. Cytokines especially TNF-α was found to be related to the pregnancy loss [21]. Others reported that there was an

increased or unaltered TNF-alpha production in peripheral blood of nonpregnant women with a history of RSA, when blood was cultivated in the presence of phytohemagglutinine (PHA) [23] or trophoblast cells [32]. Contradictory data reported decreased [41] or increased [33] in TNF-alpha levels in or at onset of spontaneous abortion, respectively, in comparison to normal pregnancies. TNF-alpha levels similar to those in normal pregnancy were reported in threatened abortion with a good outcome [34].

The presence of complicated networks of cytokines and their overlapping biological activities means that alteration of one cytokine is likely to affect others and this also makes the study of their role in implantation failure very difficult. There is an urgent need to re-examine the role played by various cytokines in reproductive failure through carefully planned and vigorously designed studies and to compare the different types of reproductive failure [35].

Our study revealed insignificant positive correlation between IL-6 and TNF- α serum levels this agreed with **Hsin-Hua Chen, et al.**[36] who predicted that there were no significant correlations among serum IL-6, TNF- alpha, and TGF-β cytokines in women with a defect in implantation and controls [36].

CONCLUSION

The current study supports the idea that suggests the imbalance of TH1, TH2 cytokine pattern may be one of the immunologic causes in unexplained miscarriage and that TNF-α could play an important role in the process of missed miscarriage and IL-6 is important for healthy pregnancy.

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أرتفاع مستوى عامل نخر الورم- الفا وأنخفاض مستوى الأنترلوكين- ٦ في مصل دم نساء عراقيات حوامل في المرحلة الأولى للحمل ويعانين من الأسقاط المهدد التلقائي والفائت مقارنة مع الحوامل السليمات

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الخلاصة

الأهداف :قياس مستويات عامل نخر الورم- الفا (TNF-α) والأنترلوكين – ٦ (IL-6) في مصل دم نساء في المرحلة الأولى للحمل ويعانين من الأسقاط المهدد التلقائي والفائت والمقارنة مع الحوامل السليمات وغير السليمات.

الطريقة: أجريت هذه الدراسة في بغداد-مستشفى اليرموك التعليمي قسم النسائية والتوليد خلال الفترة من نوفمبر ٢٠٠٩ م حتى مارس ٢٠١٠ م. اشتملت الدراسة على (٦٢) أمرأة حامل في الثلث الأول من الحمل ، منهن (١٨) أمرأة مهدد حملهن بالأسقاط التلقائي (مجموعة A) ، (٢٢) أمرأة مهدد حملهن بالأسقاط الفائت (مجموعة B) ، (٢٢) أمرأه حامل سليمات من الأمراض كنماذج ضابطة أيجابية (مجموعة C) ، وشملت الدراسة على (٢٣) أمرأة غير حامل كمجموعة ضابطة سلبية (مجموعة D) مع تطابق العمر وعامل كتلة الجسم (BMI) لجميع النساء. أستخدمت طريقة الفحص الأنزيمي المناعي (EIA) لقياس تراكيز عامل نخر الورم – الفا (TNF-α) والأنترلوكين -٦ (IL-6).

النتائج: وجد أن هناك أرتفاع كبير وملحوظ في مستويات TNF-α في مصل مريضات المجموعة B مقارنة مع مجموعة Aو D (17.68±2.90 pg/ml, 9.75±1.66pg/ml., 4.41±1.23pg/ml,) (p=0.039,p=0.0001 على التعاقب، وظهر أنخفاض ملحوظ في مستوى IL- C٦ في مصل دم المرضى مجموعة B مقارنة مع مجموعة (3.73±0.65 pg/ml, 6.99±1.02pg/ml, p=0.014)

ولم تظهر أي علاقة ارتباط ذات علامة احصائية بين مستويات TNF-α ومستويات IL-6 في مصل دم جميع المرضى.

لأستنتاج: TNF-α له دور مهم في تطور ألأسقاط المهدد التلقائي والفائت بينما IL-6 له اهمية في الحفاظ على سلامة الحمل.