

Research Article**The Role of interleukin 6 in chronic endometriosis and its impact on fertility****Authors:**

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Abstract

Endometriosis represents a chronic inflammatory gynecological condition that contributes significantly to infertility among reproductive-aged women. Interleukin-6 (IL-6) has emerged as a central mediator in sustaining lesion growth, altering immunological balance, and impairing reproductive function. This experimental study aimed to investigate the association between IL-6 levels in serum and peritoneal fluid of women with chronic endometriosis and their fertility outcomes. A case-control design was adopted, with women diagnosed with endometriosis forming the study group and healthy fertile women serving as controls. Serum and peritoneal IL-6 concentrations were quantified and correlated with clinical characteristics, menstrual cycle regularity, and conception rates. The results demonstrated significantly higher IL-6 levels in both serum and peritoneal fluid of the endometriosis group ($p < 0.001$), which correlated inversely with ovarian reserve parameters and successful conception. Women with elevated IL-6 showed poorer implantation and reduced oocyte quality compared with controls. These findings reinforce the pathological role of IL-6 in endometriosis-associated infertility and suggest that targeting IL-6 pathways may offer therapeutic potential.

Keywords: Endometriosis, Interleukin-6, Infertility

Introduction

Endometriosis is a progressive estrogen-dependent disorder characterized by the ectopic implantation of endometrial-like tissue outside the uterine cavity. It affects nearly one in ten reproductive-aged women worldwide and is strongly associated with chronic pelvic pain, dysmenorrhea, and infertility. Despite advances in diagnostic tools and management strategies, the underlying pathophysiology remains multifactorial and incompletely understood. The burden of infertility in women with endometriosis cannot be explained solely by anatomical distortion, suggesting immunological and molecular pathways have pivotal roles.¹⁻⁴

Among the many inflammatory mediators implicated, interleukin-6 (IL-6) has consistently emerged as a critical cytokine driving the chronic inflammatory microenvironment in endometriosis. IL-6 is a pleiotropic cytokine produced by activated macrophages, stromal cells, and immune cells within endometriotic lesions. It plays essential roles in cellular proliferation, angiogenesis, and modulation of immune responses. In the context of endometriosis, persistently elevated IL-6 contributes to lesion survival, peritoneal inflammation, and impaired fertility. This makes IL-6 not only a biomarker of disease activity but also a promising therapeutic target.⁵⁻⁷

Fertility impairment in endometriosis results from a combination of disrupted ovarian reserve, poor oocyte quality, altered endometrial receptivity, and defective embryo implantation. Evidence suggests that IL-6 interferes with folliculogenesis, induces oxidative stress, and disrupts normal hormonal signaling. Moreover, its impact extends to the endometrial environment by altering genes crucial for implantation, such as HOXA10 and leukemia inhibitory factor. Clinical studies demonstrate that women with higher circulating IL-6 levels exhibit lower fertilization and implantation rates, even during assisted reproduction, highlighting its clinical relevance.⁸⁻¹⁰

The peritoneal cavity in endometriosis patients is characterized by increased macrophage activity and a pro-inflammatory milieu rich in cytokines, chemokines, and growth factors. IL-6 contributes to this altered environment by polarizing immune cells, promoting angiogenesis, and inhibiting natural killer cell cytotoxicity. These immunological shifts provide a survival advantage to ectopic endometrial tissue and simultaneously create an unfavorable setting for gamete and embryo

development. Such mechanistic insights explain why endometriosis-related infertility persists even in the absence of gross anatomical abnormalities.

Recent advances in reproductive immunology underscore the need for a deeper understanding of cytokine-mediated mechanisms in infertility. Experimental and translational research increasingly supports the role of IL-6 as a mediator not just of lesion growth but of reproductive dysfunction. By characterizing IL-6 expression patterns and correlating them with reproductive outcomes, novel pathways for intervention can be identified. Anti-IL-6 therapies, including monoclonal antibodies and small-molecule inhibitors, are already in clinical use for other inflammatory disorders and may hold promise in reproductive medicine.

Given these considerations, this study was designed to provide experimental evidence on the association between IL-6 levels and fertility outcomes in women with chronic endometriosis. By comparing IL-6 concentrations between affected women and healthy fertile controls, and by analyzing correlations with ovarian and reproductive parameters, the study aimed to establish the significance of IL-6 as both a biomarker and a therapeutic target in endometriosis-associated infertility.

Methodology

This was a double-blind, case-control study conducted over a period of 18 months in RHQ Hospital, Skardu in collaboration with University College of Medicine and Dentistry. Sample size was calculated using Epi Info software, considering a confidence interval of 95%, a power of 80%, and based on expected differences in mean IL-6 concentrations reported in prior studies. The required sample size was 60 women per group, totaling 120 participants.

The study group comprised women aged 20–38 years with laparoscopically confirmed endometriosis and infertility lasting at least one year. The control group consisted of age-matched healthy fertile women with no history of gynecological disorders. Inclusion criteria included regular menstrual cycles and no use of hormonal therapy in the preceding three months. Exclusion criteria included presence of autoimmune disease, pelvic infections, prior ovarian surgery, or systemic inflammatory disorders.

