Original Article

Role of Some Cytokines Among Infertile Women Undergoing Intracytoplasmic Sperm Injection

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Abstract

Background: Infertility is the incapacity to fulfill pregnancy after an appropriate time of sexual intercourse with no contraceptive measures taken. Ovulation disorders are one of the female factors that cause infertility, including polycystic ovarian syndrome (PCOS) and poor ovarian reserve (POR). **Objective:** The aim of this study was to estimate the association between some immunological markers interleukins (IL-5, IL-12, and IL-18) and infertility causes (male factor, PCOS, and POR) of infertile patients in Iraqi women undergoing Intracytoplasmic sperm injection (ICSI). **Materials and Methods:** This was a cross-sectional study that included three groups male factor (n = 40), PCOS (n = 30), and POR (n = 30). The samples of serum and follicular fluid were collected on oocyte retrieval day and detected levels of IL-5, IL-12, and IL-18 by ELISA technique. **Results:**The serum and follicular fluid levels of IL-12 in the male factor were significantly different from PCOS and POR patients (P = 0.005). Also, about the mean of transferred embryos in non-pregnant women; there was a significant difference between Beta-Human Chorionic Gonadotropins (β. HCG) groups with (P = 0.013). Furthermore, there was a significant difference in the level of IL-18 in the serum and follicular fluid between pregnant and non pregnant women regarding Beta- Human Chorionic Gonadotropins (β HCG) hormone. In addition, the follicular fluid and serum levels of IL- 18 were significantly difference between β. HCG groups with (P = 0.005). **Conclusion:** The results have shown a non-significant difference between groups regarding cytokines levels except elevated IL-12 levels in follicular fluid and serum for male factor patients compared with PCOS and POR patients. Therefore, these markers might have no important role in the intracytoplasmic sperm injection outcomes.

Keywords: ELISA, ICSI, IL-12, IL-18, IL-5, infertility

Introduction

Infertility is a disease characterized by the failure to establish a clinical pregnancy after more than 12 months of regular and unprotected sexual intercourse.[1] Generally, 20%–35% of infertility cases are due to female causes, 20%–30% of cases are due to male causes, 25%–40% of cases due to both male and female (combined) etiologies, and 10% unexplained infertility.[2] An ovulation and abnormalities in the semen quality are the most prevalent reasons for infertility. Polycystic ovary syndrome (PCOS) is the most prevalent etiology of ovulatory infertility in women, accounting for around 40% of female infertility.[3] It is the most common chronic reproductive and metabolic endocrine disorder affecting women of childbearing age, with prevalence estimated to be 4%–21% worldwide.[4] Regarding, poor ovarian reserve (POR), it is refers to the decline in fertility caused by the loss of normal ovarian function.[5] The age for the prediction of POR in women was less than 40 years old. Furthermore, anti-mullerian hormone (AMH) is the only independent factor that is, significantly related to POR in women.[6] Assisted reproductive technology (ART) is a group of medical procedures for treating the infertile human in which both male and female gametes are used outside the body (*in vitro*) to attain pregnancy.[7] Intra-Cytoplasmic Sperm Injection (ICSI) is a type of ART,

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and has become the most commonly used technique of *in vitro* fertilization.[8] Moreover, there is an important role of some follicular fluid cytokines in reproductive physiology. The development and maturation of the follicle, ovulation, and corpus luteum formation as well as embryo implantation and maintenance of pregnancy can be influenced by these cytokines.[9] The elevated intra follicular concentrations of IL-5 seem to be a negative predictor to the pregnancy outcome in ICSI cycles.[10] The interleukin-12 is a disulfide-linked heterodimeric cytokine, produced by B cells, phagocytic cells, and other antigen-presenting cells. Increased IL12 concentration may be correlated with fragmented embryos and found at a low concentration in PCOS.[11] In addition, both serum and follicular fluid of IL-18 concentration may be positively correlated with oocyte numbers collected from patients qualified for ICSI.[9] Consequently, this study aimed To evaluate the association between some Interleukins and infertility causes of some Iraqi infertile women undergoing Intracytoplasmic sperm injection (ICSI).

