

# Association by Polymorphism of the *IL22* Gene in Situations, rs867810424 (A/G) and rs1390124543 (A/G) with a Risk of Infertility in Women

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## Abstract

Infertility is a growing and effective social disease in family relationships. The importance of controlling and measuring patient risk is determined by the individual's predisposing factors to infertility, genetic and acquired background. Inflammatory disorders are seen in many diseases, and cytokines, including *IL22*, play a role. *IL22* is a precursor cytokine and has a dual role in are associated with increased egg fertility and the expansion of fetal growth. The aim of this study was to investigate the effect of two variants rs86781042 and rs1390124543 in *IL22* on female infertility in southern Iran and compare it with healthy individuals. In this case study, evidence was used to study the polymorphism of the *IL22* gene in the blood of 200 infertile and healthy patients in Shiraz hospitals, for DNA extraction and purification, using Salting Out and Proteinase K methods, followed by electrophoresis and PCR ARM was used. The results were analysed using SPSS software and Hardy Weinberg equilibrium. According to the results, it seems that the expression of two polymorphisms of *IL22* gene is directly related to infertility in women in southern Iran and by using this relationship; it can be used as a biomarker for screening infertile women and diagnosing the disease.

**Keywords:** *IL 22* • rs867810424 • rs1390124543 • Infertility

## Introduction

Fertility is one of the great goals of creation for the survival of the generation, which is of particular importance [1]. Lack of fertility is very important in social and family issues and in many societies including Iran, childbearing is very important and plays a very important role in family survival and prevention of divorce [2]. The increase in infertility can be due to premature birth in couples, changes in sperm quality due to habits such as smoking, alcohol, and altered sexual behaviour. The prevalence of primary infertility in Iran is higher than the global trends in infertility and ovarian dysfunction is the major cause of primary infertility in Iran [3]. Lack of ovulation is a major problem for women, often with irregular menstruation. There are many factors that affect infertility in women. Some of these factors, such as age and genetic factors unfortunately do not change [4]. ISO immunization has been proven to be associated with infertility. Infertility is one of the most common chronic health disorders, regardless of age. The main infertility disorders include pathologic sperm grams, ovarian problems, tubal disease, pelvic adhesions/endometriosis, cervical and idiopathic factors. The molecular and cellular endometrial deficiency that leads to implantation failure can be associated with unknown infertility, as suppressing natural immunity does not preclude rejection of maternal immunity. Treg (T) cells are used to protect the fetus and maintain immunity against an immunosuppressive attack. A high percentage of infertile women are exposed to topical reactions leading to inflammation as well as high levels of anti-sperm serum antibodies. The anti-sperm antibody found in the mucus cervix has coagulant properties that peak in the luteal and follicular phases of the menstrual cycle; in contrast, it is low in ovulation. Mucosal immunity in the female reproductive system is affected by levels of

