Association between Interleukin-17A and IL-17F Gene Polymorphisms and the Development of Infertility in Kurdish Women

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***Abstract*— Background: Infertility is a medical disorder characterized by inability of a couple to conceive following a year of unprotected sexual activity.**

This study was aimed to demonstrate the serum interleukin-17 (IL-17A), IL-17F and demonstrate the role of IL-17A rs2275913 and IL-17F rs763780 single nucleotide polymorphism (SNPs) gene in the infertile Kurdish women.

Methods: Using the enzyme-linked immunosorbent assay (ELISA), the serum IL-17A and IL-17F levels in 50 fertile participants and 134 women with infertility diagnoses were determined in this case-control research. The genotyping of the IL-17A and IL-17F SNPs genes was found using the tetra-amplification refractory mutation system-PCR (T-ARMS-PCR) technique.

Results: Infertile women had a statistically significant lower serum concentration of IL-17A compared to fertile participants. Conversely, the serum level of IL-17F was non-significantly higher in infertile women compared to fertile women. In IL-17A, women with the AA genotype, recessive model (AA+GA) vs. GG, and A allele exhibited a higher risk for infertility. In the case of IL-17F, the TC and CC genotypes, and C allele, show a greater risk for infertility.

Conclusions: The present study confirmed that IL-17A and IL-17F gene polymorphisms were associated with an increased risk of women's infertility.

***Index Terms*— IL-17A, IL-17F, SNP, Women Infertility**

Key Messages: Significant association found between Interleukin-17A gene polymorphisms and infertility development in Kurdish women.

I. Introduction

Infertility has been defined as the failure to conceive successfully after one year of unprotected intercourse (Koraei et al., 2018). Anovulation, tubal illnesses, pelvic adhesions or endometriosis, cervical factors, and idiopathic causes, or unexplained, are the main conditions that contribute to infertility (Siristatidis and Bhattacharya, 2007).

Cytokine production is essential to mount a type of immune response for pregnancy maintenance and can regulate the inflammatory response. Chronic inflammation arises when pro-inflammatory cytokines are predominant (Zhang et al., 2017). Since cytokines can impact many facets of reproductive physiology and fertility management, their impact on human reproduction is garnering increased interest (Qian et al., 2011).

The interleukin-17 family of cytokines is consists of several close structurally related cytokines (McGeachy et al., 2019). Interleukin-17A and IL-17F are highly pro-inflammatory and have similar structures, functions, properties, and signals through the same receptors (IL-17RA and IL-17RC) (Najafi et al., 2014). Both are produced by cellular sources upon activation, with IL-17A being more effective compare to IL-17F (Dubin and Kolls, 2009).

The genesis and clinical course of human diseases have been linked in some cases to polymorphisms in IL-17A (rs2275913) and IL-17F (rs763780) (Liu et al., 2010). According to Nansook et al. (2018), the rs2275913 A allele displayed more transcriptional activity of IL-17A and a higher affinity for the transcription factor NFAT than the G allele.

The purpose of this study was to investigate the serum level and gene polymorphisms of IL-17A and IL-17F with susceptibility to infertility in the Erbil province.

II. Materials and Methods

A. Study participants

A case-control study was conducted on volunteers who attended Dr. Xawer Center for Infertility and Ashti Hospital in Erbil City from September 2021 to September 2022. The study comprised two groups: The control group included 50 fertile women; the exclusion criteria lacked a history of fertility problems and current antibiotic therapy, and their ages ranged between 21-43 years. Infertile group: 134 cases. The criteria for inclusion in the exhausted group were the lack of ability to become pregnant despite attempting for at least a year, confirmation of fertility from men, and the absence of antibiotic treatment within 30 days before this evaluation, and their ages ranged between 20-43 years. By thoroughly educating participants about the study's aims and placing a high priority on ethics, ethical issues were resolved. Consent was willingly signed by participants

B. Blood collection

Five ml of venous blood was obtained and divided into two aliquots. The first aliquot was centrifuged to measure IL-17A and IL-17F serum levels, while the second aliquot was frozen

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for genomic research.