Materials and Methods

The cross-sectional study included 100 subjects divided into three groups: male factor (n = 40), PCOS (n = 30), and POR (n = 30) enrolled in the Center for Fertilization and IVF during the period from November 2022 to April 2023. The samples of blood were collected at cycle day 2 and detected the level of follicle-stimulating hormone, luteinizing hormone, prolactin hormone, estradiol hormone, anti-mullerian hormone, and estradiol hormone at HCG injection by MINI VIDS. The serum and follicular fluid were collected on oocyte retrieval day and detected levels of IL-5,IL-12, and IL-18 by ELISA technique. The exclusion criteria included female factor due to endometriosis, cycles ending with ovarian hyperstimulation syndrome, cancelled cycles, steroid treatment, autoimmune diseases(tumor disease, cardiovascular disease, hepatitis, and kidney diseases), and azoospermic patients or sperm source from the testicular biopsy. The inclusion criteria were as follows: age (20–40 years), women with (anovulatory disorders, PCOS, tubal factor, unexplained subfertility) and all cycles that end with ova pick up and sperm injections.

Statistical analysis

Statistical analyses were performed using the SPSS statistical package for Social Sciences (version 20.0 for Windows, SPSS, Chicago, Illinois).

Ethical approval

Ethical approval was obtained from the Karbala Medical College Ethical Committee. Also, verbal approval was taken from the patients before taking on the sample. During sample collection, health measures and safety were taken.

Results

Cytokine levels according to the result of infertile women

Median of follicular fluid IL-5 in the male factor cases was (337.18), while, in POCS and POR were (325.70) and (401.27), respectively. There were no significant differences between groups (P = 0.*629*). Whereas, the median IL-5 serum level of the male factor group was (123.54), in POCS (106.50) and in POR (130.16). There were no significant differences between groups (P = 0.*169*), as shown in [Table 1].

The median of IL-12 level in the follicular fluid of male factor cases was 21.45, while in POCS and POR were 9.13 and 9.66, respectively. However, Male causes were significantly different from PCOS and POR causes (P = 0.*005*). The median of IL-12 serum level of the male factor was 9.05, in POCS (5.69) and in POR (5.24). However, male causes were significantly different from PCOS and POR causes (P = 0.*005*).

On the other hand, the median of IL-18 level in the follicular fluid of male factor cases was (244.06), while, in POCS and POR were (435.96), (378.66) respectively. There were no significant differences between groups (P = 0.*117*). The median of IL-18 serum level of the male factor was (580.20), in POCS (440.56) and in POR (508.37). There were no significant differences between groups (P = 0.*342*).

Table 1 : Median differences of cytokines according to the result of infertility

Interleukins	Causes of infertility						*P* value
	Male factor (40)		PCOS (30)		POR (30)		
	Median	IQR	Median	IQR	Median	IQR	
IL5F	337.18	478.17	325.70	534.88	401.27	608.20	0.629
IL5S	123.54	177.89	106.50	149.92	130.16	197.70	0.169
IL12F	21.45	12.97	9.13	6.16	9.66	3.29	**0.005***
IL12S	9.05	2.93	5.69	2.56	5.24	3.32	**0.005***
IL18F	244.06	329.12	435.96	383.88	378.66	439.49	0.117
IL18S	580.20	157.18	440.56	405.76	508.37	368.08	0.342

F: Follicular fluid, S: Serum, IL: Interleukin, IQR:: interquartile range, Kruskal–Wallis test

Mean differences of demographic characteristics according to the result of β HCG (pregnancy result)

Regarding nonpregnant women, the mean of age, body max index, and duration of infertility were 30.67, 28.32, and 8.44, respectively, whereas in pregnant women the mean of age, body max index, and duration of infertility were 29.97, 27.82, and 9.61, respectively. There were no significant differences between β HCG result groups with (*P = 0.542, P = 0.753, and P = 0.264*) respectively, as clarified in [Table 2].

