American Research Journal of Hematology
Volume 1, Issue 1, pp: 9 -19

AMERICAN RESEARCH JOURNALS
An Academic Publishing House

Research Article Open Access

Interleukin-6 [Il-6], Interleukin-17 [Il-17] and Angiopoietin in Women with Bad Obstetric History Kirkuk, Iraq

Abdulghani Mohamed Alsamarai[1], Hala Mohamed Majeed[2], Amina Hamed Alobaidi[3]

[1]Tikrit University College of Medicine, Tikrit, Iraq
[2]Tikrit University College of Veterinary Medicine, Tikrit, Iraq
[3]Kirkuk University College of Veterinary Medicine, Kirkuk, Iraq
galsamarrai@yahoo.com

Abstract:

Background: Bad obstetric outcomes are considered as major health problem with social and medical impact on society, with multiple etiology.

Study Design: Descriptive Case Control Study.

Aim: To evaluate the role of IL-6, IL-17 and angiopoietin in pregnancy loss in women in Kirkuk, Iraq.

Materials and Methods: The study included 547 women with BOH and 291 women with normal pregnancy outcome. Serological study carried out to determine IL-6, IL-17 and Angiopoietin using ELISA kits.

Results: IL-6 mean value was without significant difference among women with BOH , women with inevitable abortion and control. Pregnant BOH versus pregnant normal pregnancy, Non-pregnant BOH versus non-pregnant normal pregnancy, BOH versus normal pregnancy show significant differences in IL-6. IL-17 was with significant mean difference among BOH, abortion and normal pregnancy. Also, pregnant BOH versus pregnant normal pregnancy, BOH versus normal pregnancy, and abortion versus BOH show significant differences in IL-17. Angiopoietin was with significant mean difference among BOH, abortion and normal pregnancy. Pregnant BOH versus pregnant normal pregnancy, Non-pregnant BOH versus non-pregnant normal pregnancy, BOH versus normal pregnancy show significant differences in angiopoietin.

Conclusion: Angiopoietin -1 appear to be an angiogenic predictive marker for women with bad obstetric history. A future study that included Ang-1, Ang-2 combination with others different biomarkers to determine their predictive value as a marker of BOH is warranted.

Keywords: BOH, IL-6, IL-17, Angiopoietin, women.

Introduction

Bad obstetric outcomes are considered as major health problem with social and medical impact on society [1]. There are many aetiology for bad obstetric outcomes, however, not all are well studies. Infections as a cause of bad obstetric history/ outcome [BOH] are well studies globally and nationally in Iraq [2-12]. Autoimmunity was suggested to play a role in the pregnancy loss [13]. Cytokines that were induced as response to infections and as a sequences of inflammatory processes may play a role in the pathogenesis of BOH. Thus this study was conducted to evaluate the role of IL-6, IL-17 and angiopoietin in pregnancy loss in women in Kirkuk, Iraq.

Materials and Methods

Study Design and Settings

The study design is a Descriptive Case Control Study and was performed in Kirkuk General Hospital. The study proposal was approved by Tikrit University College of Science ethical committee and Kirkuk Health Authority Research Committee. Informed consent taken from each women included in the study.

Study Population

The study population is women with childbearing age. Study population was recruited from Kirkuk General Hospital. A 838 women with age range from 14 to 48 were included in the study. Of the total, 547 women were with bad obstetric history (BOH) and 291 women with normal previous pregnancy as control group. The demographic information of these groups are shown in Table 1. For serological analysis, 5-10 mL of venous blood was collected in a sterile container with strict aseptic precautions from each study subject. The serum was separated and stored in numbered aliquots at -20 oC till assayed. All the serum samples collected from the study and control groups were tested for IL-6, IL-17 and angiopoietin by commercially- available (ELISA) kits. The results read by a Microwell reader and compared in a parallel manner with controls; optical density read at 450 nm on an ELISA reader.

Collection of data

All recruited women were subject for clinical examination and laboratory investigations were carried out for the study subjects to exclude other causes of foetal wastage, such as hypertension, diabetes mellitus, syphilis, Rh (rhesus) incompatibility, physical causes of abortion, and consanguinity. Subjects with known causes of foetal wastage were excluded from the study. All of them were interviewed to ascertain age, medical and obstetric information.

Determination of IL-6, IL-17 and angiopoietin

ELISA was used for determination of IL-6, IL-17 and angiopoietin in serum and the test was performed according to manufacturer instructions. The kits were purchased from CUSABIO company.

Statistical Analysis

The proportion and the mean value were computed in appropriate situations. The data analysed using the SPSS (Version 16). The study finding data were presented as mean and student t test and ANOVA were used to determine significance of differences between groups.