C. Estimation of Serum IL-17A and IL-17A Levels

The ELISA kit (Sunlong Biotech Co., China) was used to measured serum IL-17A and IL-17A levels after the frozen serum had thawed at room temperature. Both ELISA kit analyses were performed according to established protocols from the manufacturer.

D. IL -17 Gene Polymorphisms

Tetra ARMS-PCR determined the IL-17A -197 G/A and IL-17F +7488 T/C genotypes. Using the Genomic DNA Extraction kit (Beta Bayern, Germany), genomic DNA was extracted from blood. Quantified using nano-drop (Biotek), and run in 1% gel agarose electrophoresis. Specific primers are shown in Table 1 (Macrogen, South Korean). The PCR reaction was conducted using 2X Prime Taq Premix (Genet Bio, Korea), with a 25 µl reaction mixture containing 1 µl of genomic DNA, 1 µl of each primer, 12.5 µl of 2X Taq master Mix with standard buffer, and 7.5 µl of Nuclease-free water. Negative control, including water rather than DNA, was introduced to each pair of assays to check for contamination. The PCR profile included 35 cycles after a 5-min initial melting phase at 95 °C. Denaturation stage for IL-17A (-197G/A) is set for 30 s at 95 °C, followed by 20 s of annealing at 54 °C and 20 s of elongation at 72 °C. For IL-17F (+7488T/C), the steps are as follows: 30 s of denaturation at 95 °C, 30 s of annealing at 60 °C, 30 s of extension at 72 °C, and final extension at 72 °C for 10 min. Following 2% agarose gel electrophoresis, the amplicon length revealed the genotype of each SNP and stained with 0.01 µg/ µl safe DNA gel stain Figure 1, 2.

TABLE I
MACROGEN (KOREA) SYNTHESIZED AND RECEIVED THE PRIMER SEQUENCE

IL-17A Gene	
IL-17A -197 G/A (Kaviani *et al.*, 2018)	**IL-17F +7488 T/C (Mohsen *et al.*, 2020)**
Primer sequence (5-3)	
Forward outer	
AATGGAAAATCAAGGTACATGACACC (404bp)	AGACAGGACTTGTTGCAGAGCACTG (215bp)
Reverse outer	
GATGGATGAGTTTGTGCCTGCT (404bp)	ATGAATTCCGTTCCCATCCAGC (215bp)
G Allele	Forward inner C Allele
TTCCCATTTTCCTTCAGACGG (193bp)	GAGTGGATATGCACCTCTTACTGCAAAC (158bp)
A Allele	Reverse inner T Allele
CCCCAATGAGGTCATAGAAGAATCTATT (260bp)	CGTCACCCCTGTCATCCAACA (106bp)

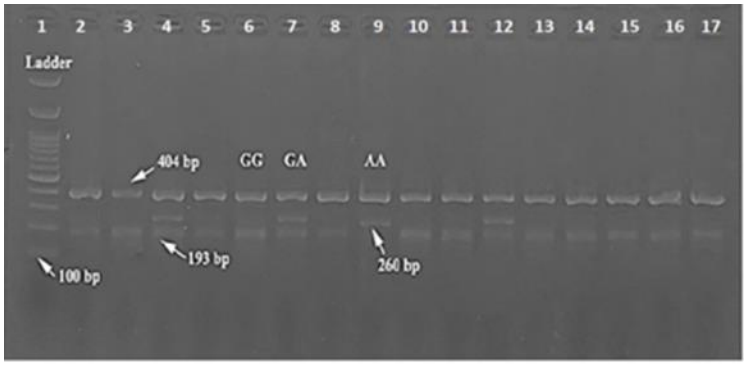

Figure 1: SNP rs2275913 polymorphism amplification bands for the various genotypes: The first lane is a 100 bp DNA ladder; lanes 2, 3, 5, 6, 8, 10, 11, 13–17 show the GG genotype; lanes 4, 7, and 12 show the GA genotype; and lane 9 shows the AA genotype.