About the infertility types in non-pregnant women, the count of primary infertility was (52) and in secondary infertility was (15). In pregnant women, the count of primary infertility was (26) and in secondary infertility was (7). There was no significant relation to the β. HCG result (*P = 0.894*).

Concerning infertility causes in non-pregnant women, the count of male factor, PCO, and POR were 28, 18, and 21, respectively, whereas in pregnant women, the count of male factor, PCO, and POR were 12, 12, and 9, respectively. There was no significant relation to the β. HCG result (*P = 0.439*).

Hormonal study according to the result of β. HCG (pregnancy result)

In non-pregnant women, the means of FSH, LH, Prolactin, E2 day 2, AMH and E2 HCG were (5.84), (5.42), (22.92), (43.22), (2.74) and (1853.90) respectively. Whereas, in pregnant women the means of FSH, LH, Prolactin, E2 day 2, AMH and E2 HCG were (6.92), (5.32), (20.29), (48.42), (2.98) and (1909.16) respectively. There were no significant difference between B HCG result groups with (*P = 0.086, 0.924, 0.318,* 0.422, 0.560 *and 0.767*), respectively, as demonstrated in [Table 3].

Clinical characteristics according to the result of β. HCG (pregnancy result)

Current study found in non-pregnant women, the mean of ICSI attempt, follicles, maturity rate, fertilization rate, embryo GI, embryo GII, and Embryo GIII were (0.43), (10.87), (79.11),(79.66), (2.34),(2.79) and (1.60), respectively, while, in pregnant women the mean of the ICSI attempt, Follicles, Maturity rate, Fertilization rate, embryo GI, embryo GII, and Embryo GIII were (0.64), (12.09), (81.51),(84.46), (2.55),(3.24) and (1.94) respectively. There were no significant difference between

Table 2 : Demographic characteristics according to the result of β. HCG (pregnancy result)

Variables	β. HCG				*P* value
	Negative (non-pregnant)		Positive(pregnant)		
	Mean	SD	Mean	SD	
Age (year)	30.67	5.44	29.97	5.31	0.542
BMI (Kg/m2)	28.32	8.50	27.82	4.48	0.753
Duration (y)	8.44	4.88	9.61	4.89	0.264
	Count	%	Count	%	
Infertility Primary	52	66.7	26	33.3	0.894
Secondary	15	68.2	7	31.8	
Cause Male	28	71.8	12	28.2	0.439
PCOS	18	58.1	12	41.9	
POR	21	70.0	9	30.0	

BMI: Body Max Index, Student *t* test, chi-square test

Table 3 : Mean differences of hormonal study according to the result of β. HCG (pregnancy result)

Variables	β. HCG				*P* value
	Negative (non-pregnant)		Positive (pregnant)		
	Mean	SD	Mean	SD	
FSH (mIU/ml)	5.84	1.98	6.92	3.26	0.086
LH (mIU/ml)	5.42	5.58	5.32	3.77	0.924
Prolactin (ng/ml)	22.92	12.60	20.29	11.70	0.318
E2 day 2 (pg/ml)	43.22	18.55	48.42	34.39	0.422
AMH (ng/ml)	2.74	1.99	2.98	1.74	0.560
E2 HCG (pg/ml)	1853.90	921.64	1909.16	771.66	0.767

Student *t* test, FSH: follicle stimulating hormone, LH: Luteinising Hormone, E2at day 2:Estradiol hormone at cycle day two, AMH: Anti Mullerian Hormon, E2 HCG: Estradiol Hormone at Human Chorionic Gonadotropin injection

Table 4 : Mean of clinical characteristics according to the result of β. HCG (pregnancy result)