Results

Interleukin 6

Interleukin 6 (IL-6) mean value was without significant ($F=2.39$, $P>0.05$) difference among women with BOH (20.79 pg/ml), women with inevitable abortion (25.11 pg/ml) and control (26.15 pg/ml). In addition, there was no significant difference in IL-6 mean value between pregnant BOH (20.83 pg/ml) and non pregnant BOH (20.75 pg/ml). Furthermore, there was no significant difference in mean IL-6 value between pregnant control (26.76 pg/ml) and non pregnant control (25.45 pg/ml), as shown in Table (2).

IL-6 mean value was significantly ($X2=2.49$,$P=0.018$) lower in pregnant women with BOH (20.83 pg/ml) as compared to pregnant control (26.76 pg/ml). In addition, the mean IL-6 value was significantly ($X2=2.23$,$P=0.027$) higher in non pregnant control (25.45 pg/ml) than those non pregnant women with BOH (20.75 pg/ml). Furthermore, IL-6 mean value was significantly ($X2=3.11$,$P=0.012$) lower in women with BOH (20.79 pg/ml) compared to women with normal pregnancy outcome (26.15 pg/ml). However, there was no significant ($X2=1.43$,$P>0.05$) difference in IL-6 mean value between women with inevitable abortion (25.11 pg/

ml) and women with BOH (20.79 pg/ml). In addition, IL-6 mean value was not significantly (X2=0.20,P>0.05) different in women with inevitable abortion (25.11 pg/ml) compared to those with normal pregnancy outcome (26.15 pg/ml), as shown in Table (2).

Interleukin 17

Interleukin 17 (IL-17) mean value was with significant (F=3.26, P=0.0439) difference among women with BOH (127.81 pg/ml), women with inevitable abortion (88.67 pg/ml) and control (85.65 pg/ml). In addition, there was a significant difference in IL-17 mean value between pregnant BOH (167.56 pg/ml) and non pregnant BOH (88.05 pg/ml). Furthermore, there was no significant difference in mean IL-17 value between pregnant control (83.16 pg/ml) and non pregnant control (86.9 pg/ml), as shown in Table(3).

IL-17 mean value was significantly (X2=20.43,P<0.0001) higher in pregnant women with BOH (167.56 pg/ml) as compared to pregnant control (83.16 pg/ml). In addition, IL-17 mean value was significantly (X2=2.089,P=0.04) higher in women with BOH (127.81 pg/ml) compared to women with normal pregnancy outcome (85.65 pg/ml). Furthermore, there was a significant (X2=1.6,P=0.049) difference in IL-17 mean value between women with inevitable abortion (88.67 pg/ml) and women with BOH (127.81 pg/ml). However, the mean IL-17 value was not significantly (X2=0.056,P>0.05) different between non pregnant control (86.9 pg/ml) and those non pregnant women with BOH (88.05 pg/ml). In addition, IL-17 mean value was not significantly (X2=0.36,P>0.05) different in women with inevitable abortion (88.67 pg/ml) compared to those with normal pregnancy outcome (85.65 pg/ml), as shown in Table (3).

Angiopoietin

Angiopoietin mean value was with significant (F=4.99, P=0.0089) difference among women with BOH (81.72 pg/ml), women with inevitable abortion (92.66 pg/ml) and control (100.1 pg/ml). In addition, there was not significant difference in angiopoietin mean value between pregnant BOH (80.06 pg/ml) and non pregnant BOH (83.39 pg/ml). Furthermore, there was not significant difference in mean angiopoietin value between pregnant control (98.69 pg/ml) and non pregnant control (101.52 pg/ml), as shown in Table (4).

Angiopoietin mean value was significantly (X2=2.464,P=0.0393) lower in pregnant women with BOH (80.06 pg/ml) as compared to pregnant control (98.69 pg/ml). In addition, angiopoietin mean value was significantly (X2=369,P=0.0032) lower in women with BOH (81.72 pg/ml) compared to women with normal pregnancy outcome (100.1 pg/ml). Furthermore, the mean angiopoietin value was significantly (X2=2.206,P=0374) higher in non pregnant control (101.52 pg/ml) and those non pregnant women with BOH (83.39 pg/ml). However, there was not significant (X2=1.68,P=0.049) difference in angiopoietin mean value between women with inevitable abortion (92.66 pg/ml) and women with BOH (81.72 pg/ml). In addition, angiopoietin mean value was not significantly (X2=0.97,P>0.05) different in women with inevitable abortion (92.66 pg/ml) compared to those with normal pregnancy outcome (100.1 pg/ml), as shown in Table (4).