natural and specific antibodies, cytokines and hormones [5]. Treg and Th17 cells play an important role in the regulation of immune regulation during pregnancy. During pregnancy, macrophages and dendritic cells are likely to support embryo acceptance in the uterus. IL10 secretion plays an important role in the regulation of immunity in decidua macrophages [6]. Estrogen helps proliferate endometrial immune cells. On the other hand, progesterone is also known to be a dominant regulator, since the greatest increase in endometrial immune cells is secreted when progesterone levels decrease. However, recognizing female organs and immune cells is crucial to the health of women and their successful pregnancies [7]. Factors due to chronic failure, such as pelvic adhesion, ovarian dysfunction, peritoneal deficiency, and endometrial variability, appear to be involved in infertility. Immune deficiency plays an important role in these cases [8]. The pathogenesis of infertility is associated with endometriosis with the involvement of biochemical, endocrine, immune, environmental and genetic factors. Immune cell types including macrophages and dendritic cells associated with inflammation are present in endometriosis and are likely to play a role in infertility associated with endometriosis [9]. Endometrium, serum, and peritoneal fluid in women with endometriosis have abnormal levels of inflammatory cytokines, angiogenic factors, growth factors, and adhesion. *IL1β* has a proliferative effect on endometrial cells, which does not occur in healthy endometrial cells [10]. *IL1β* stimulates the production of interleukins 6 and 8 in endometriosis cell culture, which further proliferates and reduces apoptosis. In addition, high levels of *IL1β* may cause the conversion of inflammation from acute to a chronic form [11]. Inherent immunity, in addition to adaptive immunity, plays an important role in pregnancy and NK cells are important in this process. Many signalling molecules and common pathways responsible for propagating an inflammatory response in somatic cells have been identified. Thus in the pregnant woman, the placenta as an organ enhances the ability of the immune cells to produce [12]. The concentration of *IL19* and *IL22* in the serum of patients with ovarian endometriosis is higher than that of women with uterine endometriosis [13]. Protein cytokines such as *IL6*, *IL4*, *IL2*, *TNF-α* and interferon- $\gamma$  are increased in endometriosis and lead to increased inflammatory reactions. The inverse correlation between serum concentrations of interleukins and endometriosis activity suggests that anticoagulant cytokines, using a variety of biological effects, stimulate the desired immune system to promote ovarian endometriosis [14]. *IL22* has a protective effect against autoimmune diseases and plays an important role in the development of various cancers such as lung, liver, etc [15]. *IL22* is

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an *IL10* family cytokine and is produced by Th17 cells, NKT cells. Initially, this cytokine targets epithelial cells and stroma of different tissues and plays a role in tissue proliferation and regeneration. Unlike many cytokines, the main effect of *IL22* is on epithelial cells and fibroblasts in tissues such as the lung, liver, kidney, thyroid, pancreas, breast, intestine, skin and synovium, which have a profound effect on tissue regeneration. Post-injury epithelial mainly promotes survival by inducing proliferation and inhibiting apoptosis of epithelial cells [16]. Abnormal levels of *IL22* and its receptors may be involved in the development of endometriosis. *IL22* plays an important role in inflammation, immune surveillance and mucosal tissue homeostasis. It's very high expression acts directly or indirectly as an inflammatory agent. Increased *IL22* expression in ectopic lesions in women with endometriosis is probably due to pelvic inflammation [17]. *IL22* is probably caused by endometrial estrogen and inflammation, stimulates tissue inflammation and regeneration, and, on the other hand, contributes to the formation of micro-environmental microenvironments in the ectopic form by stimulating the production of *IL6*, *IL8* and *VEGF* participates. These integrated effects invade the endometrial vessel and contribute to the development and development of adenomyosis [18]. The imbalance of immune cells in the uterus and the dysfunction of their cytokines may lead to pregnancy loss [19]. Specific immune cells, which express different cytokines in relation to the mother and the fetus, are critical for the survival of early pregnancy [20]. Embryonic trophoblasts express the *IL22R1* receptor and increase proliferation upon *IL22* exposure. In spontaneous abortion samples *IL22R1* expression was significantly lower than in normal pregnancies [21]. *IL23* and *IL17* are two cytokines that interact with *IL22* in various systemic inflammatory conditions [22].

The purpose of this study was to investigate the *IL22* and rs-867810424 and rs1390124543 polymorphisms in the risk of infertility in women.

## Materials and Methods

This study is a case-control study and investigates the effect of *IL22* gene polymorphisms in two positions of rs867810424 and rs1390124543 in infertile women. In this study, 200 women with infertility problems referred to