All participants provided verbal and written informed consent after being counseled regarding the study protocol. Blood samples and peritoneal fluid aspirates (obtained during laparoscopy) were collected for IL-6 quantification using ELISA. Reproductive parameters including ovarian reserve (AMH levels, antral follicle count), oocyte quality, fertilization rates, and implantation outcomes following assisted reproduction were recorded.

Statistical analysis was conducted using SPSS version 25. Data were expressed as mean $\pm$ SD. Intergroup comparisons were performed using independent t-tests, and categorical variables were analyzed using chi-square tests. Correlation analysis was conducted to evaluate associations between IL-6 concentrations and fertility outcomes. A p-value of <0.05 was considered statistically significant.

Results

Table 1. Demographic and Baseline Characteristics

Variable	Endometriosis Group (n=60)	Control Group (n=60)	p-value
Age (years)	29.8 $\pm$ 4.2	30.1 $\pm$ 4.0	0.65
BMI (kg/m ²)	24.2 $\pm$ 2.8	23.9 $\pm$ 2.6	0.58
Duration of infertility (years)	3.1 $\pm$ 1.2	—	—
AMH (ng/mL)	2.1 $\pm$ 0.9	3.4 $\pm$ 1.0	<0.001

Baseline characteristics were comparable between groups except for AMH, which was significantly lower in the endometriosis group.

Table 2. Serum and Peritoneal IL-6 Levels

Parameter	Endometriosis Group	Control Group	p-value
Serum IL-6 (pg/mL)	12.8 $\pm$ 3.6	5.2 $\pm$ 2.1	<0.001
Peritoneal IL-6 (pg/mL)	28.4 $\pm$ 6.7	10.9 $\pm$ 4.2	<0.001

Both serum and peritoneal IL-6 levels were significantly elevated in women with endometriosis compared to controls.

Table 3. Fertility Outcomes

Outcome	Endometriosis Group	Control Group	p-value
Fertilization rate (%)	54.6 ± 12.5	72.1 ± 10.4	<0.001
Good quality embryos (%)	48.3 ± 11.8	70.6 ± 12.2	<0.001
Implantation rate (%)	21.7 ± 8.2	41.9 ± 9.5	<0.001

Women with elevated IL-6 levels exhibited significantly lower fertilization, embryo quality, and implantation rates compared with healthy fertile controls.

Discussion

The findings of this study establish IL-6 as a significant mediator of endometriosis-associated infertility. Elevated levels in both serum and peritoneal fluid correlated strongly with diminished ovarian reserve, reduced oocyte quality, and impaired implantation outcomes. These results reinforce the central role of chronic inflammation in reproductive dysfunction in women with endometriosis.¹¹⁻¹³

The increased IL-6 concentrations observed highlight the immunological dysregulation characteristic of endometriosis. Chronic cytokine exposure may alter ovarian follicular environments, leading to oxidative stress and compromised oocyte maturation. Such changes could explain the significantly lower fertilization and embryo quality rates observed in this study's affected cohort.¹⁴⁻¹⁷

Furthermore, the reduced implantation rate observed in women with endometriosis underscores the impact of IL-6 on endometrial receptivity. The cytokine likely interferes with implantation-related molecular pathways, further compounding infertility. These findings parallel recent immunological models suggesting that abnormal cytokine signaling is a primary driver of defective embryo–endometrium interaction.¹⁸⁻²⁰

Another notable observation was the significantly reduced AMH levels in the endometriosis group, indicating compromised ovarian reserve. The correlation between IL-6 levels and ovarian reserve

markers suggests that inflammatory cytokines may contribute to accelerated follicular depletion in chronic endometriosis.

The clinical implications of this study are considerable. Measurement of IL-6 could be adopted as a diagnostic marker to predict reproductive outcomes in women with endometriosis. Additionally, interventions targeting IL-6 signaling may enhance fertility prospects, particularly in assisted reproduction settings. Biologic agents designed to neutralize IL-6 have shown efficacy in autoimmune disorders and may be repurposed for gynecological applications.

However, therapeutic modulation of IL-6 must be carefully balanced against potential immunosuppressive effects. Long-term studies are required to determine whether reproductive outcomes can be improved without compromising systemic immunity. Additionally, multicenter trials with larger cohorts are warranted to validate these findings and establish standardized thresholds for IL-6 measurement in clinical practice.

Overall, this study provides strong experimental evidence linking IL-6 to impaired fertility outcomes in endometriosis. The findings underscore the necessity of integrating immunological perspectives into the clinical management of infertility in affected women.

Conclusion

IL-6 plays a pivotal role in the pathogenesis of chronic endometriosis and directly contributes to infertility through impaired ovarian reserve, poor oocyte quality, and reduced implantation. This study highlights the potential of IL-6 as both a biomarker and a therapeutic target, filling a crucial gap in understanding endometriosis-associated infertility and paving the way for novel immunomodulatory interventions.

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