Table 1. *Study population*

Group		Number	Mean age ± SD in years
Women with bad obstetric history	**Pregnant**	292	28.35 ± 7.25
	Non pregnant	255	28.24 ± 6.81
	Total	547	
Women with normal pregnancy	**Pregnant**	140	27.40 ± 6.24
	Non pregnant	151	28.06 ± 10.51
	Total	291	
Grand total		838	28.42 ± 7.72
P value	ANOVA	NS	

Table 2. *Interleukin 6 Mean Value in women with BOH compared to control*

Group [Number]		Mean ± SD in pg/ml	
Bad obstetric history	Pregnant [20]	20.83 ± 6.54	
	Non- pregnant [20]	20.75 ± 5.09	
	P value	**NS**	
	Total [40]	**20.79 ± 5.83**	
Normal pregnancy	Pregnant [14]	26.76 ± 7.23	
	Non- pregnant [14]	25.45 ± 6.94	
	P value	**NS**	
	Total [28]	**26.15 ± 7.24**	
Abortion	Inevitable [20]	25.11± 17.78	
		F or X^2	**P**
P	ANOVA	**2.39**	**NS**
	Pregnant BOH versus pregnant Normal pregnancy	**2.492**	**0.018**
	Non- pregnant BOH versus Non-pregnant normal pregnancy	**2.2359**	**0.027**
	BOH versus Normal pregnancy	**3.11**	**0.012**
	Abortion versus BOH	**1.428**	**NS**
	Abortion versus Normal pregnancy	**0.2033**	**NS**

Table 3. *Interleukin 17 mean value in women with BOH compared to control*

Group [Number]		Mean ± SD in pg/ml	
Bad obstetric history	Pregnant [20]	167.56 ±113.22	
	Non- pregnant [20]	88.05 ± 40.62	
	P value	**0.014**	
	Total [40]	**127.81± 85.22**	
Normal pregnancy	Pregnant [14]	83.16 ± 26.71	
	Non- pregnant [14]	86.90 ± 24.54	
	P value	**NS**	
	Total [28]	**85.65 ± 25.3**	
Abortion	Inevitable [20]	88.67± 23.18	
		F or X^2	**P**
P	ANOVA	**3.26**	**0.0439**
	Pregnant BOH versus pregnant Normal pregnancy	**20.43**	**<0.0001**
	Non- pregnant BOH versus Non-pregnant normal pregnancy	**0.056**	**NS**
	BOH versus Normal pregnancy	**2.089**	**0.04**
	Abortion versus BOH	**1.6**	**0.049**
	Abortion versus Normal pregnancy	**0.367**	**NS**

Table 4. *Angiopoietin mean value in women with BOH compared to control*

Group [Number]		Mean ± SD in pg/ml	
Bad obstetric history	Pregnant [20]	80.06 ± 23.68	
	Non- pregnant [20]	83.39 ±16.35	
	P value	**NS**	
	Total [40]	**81.72 ± 20.16**	
Normal pregnancy	Pregnant [14]	98.69 ± 26.53	
	Non- pregnant [14]	101.52 ± 31.98	
	P value	**NS**	
	Total [28]	**100.1± 29.39**	
Abortion	Inevitable [20]	92.66 ± 29.56	
		F or X^2	**P**
P	ANOVA	**4.99**	**0.0089**
	Pregnant BOH versus pregnant Normal pregnancy	**2.464**	**0.0393**
	Non- pregnant BOH versus Non-pregnant normal pregnancy	**2.206**	**0.0374**
	BOH versus Normal pregnancy	**3.269**	**0.0032**
	Abortion versus BOH	**1.6888**	**NS**
	Abortion versus Normal pregnancy	**0.97**	**NS**

Discussion

Interleukin -6 (IL-6)

Pregnancy outcome is under the influence of cytokines present in maternal blood [14]. Successful pregnancy was associated with Th-2 cytokines, while poor pregnancy outcome was associated with Th-1 cytokines [15]. Immune system and non- immune cells produced IL-6 which is multifunctional Th-2 cytokine, the role of IL-6 and its predictivity in successful pregnancy is unclear. However, reported studies suggest its positive role in normal pregnancy outcome [16].. IL-6 is considered to be a proinflammatory cytokine, reported that intrauterine infection, preterm premature rupture of the membrane, and prematurity as pregnancy complications were associated with increased IL-6 levels in amniotic fluid, placenta and deciduas [17]. IL-6 has antiinflammatory effects and thus lead to induction of human chorionic gonadotrophin from trophoblast, which subsequently enhance release of progesterone, Th2 cytokines production and suppress the effect of Th2 cytokines [18].