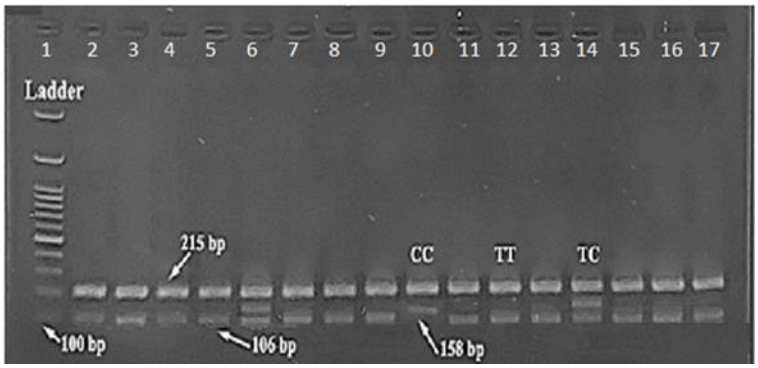

Figure 2: SNP rs763780 polymorphism amplification bands for the various genotypes: The first lane is a 100 bp DNA ladder; lanes 2- 5, 7- 9, 1-13, 15-17 show TT genotype; lanes 6, 14 show TC genotype; lane 10 show CC genotype

E. Statistical analysis

Version 9.0 of Graph-Pad Prism was utilised for all statistical analyses. The odds ratio (OR), relative risk, and 95% confidence intervals (CI) were estimated to determine the relationship between genotypes and infertility. Statistics were judged to be significant for P-values under 0.05.

III. RESULTS

A. Infertility Participants: Sociodemographic Characteristics

The study sample consisted of 184 individuals, categorized into two distinct groups: fertile females (n = 50, 27.17%) and infertile females (n = 134, 72.82%). The data concerning sociodemographic outcomes are shown in Table 2.

The average age of fertile females was found to be 29.86 ± 6.94. In contrast, infertile females with primary and secondary infertility had middle ages of 32.63±7.422 and 31.77±6.440, respectively. The age range for all groups varied from 20 to 43 years. The observed variations in age between the fertile group and infertile groups can be attributed to differences in the sample sizes of these groups. Age is one of the reasons for infertility, as shown by Zhu et al. (2022); ages 35 to 39 were linked to a greater risk of infertility, and before they are 35 years old, women should become pregnant.

Of the 134 infertile participants, 48 (35.8%) had primary infertility, and 86 (64.1%) revealed secondary infertility. This result aligns with Dhawan et al. (2014), in which primary and

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secondary infertility were 45.5% and 54.5%, respectively. While disagreeing with the study done in Erbil City, 63% had primary and 37% had secondary infertility (Ahmed and Othman, 2016). The survey conducted in Baqubah City, Iraq, found that the primary type of infertility in women was about 69.60%, and the secondary type was about 30.40% (Salman et al., 2022). The differences between types of infertility may be due to several contributing factors, such as age, which is a crucial aspect, as women experience a decline in both the quality and quantity of their eggs as they grow older, making conception more difficult. Additionally, women who have previously given birth may develop medical conditions that impact their fertility, such as Endo, PCOS, and pelvic inflammatory disease. Lastly, lifestyle factors like fluctuations in weight, poor diet, and inadequate nutrition can also influence fertility.

B. Evaluation of serum IL-17A and their correlation with Female infertility

In this investigation, the serum levels of IL-17A are shown in Figure 3. The fertile and infertile group exhibited a serum IL-17A level of 259.4±254.4 pg/ml and 175.2±46.33 pg/ml, respectively. The results indicated that infertile females had a lower concentration of IL-17A compared to their fertile counterparts. The infertile group demonstrates statistically significant differences when compared to the fertile group.