Variables	β. HCG				*P* Value
	Negative (non-pregnant)		Positive (pregnant)		
	Mean	SD	Mean	SD	
ICSI attempt	0.43	0.70	0.64	0.82	0.201
Follicles	10.87	5.82	12.09	6.07	0.332
Maturity rate	79.11	17.33	81.51	16.51	0.509
Fertilization rate	79.66	18.15	84.46	14.60	0.189
Embryo GI	2.34	1.97	2.55	1.75	0.619
Embryo GII	2.79	1.81	3.24	1.92	0.252
Embryo GIII	1.60	1.52	1.94	1.75	0.316
Transferred embryo	3.25	0.91	3.73	0.80	**0.013***

ICSI Intracytoplasmic sperm injection:, GI: Grade l, **β.** HCG: Beta-Human Chorionic Gonadotropins, ANOVA test (LSD test), chi-square test

Table 5 : Median differences of cytokines according to the result of B HCG (pregnancy result)

Interleukins	B HCG				*P* Value
	Negative (nonpregnant)		Positive (pregnant)		
	Median	IQR	Median	IQR	
IL- 5 F (pg/ml)	517.17	619.46	212.14	164.69	**0.005***
IL -5 S (pg/ml)	151.78	213.04	67.71	93.11	**0.005***
IL- 12 F (pg/ml)	11.79	9.72	10.70	10.09	0.953
IL -12 S (pg/ml)	7.05	4.00	6.40	4.38	0.674
IL- 18 F (pg/ml)	279.77	229.59	743.24	335.59	**0.005***
IL- 18 S (pg/ml)	458.16	260.00	795.53	242.61	**0.005***

Kruskal–Wallis test

groups with (P = 0.201, 0.332, 0.509, 0.189, 0.619, 0.252 and 0.316), respectively, while the mean of transferred embryo in non-pregnant women was (3.25) and in pregnant women was (3.73). There was a significant difference between *β*. HCG groups regarding transferred embryo (*P* = 0*.013*), as clarified in [Table 4].

Cytokines according to the result of *β*. HCG (pregnancy result)

Regarding the median of IL-5 in follicular fluid, in non-pregnant women was (517.17) and in pregnant women was (212.14),while the median of serum IL-5, in non-pregnant women was (151.78) and in pregnant women was (67.71). However, there was a significant difference between B HCG groups regarding follicular and serum level of IL-5 with (*P* = 0*.005*)

About the median of IL-12 in follicular fluid, in non-pregnant women was (11.79) and in pregnant women (10.70). However, there was no significant difference between B HCG groups (*P* = 0*.953*), while the median of serum IL-12, in non-pregnant women was (7.05) and in pregnant women was (6.40).There was no significant difference between B HCG groups (*P* = 0*.674*).

Concerning the median of IL-18 in follicular fluid, in non-pregnant women was (279.77) and in pregnant women was (743.24),while The median of serum IL-18, in non-pregnant women was (458.16) and in pregnant women was (795.53). However, there was a significant difference between B HCG groups regarding follicular and serum level of IL-18 with (*P* = 0*.005*), as in [Table 5].

Discussion

Regarding the median of follicular fluid and serum IL-5 levels, there were no significant difference between groups as in [Table 1]. IL5 is found in serum and follicular fluid of women undergoing ICSI. It has effect on folliculogensis, maturity of Oocytes, quality of embryos and pregnancy rate. This study agreed with the study by Terenina *et al*,[12] who suggested that IL-5 acts as one of the upstream key regulators of porcine ovarian follicular atresia. And the study by Niu *et al*[13] who demonstrated a non-significant correlation between FF IL-5 of patients with or without PCO syndrome undergoing *in vitro* fertilization (IVF). Also the study by Alhilali *et al*,[10]who observed that the increased level of follicular fluid IL-5 was associated with quality of poor oocyte.In addition, Bouet *et al*[14] reported that IL-5 in FF was no significant result in POR patients.