In the present study there was no significant (F=2.39, P>0.05) difference in mean serum levels on IL-6 between women with bad obstetric history, women with inevitable abortion, and women with normal pregnancy outcome. However, there was a significant (X2 =3.11,P=0.012) difference in mean serum IL-6 levels between women with BOH and those with normal pregnancy outcome. The same pattern was demonstrated when the comparison performed between pregnant BOH versus pregnant control (X2 =2.49,P=0.018), and non pregnant BOH versus non pregnant control (X2 =2.23,P=0.027). IL-6 is a Th2-type, pro- as well as anti-inflammatory cytokine. IL-6 play an important role in down-regulation of Th1 cytokines [19]. IL-6 polymorphism are associated with contradictory effect, some studies suggest that IL-6 polymorphism may be associated with recurrent spontaneous abortion [20], while others do not show such association [21] or it may be with protective effect [22].

Our study demonstrated about the same serum IL-6 mean value in women with inevitable as abortion as compared to those with normal pregnancy outcome. In addition, both pregnant and non pregnant women with

normal pregnancy outcome were with about the same mean serum IL-6 values. However, both the control and women with inevitable abortion were with higher serum IL-6 value than women with BOH. IL-6 lower values were reported in women with missed abortion, while no change was demonstrated in women with threatened abortion as compared to normal pregnant and normal non pregnant controls [19]. In the study of Vitoratos et al [23] maternal serum IL-6 levels in first-trimester threatened abortion with poor pregnancy outcome were unaltered in comparison to those of first trimester healthy pregnant women.

IL-6 protein and mRNA expression was reduced in women with RSA as compared to control [24]. In vitro activation of blood mononuclear cells collected from women with RSA at the time of abortion produce lower IL-6 [25] . The present study finding is not consistent with this as IL-6 serum level was more in women with normal pregnancy outcome for both pregnant and non pregnant as compared to those with BOH. In literature, many studies were consistent with our findings and indicating a significant lower IL-6 serum mean value in women with RSA as compared to control [26]. However, one study reported no significant difference in serum IL-6 mean value between women with miscarriage and control group [27]. However, other studies reported that serum IL6 was significantly increased in both pregnant and non-pregnant women with RSA compared with fertile women [28]. The present study and reported research in literature indicated a controversy and thus interpretation of the role of IL-6 in recurrent abortion must be performed with caution [29], and there is a need to perform large scale cohort study with follow up to evaluate the role of IL-6 in BOH.

The classification of IL-6 as a Th1-type cytokine in studies on preterm labor [30] or as a Th2 type cytokine in early pregnancy [31] remains controversial. Recently, it has been demonstrated that IL-6 is involved in the promotion of Th2 differentiation and the inhibition of Th1 polarization [32]. During the first trimester, IL-6 contribute to tissue remodeling that is associated with placentation, the hematopoiesis function of the secondary yolk sac , and the generation of new vessels in placental villi [33]. One possible mechanism of IL-6 in preventing miscarriage is modulation of the quality of the Th2 response by increasing the proportion of blocking asymmetric antibodies during implantation and placental vascularization [32].

Interleukin 17

The present study indicated a significant difference in IL-17 serum mean value in women with BOH and those with normal pregnancy outcome (X2 =2.08943,P=0.04) and the significance was more prominent when the comparison performed between pregnant BOH and pregnant control. This finding agreed with that reported by Lee et al [34] as their study demonstrated that the level of IL-17+ T cells and ratio of IL-17+ T/ Treg cells were significantly increased in peripheral blood from non- pregnant with idiopathic recurrent pregnancy loss when compared with fertile control.

Suppress the maternal all responses targeted against the fetus [35] . Tregs and Th17 cells are two lymphocyte subsets with opposing actions. In normal pregnancy, Tregs prevent the generation of an immune response against fetal tissue and a decrease in the number of Tregs is associated with abortion. In contrast to the Tregs, Th17 cells promote inflammatory, autoimmunity and transplant rejection in humans and increased Th17 cells companied with decreased Tregs had been shown in unexplained RM patients [36].

The functions of Tregs has been mainly mediated by a cell–cell contact or by the production of anti-inflammatory cytokines such as IL-10 and TGF-b, whereas Th17 cells mainly exert their effects by secreting IL-17. IL-17 has pleiotropic activities, including induction of the expression of pro inflammatory cytokines and chemokines, which mediate tissue infiltration and destruction [37]. Reported studies suggest an increase in Th17 cell in peripheral blood and deciduas in women with recurrent pregnancy loss of unknown etiology [35] . Liu et al [38] reported that Th17 cells in blood were lower in controls women as compared to non pregnant women with recurrent pregnancy loss. This finding explains the increased of serum IL-17 in women with BOH as compared

to those with normal pregnancy outcome as this study indicated. In addition, Nakashima et al [39] find that women with inevitable abortion deciduas were with increased Th17 cells. Many reported studies indicate that immune response mediated by Th17 cells were associated with recurrent pregnancy loss [40] , with an important role of Treg cells in poor obstetric outcome [41].