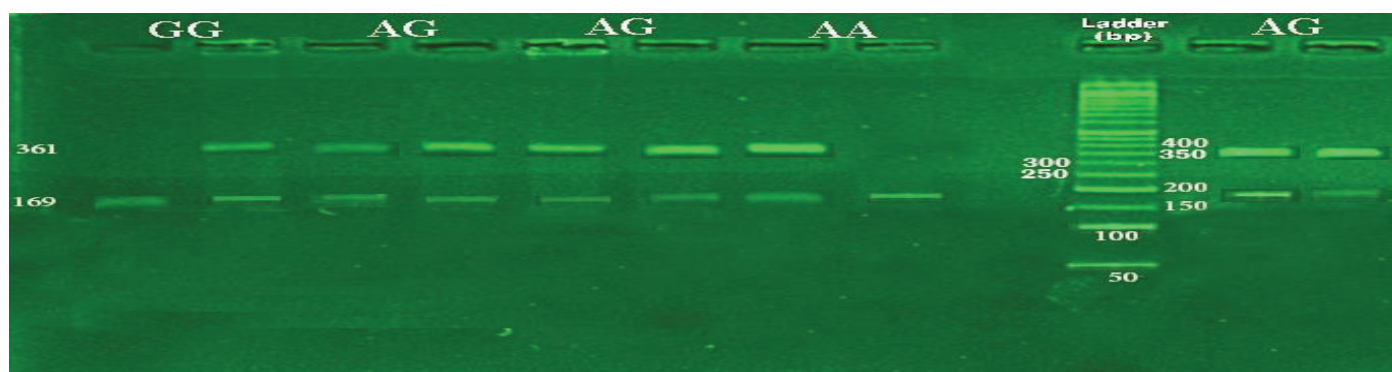
gynaecology hospitals in the reproductive age range 20–45 ( $\pm 5$ ) years in the south of the country were diagnosed by a physician using laboratory and clinical findings. It was compared with a group of 200 normal women in the age range 20–45 ( $\pm 5$ ) years. Control subjects were selected and studied from referrals to specialist physicians. The demographic and personal information forms were completed by the patient. After receiving consent, all patients underwent 5 cc venous blood transfusion and transferred to a tube containing 0/5 cc EDTA. Proteinase K and Salting Out method were used for DNA extraction. The PCR ARMS method was used to evaluate the mentioned polymorphisms and to determine the genotypes of the individuals. Two PCR reactions were performed using a template DNA in two separate tubes, one containing mutant primers and the other containing normal primers. In each reaction, a common primer with one of the two allele-specific primers was used. For each position of the *IL22* gene, the primers of both positions were designed using the Oligo software of 7, shown in Table 1. For PCR reaction at position rs867810424, each tube contained 0.7  $\mu$ L of DNA, 8  $\mu$ L of water, 11  $\mu$ L of amplicon and each of the internal primers with a concentration of 20 picomolar, 0.2  $\mu$ L and forward and backward primers respectively. The A and G alleles were applied to 0.3  $\mu$ L with a final volume of 20.7  $\mu$ L.

At position rs1390124543 in each tube 0.7  $\mu$ L DNA and 8  $\mu$ L water, 11  $\mu$ L amplicon and 20 pM intracellular primers, each containing 0.6  $\mu$ L for forward and reverse primers in the A and G alleles, 0.5  $\mu$ L was applied and the final volume was 21.9  $\mu$ L. The resulting mixture was then heated at 94°C for 5 min and then rs867810424, 32 rpm and rs1390124543, 31 rpm for PCR. This process involves 40 seconds of denaturation at 94°C, 40 seconds of annealing at 56°C and 40 seconds at 72°C for the elongation (extension) step and finally it was kept as Final extension at 72°C for 5 minutes. PCR products were separated on 1.5% agarose gel by electrophoresis (Figures 1 and 2). The data were analysed using SPSS 24 software and the results were analysed by Chi-square test. The level of  $PV \leq 0/05$  was considered as the significant level.

Hardy-Weinberg equilibrium test was used to determine if the study was in accordance with population genetic balance. According to the equilibrium law, the distribution of observed genotypes showed a significant difference with the expected genotypes distribution ( $PV < 0/05$ ), but for alleles, this distribution was not significant. ( $PV > 0/05$ ).

