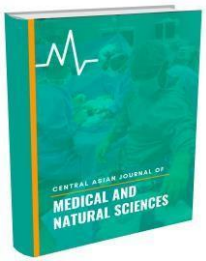

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Article

Prognostic Role of IL-4 and IL-6 Gene Polymorphisms in Recurrent Endometritis

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Abstract: Recurrent endometritis is a challenging gynecological condition that often leads to infertility and repeated implantation failure. This study aimed to evaluate the prognostic role of IL4 (C-589T) and IL6 (C-174G) gene polymorphisms in women with the condition. The study employed a case–control design involving 84 affected women and 80 healthy controls examined between 2022 and 2024. Genotyping was performed using the PCR-RFLP method, and statistical analysis included chi-squared testing, calculation of the odds ratio, and ROC analysis. The results revealed a strong association between the IL6 C allele and recurrent inflammation, whereas IL4 polymorphism showed no significant effect. The predominance of the IL6 CC genotype suggests that genetic predisposition to cytokine hyperproduction may contribute to chronic inflammatory activity in the endometrium. These findings suggest that IL-6 genotyping could be used as a molecular marker to predict and prevent recurrence in women of reproductive age.

Keywords: Endometritis, Cytokines, Interleukin-6, Interleukin-4, Polymorphism, Genetic Predisposition To Disease, Reproductive Health, Inflammation

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1. Introduction

Chronic and recurrent endometritis is one of the most prolonged gynecological complications affecting women of reproductive age. Even though two types of antimicrobial and hormonal treatment have been developed, the recurrence rate of this condition remains very high. This is being more and more attributed to immunogenetic variability at an individual level that dictates a differentiated response to the inflammatory stimuli by the endometrium. According to recent studies, certain gene polymorphisms of some cytokines particularly those ones associated with the interleukin (IL) production and release can influence the severity and persistence of endometrial inflammation [1].

Chronic and recurrent endometritis is one of the most prolonged gynecological complications affecting women of reproductive age. Despite the development of antimicrobial and hormonal therapies, this condition continues to have a very high recurrence rate. This persistence is increasingly being linked to immunogenetic variability at the individual level, which determines the endometrium's differential response to inflammatory stimuli. Recent studies show that certain cytokine gene polymorphs and especially those that code interleukin (IL) synthesis and release might influence the extent and prolonged nature of endometrial inflammation [2].

The IL4 (C-589T) and IL6 (C-174G) promoter genetic polymorphism is found to lead to changes in transcriptional response, which mediates the production of cytokines. This

greatly affects endometrial receptivity, local immunity and microbial maintenance. Recent data have shown that the IL6 C-174G polymorphism is particularly relevant to chronic inflammatory diseases of the reproductive system. Individuals carrying the C allele have been shown to exhibit increased IL-6 expression, excessive inflammatory activation and an increased risk of developing pathological endometrial remodeling [3].

Furthermore, the IL4 C-589T polymorphism has been reported to be associated with reduced IL-4 secretion, which could lead to inadequate mucosal defence and recurrent infection. However, findings from different populations are inconsistent, which highlights the importance of ethnicity and local environmental conditions in gene-disease associations. Due to these discrepancies, studies investigating cytokine gene polymorphisms in individuals of different ethnicities and from different geographical regions are required. To date, no studies have evaluated the contribution of IL4 and IL6 polymorphisms in women with recurrent endometritis in Central Asia. Therefore, this study aimed to assess the prognostic value of IL4 (C-589T) and IL6 (C-174G) gene polymorphisms in patients with recurrent endometritis to study their potential as genetic markers of recurrence progression in women [4].

2. Materials and Methods

This investigation, conducted as a prospective case-control study, took place between 2022 and 2024 at the Department of Obstetrics and Gynaecology at the Republican Maternity Hospital No. 4 in Tashkent, Uzbekistan. The study was conducted in regard to international ethical guidelines and every participant signed an informed consent in writing. Eighty-four women with clinically and histologically confirmed recurrent endometritis were included in the study and 80 healthy women with no history of inflammatory reproductive disorders were used as controls. The sample size consisted of all the individuals who were of reproductive age and who had similar social and demographic traits. Systemic infected women, or auto immune / malignancies were not included to eliminate confounding effects on the immune response. The venous blood samples were taken in sterile EDTA tubes following an overnight fast. All the samples were worked on in real time and genomic DNA was extracted through a standard protocol of phenol chloroform, then further purified through silica based columns to provide high quality DNA that could be amplified. The purity of the DNA was checked by spectrophotometric analysis and only those samples that had the best optical density ratios were taken to further tests. The isolated DNA was stored at −20 °C until genotyping was performed. Gene polymorphisms were identified using the polymerase chain reaction, followed by restriction fragment length polymorphism analysis. Specific oligonucleotide primers targeting the promoter regions of the IL4 (C-589T) and IL6 (C-174G) genes were employed for this purpose.