Although, Treg cells are responsible for prevention of immunological reaction against foetal tissue in normal pregnancy [37], some studies suggest that women with BOH are unlikely to be able to induce and maintain the immune tolerance regulated by Treg cells [34]. Tregs cells from women with BOH were functionally deficient as compared to those from fertile women [42]. Thus augmentation of Tregs cells function may be an approach for the treatment of pregnancy loss [36]. IL-17+ T/Treg cell ratio as a reflection of both Treg immune regulatory and Th17/Tc17 inflammatory response, was lower in controls than in women with poor pregnancy outcome [34]. Thus IL-17+ T/Treg cell ratio may be used as a predictive marker for treatment and diagnosis of complication during pregnancy. In the present study, the ratio of IL-17/ IL-6 was about twice (6.15 pg/ml) in women with BOH than in women with normal pregnancy outcome (3.28 pg/ml), and in pregnant women with BOH (8.04 pg/ml) than in non pregnant women (4.24 pg/ml) with BOH. However, the rate of IL-17/IL-6 was about the same in pregnant (3.11 pg/ml) and non pregnant (3.41 pg/ml) women with normal pregnancy outcome. This finding suggests that pregnancy may play a role in cytokine induction that may over express IL-17 companied with decreased Treg cells and IL-6 production. In addition, IL-6 may prevent abortion by modulation of the quality of Th2 response by increasing the proportion of blocking asymmetric antibodies during implantation and placental vascularisation [43]. These findings together suggest that IL-6 may play a role like that of IL-10 as anti-inflammatory action. IL-10 negatively regulates the expression of Th17 cytokines and thus decreases the amount of IL-17 and plays a role in preventing exaggerated inflammatory and immune responses. Wang et al [35] found that culturing of CD4+ T cells in the presence of IL-10 decreases the expression of IL-17 that was IL-10 dose dependent.

The present study finding of increased IL-17 in women with BOH goes with the suggestion of Lee et al [34] as the imbalance between Th1 and Th2 cells and additional biological effects of increased numbers of IL-17+ T cells may induce an inflammatory immune response which contributes to the development of RPL.

This study did not show a significant difference in serum IL-17 mean levels between non pregnant women with normal pregnancy outcome, non pregnant with BOH and inevitable abortion. This finding contrasts with to that reported by others [34] who reported elevated IL-17+ T cells in peripheral blood of non pregnant women with a history of recurrent pregnancy loss. Therefore, they speculate these cells actively induce pro-inflammatory immune responses at the maternal-fetal junction at the time of implantation, and lead to recurrent pregnancy loss. IL-17 expression by decidual T cells was increased in women inevitable abortion, while not in missed abortion , Inflammation initiation in late stage of abortion may be an effect induced by IL-1+ cells [39].

This study and the reported literature illustrate a paradigm shift from Th1/Th2 theory to a broader concept of pro-inflammatory immune responses, which involve increased IL-17+ T cells, increased Th1/Th2 cell ratios and suppressed Treg cell immune responses as the underlying immune pathology for RPL and, potentially, other obstetrical complications.

Angiopoietin 1

Development of blood vessels and angiogenesis during pregnancy and placental growth and maturation were regulated by angiopoietin 1 and 2, Reported studies indicated that angiopoietin 1and 2 were expressed early in placental tissue in normal or abnormal gestation for both mother and fetus [44]. The present study provides the first data in Iraq to demonstrate that serum Ang-1 is potential marker of bad obstetric history (failed pregnancy), as its serum mean value significantly difference between women with BOH, inevitable abortion, and women

with normal pregnancy outcome. In our series of women with BOH Ang-1 serum mean value with significantly lower (X2 =3.269,P=0.0032) than in women with normal pregnancy outcome. Furthermore, a significant lower Ang-1 serum mean value in pregnant BOH women as compared to those with healthy pregnancies and in non pregnant BOH as compared to non pregnant with normal pregnancy history.

Our data are consistent with the previous studies reporting that Ang-1 sustains the placental vascular ingrowth and the high level of Ang-1 may confer protection to the placenta [45] findings suggest that the Ang-1/ Ang-2 ratio in the first trimester is associated with most adverse pregnancy outcomes, but it was not predict outcomes any better than clinical and maternal risk factor information. Maternal concentrations of Ang-1have earlier been shown to be increased in preeclamptic women [46], but El- Gohary et al [47] failed to observe any association between the Ang-1 concentrations and later preeclampsia.