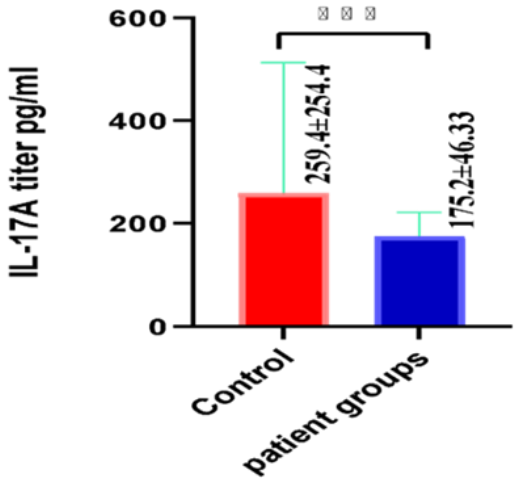

Figure 3: Level of serum IL-17A among volunteer participants

Initiating and sustaining chronic inflammation are crucial functions of the pro-inflammatory cytokine interleukin-17A (Zhang et al., 2017), autoimmunity, and host defense (Ciraci et al., 2023); (Crosby et al., 2020). The results disagree with (Wang et al., 2019); they revealed that women with repeated implantation failure and chronic endometritis have increased IL-17 expression, which is often related to poor reproductive outcomes, such as recurrent pregnancy losses. Ciraci et al. (2023) showed that reduced expressions of IL-17A in the endometrium of unexplained infertility individuals might be one of the potential cellular and molecular alteration mechanisms of infertility. Zhao et al. (2020) demonstrated that the observed variations in cytokine levels during miscarriage or reproductive failure could potentially be attributed to the reproductive failure itself, rather than being the primary cause of it and successful pregnancy outcome is associated with increased levels of Th-2 and decreased level of Th-1 cytokines, particularly in mice.

C. Associations of IL-17A (-197G/A) genotypes and Allele Frequency with women's infertility

The distribution of IL-17A (G/A) variants in both infertile and fertile females is summarized in Table 2. The frequency of GG, GA, and AA genotypes among infertile females was 94 (70.14%), 36 (26.86%), and 4 (2.98%); and among fertile females, it was 39 (78%), 11 (22%), and 0 (0%), respectively. Analysis of the IL-17A genotypes GG and GA revealed differences in their frequencies between all infertile and fertile groups, although these differences did not achieve statistical significance. Conversely, the frequencies of the major allele G compared to the minor allele A in infertile women were 83.58% and 16.41%, respectively, with controls having 89% and 11%. Furthermore, women with the AA genotype exhibited a higher risk for infertility, with hazard ratios (RR) of 3.48. The rs2275913 variant was likewise linked to a higher risk of infertility in the recessive model (AA+GA) vs. GG, with RR values of 1.51. However, correlations were not statistically significant ($p > 0.05$).

TABLE II
THE GENOTYPES, GENETIC MODELS, AND ALLELE FREQUENCIES OF IL-17A (-197G/A) IN THE INFERTILE AND FERTILE WOMEN

	Genotype	Infertile female frequency	Control female frequency	Relative Risk	Etiology or Preventive Fraction	Exact Fishers Probability	95% Confidence Intervals
IL-17A (G/A)	GG	94 (70.14%)	39 (78%)	0.66	0.26	0.356	0.31-1.41
	GA	36 (26.86%)	11 (22%)	1.30	0.06	0.572	0.61-2.80
	AA	4 (2.98%)	0 (0%)	3.48	0.02	0.576	0.19-64.10
	(GG+GA) vs. AA	130 (97.01%)	50 (100%)	NA			
	(AA+GA) vs. GG	40 (29.85%)	11 (22%)	1.51	0.1	0.356	0.71-3.22
	Allele						
	G allele	224 (83.58%)	89 (89%)	0.63	0.33	0.250	0.31-1.27
	A allele	44 (16.41%)	11 (11%)	1.59	0.06	0.250	0.79-3.21

NA: Not applicable

Although variations in GG and GA genotype frequencies were noticeable among infertile and fertile groups, these disparities did not achieve statistical significance. The AA genotype was associated with a slightly elevated risk for infertility. According to Najafi et al. (2014), women's infertility and the SNPs in the IL-17A rs2275913 AG genotype are related..