About the median of follicular fluid and serum IL-12 levels. The male factor was significantly different from

PCOS and POR causes with ($P = 0.005$). IL- 12 has a role in follicular fluid and correlation of their concentration with follicular and embryo development during fertility procedures. A study conducted by Lédée *et al*,[15] who reported the significant elevation of IL-12 in highly fragmented embryos on Day 2, suggests that it has a deleterious role.While the study by Sarapik *et al*,[16] who noted that positive association between the follicular level of IL-12 and the number of fertilized oocytes and good-quality embryos proportion. And study by Piccinni *et al*,[11] who found that IL- 12 has a role in increased follicle diameter during Puncture. Also the study by Adamczak *et al*[9] who noted about the IL-18 as well as IL-12 role are thought to be of particular importance in the embryo implantation.

On the other hand, about the median of IL-18 level in the follicular fluid and serum. There were no significant difference between groups. IL-18 is important in implantation and successful IVF. Endometrial cytotoxicity by recruiting the uterus natural killer (uNK) cells, which associated with over expression of IL-18, but some mediators can control this process and allowing for proper angiogenesis and embryo implantation.

Some studies consistent with present study such as the study by Sarapik *et al*,[16] who demonstrated the median of IL- 18 in FF of Male factor infertility was (311.0), in PCO was (463.4) with no significant association between groups. While another studies disagree with current study such as the study by Chen *et al*,[17] who found that IL-18 levels were significantly higher in serum than in follicular fluid. And IL-18 levels in follicular fluid also increased with a rising BMI, the correlation between IL-18 levels in serum and the ovarian stimulation response was not statistically significant ($P = 0.116$), whereas the correlation between IL-18 levels in follicular fluid and the ovarian stimulation response was significant ($P = 0.003$).Also, study by Al-Musawy *et al*,[18] who reported that level of IL18 was highly statistically significant in PCOS women comparing to normal women, and these high levels were related to PCOS independent on the presence of obesity or hyperandrogenism, and there is a positive correlation between IL18 and negative correlation between these markers and obesity and hyperandrogenism. In addition, the study by Ibrahim and Al-Saffar[19] Whose demonstrated IL-18 in serum of PCO patients and control were highly significant. And there is a significant difference of IL-18 level between PCOS patients and BMI according to the normal weight, overweight and obese PCOS women.The differences of these results may be due to the ethnicity in different populations.

Regarding the demographic characteristics in [Table 2], there were no significant difference between B HCG result groups. Concerning the age, this study different with many studies such as the study by Ahmed *et al*[20] who found the mean of age of non-pregnant women was (33.5) while, the mean of age of pregnant women was (29.8) with highly significant result ($P = 0.001$).Also studies by Zahir *et al*[21] and Chen *et al*,[22] whose mentioned that age of the female was the main predictor of pregnancy but its significant effect in decreasing pregnancy rate appear if age was increased more than 35. While this study agreed with the study by[23] whose demonstrated the age mean of non-pregnant women was (31.80) while the age mean of pregnant women was (30.86) with no significant result ($P = 0.61$).

About BMI, current study consistent with the study by Ahmed *et al*,[20] who found that the BMI of non-pregnant women was (28.8) and pregnant women was (28.6) with non-significant result ($P = 0.825$). The study by Swadi, Edan and Al-Dulaimi,[23] revealed to the BMI of non-pregnant women was (28.23) and pregnant women was (26.50) with no significant result ($P = 0.24$).While, the mean of infertility duration in this study compatible with study accomplished by,[23] whose reported that the mean of infertility duration of non-pregnant women was (8.30) while pregnant women was (9.06) with no significant differences ($P = 0.63$).

About the primary and secondary types of infertility, there were no significant relationship to the β. HCG results ($P = 0.894$).There is no significant influence of infertility type on pregnancy rate and that consistent with other studies of Metello *et al*[24] and Swadi, Edan and Al-Dulaimi,[23] whose reported the primary and secondary types of infertility in pregnant women were (9) and (6) respectively, whereas, in non-pregnant women were (28) and (7) respectively with no significant result ($P = 0.13$).