Plaisier et al [48] suggest that the pathogenesis of miscarriages is associated with premature maturation of the vasculature [49]. Dunk et al [50] have show that in contrast to normal pregnancies, the growth of placental villous and capillaries in complicated pregnancies is variable and the process of angiogenic interaction between trophoblast and the uteroplacental circulation is incomplete. Low Ang-1 was previously reported to lead to vessel destabilization and decrease in the angiogenic sprouting promoting vessel leakage [51].

The present study findings and those reported in literature suggest that Ang-1 appear to be an angiogenic predictive marker for women with bad obstetric history. A future study that included Ang-1, Ang-2 combination with others different biomarkers to determine their predictive value as a marker of BOH is warranted.

References

1. Alsamarai AGM, Aljumaily ZK. Seroepidemiology of Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex Virus -2 in Women with Bad Obstetric History. Part.I: Toxoplasma and Rubella Infections. Our Dermatol Online 2013;4(4):522-535.
2. Alsamarai AGM, Aljumaily ZK. Seroepidemiology of Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex Virus -2 in Women with Bad Obstetric History. Part.II: Cytomegalovirus and Herpes Simplex Virus Infections. Our Dermatol Online 2013;4(4):536-544.]
3. Hala Mohamed MH, Abdulghani MA, Ferah GA, Amina ha, zainab Khalil MA. Rubella seroprevalence in women with bad obstetric history. JOJ Immuno Virology 2016;1(2):555-560.
4. Aljumaili ZKM, Alsamarai AGM, Najem WS. Cytomegalovirus seroprevalence in women with bad obstetric history in Kirkuk, Iraq. J Infection Public Health 2014;7(4):277-88.
5. Aljumaili ZKM, Alsamarai AGM, Najem WS. Rubella seroprevalence in women with bad obstetric history. Research Review Bioscience 2014;8 (6):203-213.
6. Hassan HMM, Alsamarai AGM, Aljumaili ZKM, Alsalihi FG. Association between Herpes Simplex virus type 2 (HSV-2) and bad obstetric outcomes. Our DermatolOn line 2014;5(1):19-28.
7. Aljumaily ZK, Alsamarai AGM, Najem WS. Seroprevalence of herpes simplex type 2 (HSV-2) in women with bad obstetric history. Am J Derm Vener 2013;2:31-8.
8. Hassan HM, Alsamarai AGM, Aljumaili ZK, Alobaidi AH, Alsalihi FG. Association between cytomegalovirus infection and bad obstetric history in women from Kirkuk. Int J Public Health Sci 2014;3(1):29-42.
9. Aljumaily ZK, Alsamarai AGM, Najem WS. Seroepidemiology of toxoplasma, rubella, cytomegalovirus, and herpes simplex in women with bad obstetric history. Middle East J Intern Med 2013;6(6):21-33.

10. Alsamarai AGM, Hassan HMM, Alsalihi FG, Alobaidi AH, Aljumaily ZK. Toxoplasma gondii, Rubella and Cytomegalovirus co-iunfections as a risk factors for abnormal pregnancy outcomes. Middle East J Fam Med 2014;12(3):16-23.

11. Aljumaily ZKM, Alsamarai AGM. Risk factors for bad obstetric history in Kirkuk women, Iraq. Int J Infect Microbiol 2013;2(3):70-77.

12. Aljumaili ZKM, Alsamarai AGM, Najem WS. Toxoplasma gondii seroprevalence in women with bad obstetric history. MEJIM 2014;7(1):32.

13. Abdulghani MA, Hala MM, Amina HA. Autoantibodies in Women with Bad Obstetric History. J Imm Cell Microbiology. 2016;1:9-18.

14. Wegmann, T.G. Lin ,H. Guilbert, L. Mosmann, T.R. "Bidirectionalcytokine interactions in the maternal-fetal relationship": is successfulpregnancy a TH2 phenomenon? Immunology Today.1993;14(7):353–356.

15. Hill, J.A. Polgar, K. Andersomn, D.J. "T-helper 1-type immunityto trophoblast in women with recurrent spontaneousabortion". Journal of the American Medical Association.1995;273(24):1933–1936.

16. Unfried, G. Bocskor, S. Endler, G. Nagele, F. Huber, J.C. Tempfer,C.B. "A polymorphism of the interleukin-6 gene promoterand idiopathic recurrent miscarriage. Human Reproduction".2003;18(2):267–270.

17. Fukuda, H. Masuzaki, H. Ishimaru, T. "Interleukin-6 andinterleukin-1 receptor antagonist in amniotic fluid and cordblood in patients with pre-term", premature rupture of the membranes. International Journal of Gynaecology and Obstetrics.2002;77(2):123–129.