**Table 1.** Specific sequences of primers used for *IL22* polymorphism.

Gene Position	Sequences of primers 5' to 3'	Product length (bp)
F. rs867810424 (F)	GCAGAATCTTCAGAACAGGT	
R. rs867810424 (RA)	AAGAGCAGGATTGAGATGTATA	
R. rs867810424 (RG)	AAGAGCAGGATTGAGATGTATG	
F.PCR.CONTROL (FC)	CCTCTGCACAGTTTGGAC	361
R.PCR.CONTROL (RC)	TCTGTCCAGCAATCCAGG	
F. rs1390124543 (F)	TGGATTCTGGCGTCCAAG	
R. rs1390124543 (RA)	GCATTGACAGTTATCAGTCCTA	
R. rs1390124543 (RG)	GCATTGACAGTTATCAGTCCTG	
F.PCR.CONTROL (FC)	CCTCTGCACAGTTTGGAC	276
R.PCR.CONTROL (RC)	TCTGTCCAGCAATCCAGG	



**Figure 1.** Determination of different genotypes of rs867810424 polymorphism of *IL22* gene in 1.5% agarose gel.

## Results

In this study, the mean age of the patients was 32/23 ± 5/99 years and the mean age of the control group was 32/65 ± 6/23 the results of the PCR test led to the creation of fragments of the genome described in Materials and Methods section. Of the 200 infertile patients studied, 867810424 polymorphism showed GG (14%), AA (10%) and AG (75%). The frequency of genotypes in the control group were GG (7%), AA (3/5%) and AG (89/5%), respectively. Logistic regression and chi-square tests showed significant differences between patients and control group in all three genotypes (PV=0.001) (Tables 2 and 3).

In the variant rs1390124543 of the *IL22* genes in the 200 patients studied, they showed GG genotype (8.5%), AA genotype (17.5%) and AG genotype (73.5%). In control group the frequency of genotypes were GG (4.5%), AA (8%) and AG genotype (87.5%) respectively. Statistical tests showed significant difference between patients and control group. All three genotypes were observed (PV=0/005) (Tables 2 and 3).

On the other hand, analysis of the *IL22* alleles in polymorphism rs867810424 showed that 52% of the patients had G allele and 48% had Group A allele, which in the control group was 51.8% and 48.2%, respectively. (PV=0/939). In the variant rs1390124543 this gene was also found in the patient group, 45.5% of the G allele and 54.5% of the A allele, and in the control group the frequency of alleles was 48.2% and 51.8%, respectively. (PV=0/433) (Table 4). The results were analysed by chi-square test and logistic regression analysis. There was no significant difference between the two alleles and infertility in both *IL22* polymorphisms.

All clinical factors were significantly correlated with rs867810424

polymorphism, as their P Chi- Square was zero and less than 0/05. In this polymorphism, age and IUI were not associated with the disease, respectively, P=0/204 and P=0/223, respectively, and IVF, P=0/033, were significantly associated with the disease. In the rs1390124543 variant, age and IUI were not significantly correlated with infertility P=0/888 and P=0/734 respectively, and IVF P=0/092 was significantly associated with disease. All clinical factors were significant with this variant because PV=0.00 and less than 0.05 consequently, all clinical factors in these two polymorphisms of the *IL22* gene can be effective in female infertility.

## Discussion

Infertility is a potentially serious, costly and burdensome problem for affected families. To accurately assess the prevalence of infertility using epidemiological studies, it is necessary to plan appropriately for prevention, treatment, management of infertility, its social and economic consequences [3]. During pregnancy, macrophages and dendritic cells support embryo acceptance in the uterus, and the number of IL10 secretory cells in decidua macrophages is higher than peripheral blood monocytes [6]. This means that decidua macrophages play an important role in the regulation of immunity in the primordial uterus. Autoimmune-related infertility is a polyclonal event characterized by immunodeficiency at the Tcell surface and, like autoimmune diseases, produces abnormal antibody production [23]. Cytokines are protein molecules that are involved in acquired and innate immunity and regulate the immune response. Their effects stimulate the development and activation of the immune response or inhibit the appropriate response. Among these cytokines, *IL22* is a pro inflammatory protein that is involved in the maintenance and regeneration of tissue and the inhibition of apoptosis [24]. *IL22* function depends