Furthermore, Xie et al. (2023) found that endometriosis patients had a notably greater frequency of the rs2275913 AA

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genotype than control participants did, with an odds ratio of 2.28 and a 95% confidence range of 1.37–3.80 (p = 0.001). However, there is still limited research on how IL-17A polymorphisms affect the likelihood of endometriosis. No prior research has shown this kind of correlation.

The frequencies of IL-17A genotype were assessed for HWE in both infertile and fertile women. There were statistically insignificant variations between the predicted and actual genotype frequencies in women who were fertile and infertile (p > 0.05). These results indicate that the genotype distribution in these infertile groups conformed to HWE, as illustrated in Table 3.

TABLE II
COMPARISON OF IL-17A (RS2275913) GENOTYPE AND ALLELE DISTRIBUTIONS BETWEEN INFERTILE WOMEN AND FERTILE PARTICIPANTS: HARDY-WEINBERG EQUILIBRIUM TEST

Case Categories		IL-17A gene at position G/A (rs2275913)					
		Genotypes			HWE	Alleles	
		GG	GA	AA	p. value	G	A
Infertile group	Observed	94	36	4	0.807	224	44
	Expected	93.61	36.78	3.61		NA	
Fertile Female	Observed	39	11	0	0.382	89	11
	Expected	39.61	9.79	0.61		NA	

NA: Not applicable

D. Evaluation of serum IL-17F and their correlation within groups

In this investigation, the analysis focused on the examination of serum IL-17F levels within distinct groups. Within the fertile and infertile groups, serum IL-17F levels were 104.0±164.6 pg/ml and 168.4±243.3 pg/ml, respectively. These findings highlight discernible differences in IL-17F levels between infertile females and their fertile counterparts. Conversely, the infertile groups presented higher serum levels in comparison to the fertile group, though statistical significance was not observed, as shown in Figure 4.

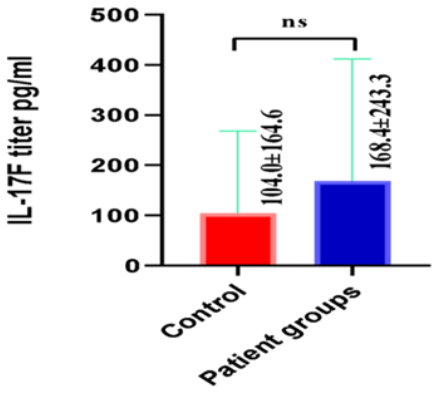

Figure 4: Level of serum IL-17F among volunteer participants

The results indicate that there could be a connection between IL-17F and female infertility since the infertile group had higher IL-17F levels. Supporting evidence from Özcxaka et al. (2013) indicates elevated IL-17F levels in females with PCOS compared to the fertile group. Endometriotic stromal cells (ESCs) express COX2 and secrete IL-8 in response to IL-17F, since IL-8 facilitates the proliferation of endometrial stromal cells, therefore it's hypothesized that IL-17F could use these processes to promote endometriosis (Shi et al., 2022).