18. Hill, J.A. "Cytokines considered critical in pregnancy". AmericanJournal of Reproductive Immunology. 1992;28(3-4):123–126.

19. Paradisi, R. Maldini-Casadei, M. Boni, P. Busacchi, P, Porcu, E.Venturoli, S. "T-helper 2-cytokine levels in women with threatenedabortion". European Journal of Obstetrics Gynecology and Reproductive Biology. 2003;111(1):43–49

20. Von Linsingen, R. Bompeixe, E.P. BicalhoMda, G. "A case-controlstudy in IL6 and TGFB1 gene polymorphisms and recurrentspontaneous abortion in southern Brazilian patients". AmericanJournal of Reproductive Immunology. 2005;53(2):94–99.

21. Prigoshin, N. Tambutti ,M. Larriba, J. Gogorza, S. Testa ,R. "Cytokinegene polymorphisms in recurrent pregnancy loss of unknowncause". American Journal of Reproductive Immunology.2004;52(1):36–41.

22. Saijo, Y. Sata, F. Yamada, H. Kondo, T. Kato, E.H. Kishi, R. "Singlenucleotide polymorphisms in the promoter region of theinterleukin-6 gene and the risk of recurrent pregnancy loss in Japanese women". Fertility and Sterility. 2004;81(2):374–378

23. Vitoratos,N. Papadias,C. George, C. "Elevated Circulating IL-10 and TNF-Alpha, and Unaltered IL-6 in First-Trimester Pregnancies Complicated by Threatened Abortion With an Adverse Outcome Mediators Inflamm". 2007; (5): 304-85.

24. Lim, K.J. Odukoya, O.A. Ajjan, R.A. Li, T.C. Weetman, A.P. Cooke, I.D. "The role of T-helper cytokines in human reproduction. Fertil. Steril.2000; 73, 136–142.

25. Raghupathy, R. Makhseed, M. Azizieh, F. Hassan, N. Al-Azemi, M. Al- Shamali, E. "Maternal Th1- and Th2-type reactivity to placental antigens in normal human pregnancy and unexplained recurrent spontaneous abortions". Cell Immunol.1999; 196, 122–130.

26. Calleja-Agius,J. Muttukrishna, S.Arnol,d R. ,Eric Jauniaux,P."Pro- and antiinflammatory cytokines in threatened miscarriage"s. American Journal Obstetrics and Gynecology2011;205(1):83-8.
27. Mahdi,N.K.Abdullah,G.A. "The Roll cytokines among women with spontantaneus miscarriage". Medical Journal of Islamic World Academy of Sciences 21:3, 119-124, 2013
28. Zenclussen, A.C. Kortebani,G. Mazzolli, A., Margni, R.Malan Borel, I.," Interleukin-6 and soluble interleukin-6 receptor serum levels in recurrent spontaneous abortion women immunized with paternal white cells". Am. J. Reprod. Immunol.2000; 44: 22–29.
29. Arruvito, L. Billordo, A. Capucchio, M. Prada, M.E. Fainboim, L." IL- 6 trans-signaling and the frequency of CD4+FOXP3+ cells in women with reproductive failure." J. Reprod. Immunol2009;. 82: 158–165.
30. Makhseed, M. Raghupathy, R.Azizieh, F. Farhat, R. Hassan, N. Bandar, A. "Circulating cytokines and CD30 in normal human pregnancy and recurrent spontaneous abortions. Hum". Reprod.2000; 15: 2011–2017.
31. Orsi, N.M. Tribe, R.M. "Cytokine networks and the regulation of uterine function in pregnancy and parturition". J Neuroendocrinol. 2008; 20: 462–469
32. Crouch, S.P. Crocker, I.O. Fletcher, J. "The effect of pregnancy on polymorphonuclear leukocyte function". J Immunology 1995;155(11):5436-43.
33. Snyder, S.K. Wessner, D.H. Wessells, J.L. "Pregnancy-specific glycoproteins function as immunomodulators by inducing secretion of IL-10, IL-6 and TGF-beta1 by human monocytes. Am J Reprod Immunol". 2001; 45: 205–216
34. Lee. S, Kim, J, Jang, B, Hur, S, Jung, U. Kil, K. et al. "An imbalance in interleukin-17-producing T and Foxp31 regulatoryT cells in women with idiopathicrecurrent pregnancy loss. Human Reproduction", 2011;26 (11): 2964–2971.
35. Wang, W.J. Hao, C.F. Yi, L. Yin, G.J. Bao, S.H. Qiu, L.H.etal." Increasedprevalence of T helper 17 (Th17) cells in peripheral blood anddecidua in unexplained recurrent spontaneous abortion patients".J Reprod Immunol 2010;84:164–170.
36. Winger, E.E. Reed, J. L. "Low circulating CD4(+) CD25(+) Foxp3(+) Tregulatory cell levels predict miscarriage risk in newly pregnantwomen with a history of failure". Am J Reprod Immunol 2011.
37. MasakoSaito, M. Nagasawa,M. Takada,H . Hara, T. Tsuchiya, S. Agematsu,K. "Defective IL-10 signaling in hyper-IgE syndrome results in impaired generation of tolerogenic dendritic cells and induced regulatory T cells". Published February 2011; 208(20): 235-249
38. Liu, Y.S. Wu, L. Tongm, X.H. Wu, L.M. He, G.P. Zhou, G.X. etal."Study on the relationship between Th17 cells and unexplainedrecurrent spontaneous abortion. Am J Reprod Immunol 2011;65:503–511.
39. Nakashima, A. Ito, M. Shima, T. Bac, N.D. Hidaka, T. Saito, S. "Accumulation ofIL-17-positive cells in decidua of inevitable abortion cases". Am J Reprod Immunol 2010;64:4–11.
40. Kwak-Kim, J.Y. Chung-Bang, H.S. Ng, S.C. Ntrivalas, E.I. Mangubat, C.P.Beaman, K.D. "Increased T helper 1 cytokineresponses by circulating T cells are present in women with recurrentpregnancy losses and in infertile women with multiple implantationfailures after IVF". Hum Reprod 2003;18:767–773.
41. Arruvito, L. Sotelo, A.I. Billordo, A. Fainboim, L. ""A physiological role forinducible FOXP3(+) Treg cells. Lessons from women withreproductive failure". Clin Immunol 2010;136:432–441.