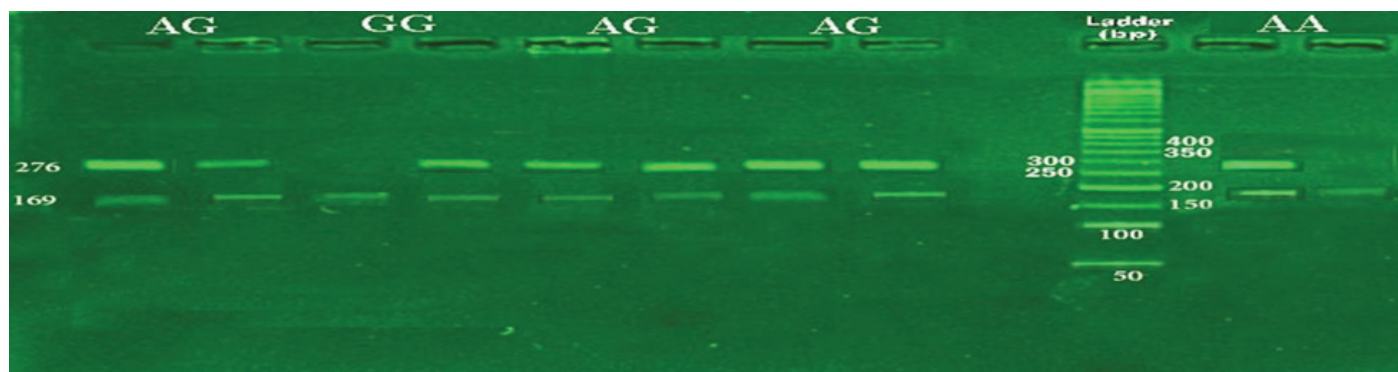


Figure 2. Determination of different genotypes of rs1390124543 polymorphism of *IL22* gene in 1.5% agarose gel.

Table 2. Frequency of genotyping of the *IL22* gene polymorphism rs867810424 and rs1390124543 in infertile women and control group.

P Chi-Square	Sum of total samples	Mis	AA	GG	AG	Study group
0/001	100% (200)	1.0% (2)	10% (20)	14% (28)	75% (150)	Patient
	100% (200)	0% (0)	3.5% (7)	7% (14)	89.5% (179)	rs867810424
	100% (400)	0.5% (2)	6.8% (27)	10.5% (42)	82.3% (329)	Control
	100% (200)	0.5% (1)	17.5% (35)	8.5% (17)	73.5% (147)	rs867810424
0/005	100% (200)	0% (0)	8.1% (16)	4.5% (9)	87.5% (175)	Control rs1390124543
	100% (400)	0.3% (1)	12.8% (51)	6.5% (26)	80.5% (322)	Total number of samples

Table 3. Frequency of genotypes of the in *IL22* gene polymorphism rs867810424 and rs1390124543 in infertile women and control group.

CI	OR	PV	Control	Patient	Study group rs867810424
-	-	-	7	20	AA
1/4 - 8/23	Mar-41	0/004	179	150	AG
0/4 - 4/17	4-Jan	0/5	14	28	GG
CI	OR	PV	Control	Patient	Study group rs1390124543
-	-	-	8.0% (16)	17.5% (35)	AA
1/38- 4/89	6-Feb	0/002	87.5% (175)	73.5% (147)	AG
0/4-3/1	1-Jan	0/7	4.5% (9)	8.5% (17)	GG

**Table 4.** Allelic frequency of two polymorphisms rs867810424 (A/G) and rs1390124543 (A/G) gene *IL22* in infertile women and control group.