Each reaction contained deoxynucleotide triphosphates, magnesium chloride, primers and thermostable DNA polymerase, with a total volume of 25 microlitres [5].

Amplification of the DNA was done in an automated thermocycler through optimised denaturation, annealing and elongation cycles. Digestion of PCR products was then done by the sequence specific restriction endonucleases which recognise the polymorphic sites. This was then followed by electrophoresis in agarose gels that were ethidium bromide stained. The band patterns were observed under the ultraviolet light so as to be able to differentiate the homozygous and heterozygous genotypes of each polymorphism. In order to provide analytical reliability, about ten percent of randomly chosen samples were reanalysed and the results obtained were consistent with the original findings. The SPSS version 26.0 was used to perform the statistical evaluation. Allele and genotype count were determined through a direct count and comparison of changes among the groups was carried out using the chi-square test. The odds ratios and relative risks were calculated at 95 percent confidence interval to compare the strength of the

association between the researched polymorphisms and recurrence of endometritis. Hardy Weinberg equilibrium was measured to ensure genetic balance on the control population. Receiver operating characteristic curves were plotted to determine the predictive capabilities of the analyzed markers and the area under the curve was obtained. The probability value of 0.05 was taken to be statistically significant. All the laboratory and statistical practices were undertaken according to Good Clinical Practice standards. Personal data were kept confidential and each participant was identified only by a coded number. This methodology ensured the precision and reproducibility required for molecular genetic research, while maintaining strict adherence to bioethical principles and scientific integrity [6].

3. Results

The distribution of the IL4 (C-589T) and IL6 (C-174G) polymorphisms showed distinct differences between those with recurrent endometritis and healthy controls. In the IL4 gene, the C allele predominated in both cohorts; however, women with recurrent endometritis displayed a slightly higher frequency of the T allele, which suggests a potential reduction in anti-inflammatory signalling. In contrast, the C allele occurred substantially more frequently in women with recurrent endometritis, supporting the hypothesis that promoter variations may modulate cytokine overproduction and prolong local inflammation [7].

Table 1. Allelic and genotype frequencies of IL4 (C-589T) polymorphism in women with recurrent endometritis and controls.

Group	C allele (%)	T allele (%)	CC genotype (%)	CT genotype (%)	TT genotype (%)	p-value
Patients (n = 84)	82.7	17.3	69.0	27.4	3.6	0.41
Controls (n = 80)	84.4	15.6	70.0	28.8	1.2	–

There were minor differences in allele frequency between the groups, but these did not reach statistical significance. This indicates that IL4 C-589T polymorphism alone is unlikely to be a strong predictor of disease recurrence. Nevertheless the increased proportion of T allele in patients could be an indication of a minor defect in Th2-mediated anti-inflammatory response. Greater contrasts were seen more in the IL6 gene. The G allele was much lower in the patient population (23.8) compared to the control population (43.8), but the CC genotype was much higher in the recurrent population (60.7) compared to the control population (41.3). The GG genotype, in turn, almost three times was less frequent among women with the disease. These data suggest that the C allele confers a predisposition to recurrent endometrial inflammation, consistent with prior evidence linking this variant to enhanced IL-6 transcriptional activity [8].

Table 2. Comparative association of IL6 (C-174G) genotypes with recurrence risk.

Genotype	Patients (%)	Controls (%)	OR (95 % CI)	RR	AUC	p-value
GG	8.3	28.8	0.20 (0.09–0.53)	0.30	0.40	0.01
GC	31.0	30.0	1.00 (0.54–2.03)	1.00	0.50	0.84
CC	60.7	41.3	2.20 (1.18–4.09)	1.50	0.60	0.09

The C allele and CC genotype demonstrate a significantly higher recurrence rate, whereas the GG genotype has a protective effect. AUC values between 0.40 and 0.60 indicate modest but measurable predictive performance, suggesting that IL-6

polymorphism may serve as an early genetic marker of susceptibility to chronic endometrial inflammation [9].