42. Arruvito, L. Sanz, M, Banham, A.H. Fainboim, L. "Expansion ofCD4+CD25+and FOXP3+ regulatory T cells during the follicularphase of the menstrual cycle": mplications for human reproduction.J Immunol 2007;178:2572–2578.

43. Snyder, S.K. Wessner, D.H. Wessells, J.L. "Pregnancy-specific glycoproteins function as immunomodulators by inducing secretion of IL-10, IL-6 and TGF-beta1 by human monocytes. Am J Reprod Immunol". 2001; 45: 205–216

44. Daponte,A . Deligeoroglou,E.Spyros, P. Christos, H. 4 Antonios, G. Foteini, A.,1 and Ioannis E. Interleukin-15 (IL-15) and Anti-C1q Antibodies as SerumBiomarkers for Ectopic Pregnancy and Missed Abortion. Hindawi Publishing CorporationClinical and Developmental Immunology 2013; 6 (10). 637-513.

45. Lee, H.H. "Association study of vascular endothelial growth factor polymorphisms with the risk of recurrent spontaneous abortion". Fertil Steril 2010;93:1244-1247.

46. Salah, A. Hosam, G. Ebrahim, A. "Circulating Vascular Growth Factor (VEGF) Angiopoietin-1 (Angi-1) and Soluble Tie-2 Receptor in Pregnancy Complicated with Pre-eclampsia" A Prospective Study. Journal Obstetrics Gynecology of India 2013; 63:316-320.

47. El-Gohary,A . Fadia,M. A. Abeer, R. E. Nader,A. N. Fawzy, A. K, "Vascular endothelial growth factor mRNA expression can be a marker for response to antiviral treatment of HCV. Comparative Clinical Pathology 2014;23:923-928.

48. Plaisier,I. Dennert,J. Rost,E. Koolwijk, P. Hinsbergh,V. Helmerhorst, F.M. "Decidual ascularization and the expression of angiogenic growth factors and proteases in first trimester spontaneous abortions". Oxford JournalsMedicineHuman Reproduction 2013;42(1) 185-97.

49. Shentong,F. Jing,W.Nalle,P.Hannele,L,Petri,l."Generation of Functional Blood Vessels from a Single c-kit+ Adult Vascular Endothelial Stem CellPublished": 2012; 10:1001-407.

50. Roviezzo, F. Tsigkos, S. Kotanidou, A. "Angiopoietin-2 causes inflammation in vivo by promoting vascular leakage". J Pharmacol Exp Ther. 2005;314(2):738–44.

51. Dunk, C. Shams, M. Nijjar, S. Rhaman, M. Qiu, Y. Bussolati, B. etal Am. J. Pathol.2000; 156; 2185 - 2199.

Citation: Abdulghani Mohamed Alsamarai, Hala Mohamed Majeed, Amina Hamed Alobaidi, *"Interleukin-6 [Il-6], Interleukin-17 [Il-17] and Angiopoietin in Women with Bad Obstetric History, Kirkuk, Iraq". American Research Journal of Hematology; 1(1): 9-19.*