CI	OR	PChi-Square	Sum of total samples	Allel A	Allel G	Study group
0/765 -1/335	1/011	0/939	100% (396)	48% (190)	52% (206)	Patient rs867810424
			100% (400)	48.2% (193)	51.8% (207)	Control rs867810424
			100% (796)	48.1% (383)	51.9% (413)	Total number of samples
0/677 -1/182	0/898	0/433	100% (398)	54.5% (217)	45.5% (181)	Patient rs1390124543
			100% (400)	51.8% (207)	48.2% (193)	Control rs1390124543
			100% (798)	53.1% (424)	46.9% (374)	Total number of samples

on the presence and relative amounts of other cytokines, the concentration and the presence of the sequestering agents [25]. The important role of this cytokine in inflammation is to monitor immune and tissue homeostasis and to increase its expression in endometriosis and non-malignant lesions [26]. Its high expression is either directly or indirectly as an inflammatory factor, and the increase in endometrial cytokines is directly "stimulated by inflammatory mediators, on the other hand, it enhances the proliferation and growth of uterine stromal cells that produce Ectopic endometriosis foci are ultimately associated with infertility [17]. *IL22* has several single- or multi-nucleotide polymorphisms. There has been no study on the polymorphism of this cytokine in the indicated cases and infertility, but previous studies have suggested the role of this cytokine and other cytokines in some diseases. In a 2013 study by Wang et al., Researchers have shown that *IL22* is involved in placental proliferation and that spontaneous miscarriage is more likely to occur if expression of this gene is reduced [22]. In a 2017 study by Sikora et al., The researchers concluded that IL8 plays an important role in the development of endometriosis. Endometrial mesenchymal stem cells play an important role in the secretion of cytokines and endometriosis and ultimately infertility [27]. In a 2013 study, Santulli et al., concluded that decreased serum levels of IL 19 and 22 in women with endometrioma are associated with deep dyspareunia and chronic pelvic pain [28]. In a study by Wolk et al., the researchers examined the association of *IL22* with various diseases and found that leukocyte-mediated *IL22* was mainly targeted to tissue epithelial cells rather than immune cells. Which protects the tissue against attack by extracellular bacteria [29]. In a 2012 study, Paget et al., showed that *IL22* protects bronchial epithelial cells from damage caused by influenza a virus [30]. In this study, we investigated the polymorphisms of rs 867810424 and rs1390124543 of the *IL22* gene and their association with infertility. According to the reviews, it seems that this is the first study and so far no study has been done. The results indicate that all three genotypes (GG, AA, AG) in both positions, in both patient and control groups with infertility showed a significant difference for alleles in both variants. Is not. Studies have shown that any mutations in the 5' - UTR region of the *IL22* gene that lead to these two polymorphisms are likely to increase infertility in women.

## Conclusion

In the present study, the frequency of *IL22* genotypes in the patient and control groups was significant. 5'- UTR has become a gene promoter that will play a role in splicing and harvesting introns, As a result, the exons bind, complement, and segregate the target mRNA, eventually increasing the expression of the *IL22* gene by lowering its serum levels in the body. In this case, this gene will act as a pro inflammatory factor in the development of inflammation and infertility. Thus, if both polymorphisms are present in the 5' *IL22* gene, the risk of female infertility is increased. To better understand the mechanism of action of this cytokine in the development or resistance to infertility, it is recommended that further studies be carried out to investigate the expression level of this cytokine in patients and compare it with healthy controls and its association with the mentioned polymorphisms, to be paid.

## Acknowledgment

This article is a thesis on the study of *IL22* gene polymorphisms at positions rs867810424 (A/G) and rs1390124543 (A/G) in infertile women in

south of Iran in 1398 with code: IR.IAU.KAU.REC.1398.008 The Islamic Azad University of Kazeroon Branch has been completed. This is a great tribute and appreciation to the Honourable Vice President of Research and Technology at Kazeroon Azad University.

## Conflicts of Interest

No conflict of interest has been stated by the author.

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