There were a non-significant association to the β.HCG results ($P = 0.439$) concerning the infertility causes,. This results consistent with the study by Swadi, Edan and Al-Dulaimi,[23] whose reported there is no significant influence of infertility causes on pregnancy rate, this can be attributed to the role of ICSI in overcoming almost all causes of subfertility.

There were non-significant differences between β HCG result groups regarding the hormonal study according to the result of β. HCG (pregnancy result). This finding consistent with many studies such as the study by Bjercke *et al*. Bedaiwy *et al*. Al-Ghazali and Al-Jarrah, Ashrafi *et al*. Cicek *et al*. and Ali, Al-Murshidi and Al-Jarrah,[25-30] whose mentioned the same results of current study.

About the clinical characteristics according to the result of β. HCG (pregnancy result), there were no significant difference between groups, while concerning the transferred embryo in pregnant and non-pregnant women, there were a significant difference with ($P = 0.013$) between β. HCG groups. The present study agreed with the study conducted by Al-Ghazali and Al-Jarrah,[27] whose revealed to the mean of embryos was higher in pregnant women with significant result. Also, the study

by Ali, Al-Murshidi and Al-Jarrah[30] whose demonstrated that ICSI outcome is similar in pregnant compared with non-pregnant patients. In addition, the follicles, maturity rate, embryo GI, embryo GII, and embryo GIII were no significant results while transferred embryos was significant, but this study inconsistent with current study regarding fertilization rate. The chance of pregnancy increases along with number of embryo transferred.

Regarding the median of IL-5 in follicular fluid and serum levels in pregnant and non-pregnant women, there were a significant difference between *β*. HCG groups with (*P* = 0.*005*).This study disagreed with the study accomplished by Niu *et al.*,[13] who found a significant correlation between FF IL-5 from the largest follicle with top-quality embryo and the potential development of embryo and ICSI outcome in a cohort of patients with or without PCO syndrome undergoing IVF. Also, this result compatible with study by Alhilali *et al.*,[10] who reported that elevated IL-5 level in follicular fluid was related with poor quality of oocyte and confirmed that IL-5 could be a negative predictor to the outcome of pregnancy in ICSI cycles.

Moreover, this study disagree with many studies such as the study by Bedaiwy *et al.*[26] regarding the median of IL-12 in follicular fluid and serum levels., who revealed to the concentrations of IL-12 in FF were significantly lower in pregnant compared with non-pregnant women with (*P* = 0.*0002*). Higher concentrations of IL-12 is associated with a negative outcome in IVF treatment. Interleukins-12 is one of biological markers that appear to affect IVF outcome.Also, the study by Lédée *et al.*,[15] who reported the significant elevation of IL-12 in highly fragmented embryos on Day 2, suggests that it has a deleterious role. In addition, the elevated IL-12 levels in pooled FF is associated with a poor pregnancy rate. While the study that conducted by Sarapik *et al.*,[16] who reported that successful fertilization of the ovum and development of an embryo correlated with the higher concentration of IL-12.

Furthermore, There was a significant difference between *β*. HCG groups with (*P* = 0.*005*) concerning the interleukin-18 in follicular fluid and serum of pregnant and non-pregnant women. This study consistent with the study by Günther *et al*,[31] who found that IL-18 have a significant result with (*P* = 0.*0001*),the presence of this cytokine in the follicular fluid indicates ovarian secretion and this interleukin seems to be a prognostic marker of success in treatment of reproductive process.[32,33]

Conclusion

The level of IL-12 in serum and Follicular fluid were statistically significant in male factor cases comparing to PCOS and POR women. Further studies needed to confirm the association between these cytokines and women infertility.

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Conflicts of interest

There are no conflicts of interest.

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