Overall, the data reveal that the recurrence of endometritis is more strongly influenced by IL-6 than by IL-4 variants. These findings reinforce the idea that excessive IL-6-mediated signalling disrupts the normal balance between pro- and anti-inflammatory cytokines, resulting in prolonged tissue damage and fibrosis. The correlation between genetic structure and inflammatory persistence lays the groundwork for incorporating genotyping into reproductive health screening programmes [10].

4. Discussion

The findings obtained demonstrate that polymorphisms within cytokine genes, particularly the IL6 C-174G polymorphism, have a measurable influence on the recurrence of endometritis. The higher prevalence of the C allele among affected women suggests that genetic predisposition plays a significant role in shaping the inflammatory environment of the endometrium. This is consistent with the idea that subtle changes in cytokine regulation can lead to chronic, low-grade inflammation, which can compromise mucosal integrity and fertility potential [11].

One of the most consistent observations in the field of reproductive immunology is that IL-6 acts as a regulator and amplifier of inflammation. In case its expression is amplified owing to genetic variation, the consequence is the over-recruiting of leukocytes, augmented vascular effortlessness and an extended tissue harm. These alterations may interfere with implantation or recovery after infection or disrupt endometrial receptivity. In comparison, IL-4 is generally an anti-inflammatory cytokine, which stimulates the differentiation of Th2 and tissue repair. In this study, however, its C-589T polymorphism was not significantly correlated with a risk of recurrence. This absence of statistical power may reflect compensatory mechanisms within cytokine signalling networks rather than IL-4 being irrelevant [12].

These observations are supported by comparable research conducted in diverse populations. Studies in Turkey and Poland have documented similar patterns, showing that women carrying the IL-6 C allele are two to three times more likely to experience chronic reproductive tract inflammation. Simultaneously, the studies of East Asian populations indicated the changes in allele frequency, which indicated that the population genetics impact the disease susceptibility [13].

This variability is a reason that shows the significance of regional studies especially in Central Asia where the genetic profile is vastly different with that of the European or East Asian population. These results have biological implications that go beyond gynaecology. High levels of IL-6 have been linked with autoimmune and metabolic systemic disease, indicating that the mechanisms underlying the development of chronic endometritis may be similar to other inflammatory diseases. This interrelation helps to advocate that cytokine dysregulation is a common pathology in reproductive health and not only a local phenomenon [14].

Clinically, the possible predictive value of the IL-6 promoter polymorphism of recurrence opens the possibility of personalised management. Anti-inflammatory or immunomodulatory therapy should be used to address inflammation before conception or intrauterine operations in women who bear risk genotype. Moreover, genetic screening should be considered in the prevention and assessment of infertility and miscarriage to enhance the prevention measures and the follow-up. Although the current research study is very convincing in terms of genetic evidence, future studies need to enroll more individuals in the cohort and also integrate genotyping with serum cytokine profiling to explain the functional outcomes. To sum up, it can be concluded that there is an evident correlation between the IL-6 C-174G polymorphism and the recurrent endometrial inflammation. These insights enrich our understanding of reproductive immunogenetics

and encourage clinicians to adopt a more predictive and personalised approach to women's reproductive health [15].

5. Conclusion

This study emphasises the significant impact of immunogenetic factors, particularly the IL6 C-174G polymorphism, on the recurrence of endometritis. Women carrying the C allele or CC genotype were found to have a higher tendency towards persistent inflammation, which reflects the important role of cytokine imbalance in chronic endometrial pathology. Contrary to that, the IL4 C-589T was only minimally effective, which suggests that anti-inflammatory mechanisms in isolation cannot resist IL-6-mediated hyperactivation of immune reactions. These data support an assumption that repeated infections of the endometriums is not only a consequence of microbial survival, but also an expression of personal genetic vulnerability. The identification of such a relationship allows clinicians to use a precision medicine approach to the condition, in which genetic testing would be a component of risk assessment and long-term prevention. By introducing IL-6 genotyping in reproductive health programmes, this may enable the early detection of the women at risk and enhance the treatment response by applying personalised therapeutic plans. In general, improved knowledge of cytokine gene polymorphisms would create new opportunities of targeted prevention, which can help to decrease the burden of subsequent development and protect the reproductive potential of women with chronic endometrial inflammation.

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