E. Associations of IL-17F (+7488 T/C) (rs763780) genotypes and allele frequency with women's infertility

Table 4 provides a comprehensive overview of the pattern of IL-17F (T/C) distinctions in both infertile and fertile women. The TT, TC, and CC genotypes' frequencies among infertile females were 104 (77.61%), 25 (18.65%) and 5 (3.73%), respectively. Fertile women exhibited only TT genotype with 50 (100%) frequency. Significant differences in the frequencies of IL-17F genotypes TC were observed among infertile women. Additionally, the comparison of major allele T and minor allele C frequencies in cases demonstrated percentages of 86.94% and 13.05%, respectively. In contrast, only a major T allele was observed in fertile women. Furthermore, individuals with the TC and CC genotypes displayed an increased risk for infertility, with hazard ratios of RR= 23.52, P= 0.000, and RR= 4.29, P= 0.325, respectively. The rs763780 variant also exhibited an association with elevated infertility risk in the recessive model (CC+TC) vs. TT, with values of RR=29.48, P=0.000. There was statistical significance (p < 0.05) in these connections.

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TABLE IV
THE GENOTYPES, GENETIC MODELS, AND ALLELE FREQUENCIES OF IL-17F (T/C) (+7488) IN THE INFERTILE WOMEN

	Genotype	Infertile female frequency	Control female frequency	Relative Risk	Etiology or Preventive Fraction	Exact Fishers Probability	95% Confidence Intervals
IL-17F (T/C)	TT	104 (77.61%)	50 (100%)	NA			
	TC	25 (18.65%)	0 (0%)	23.52	0.18	0.000	1.44-383.43
	CC	5 (3.73%)	0 (0%)	4.29	0.03	0.325	0.24-76.88
	(TT+TC) vs. CC	129 (96.26%)	50 (100%)	NA			
	(CC+TC) vs. CC	30 (22.38%)	0 (0%)	29.48	0.21	0.000	1.82-478.59
	Allele						
	T allele	233 (86.94%)	100 (100%)	NA			
	C allele	35 (13.05%)	0 (0%)	30.56	0.12	0.000	1.88-496.18

NA: Not applicable

Notable variations were found in the frequencies of the TT and TC genotypes of IL-17F when comparing infertile groups to the control group, indicating the potential involvement of IL-17F gene variations in the development of women's infertility. The relative ratios further highlight those individuals with the TC genotype face a significantly elevated risk of infertility. According to these results, women who have the C allele of the IL-17F gene may be more susceptible to infertility or may experience a less severe case of the illness. To the best of our knowledge, there is no prior research indicating a correlation between women's infertility and polymorphisms in the IL-17F gene. The relationship between women's infertility and IL-17F polymorphism remains largely unexplored in the existing

research. A research by Najafi et al. (2014) suggested a possible connection between rs763780, or IL-17F 7488 T/C, and an elevated risk of recurrent pregnancy loss in Iranian women. This specific polymorphism causes arginine to replace histidine at amino acid 161, and it is situated within the coding area of IL-17F. The cytokine variation that results from this substitution has been shown to oppose the action of wild-type IL-17F and is unable to produce pro-inflammatory cytokines and chemokines.

The IL-17F genotype frequencies were examined for HWE in both infertile and fertile women. The comparisons between observed and expected genotype frequencies revealed statistically significant differences in infertile women ($p = 0.03$). According to Table 5, it implies that this cohort's distribution outside of HWE.

TABLE V
SHOWS THE RESULTS OF THE HWE TEST FOR THE GENOTYPES AND ALLELES DISTRIBUTIONS OF IL-17F (T/C) (RS763780) GENE IN THE INFERTILE AND FERTILE WOMEN

Case Categories		IL-17F gene at position T/C (rs)					
		Genotypes			HWE	Alleles	
		TT	TC	CC	p.value	T	C
Patient groups	bserved	104	25	5	0.038	233	35
	xpected	101.29	0.43	2.29		NA	
ertile Female	bserved	50	0	0	NA	100	0
	xpected	50	0	0		NA	

NA: Not applicable

CONCLUSION

In conclusion, compared to their fertile counterparts, infertile females exhibited statistically substantially lower levels of IL-17A. Additionally, it is possible that IL-17A gene variants have a role in the development of infertility in women.

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