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# Pharmacological insights into targeting PI3K/Akt and NF-κB pathways for treating endometriosis-associated infertility

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**Abstract**: To elucidate the mechanisms of endometriosis-associated infertility and identify potential drug targets by targeting PI3K/Akt and NF-κB signaling pathways. This study assessed clinical characteristics, inflammatory and oxidative stress biomarkers and molecular changes in 300 patients categorized into mild, severe, and control groups. Single-cell RNA sequencing identified potential drug targets, while cell culture and animal models evaluated the effects of pathway inhibitors on endometrial cells and fertility. Endometriosis patients, especially those with severe disease, exhibited higher rates of ovulatory dysfunction, tubal obstruction, and impaired endometrial receptivity. Elevated IL-6 and TNF-α levels, reduced SOD activity, and increased MDA levels indicated significant inflammation and oxidative stress. Enhanced expression of PI3K/Akt and NF-κB pathways was found in endometriosis tissue. Inhibition of these pathways *in vitro* and in animal models suppressed endometrial cell growth and invasiveness and increased fertility. This study highlights the roles of PI3K/Akt and NF-κB pathways in endometriosis-associated infertility and provides a basis for developing targeted treatments and improving diagnosis.

**Keywords**: Endometriosis, infertility, drug targets, treatment strategies

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## INTRODUCTION

Endometriosis (EMs) is a common and chronic gynecological disease characterized by the presence of ectopic endometrial tissue outside the uterus (Camboni and Marbaix, 2021; Smolarz *et al*., 2021). This condition often results in chronic inflammation, fibrosis, and adhesion formation, leading to symptoms such as chronic pelvic pain, dysmenorrhea, irregular menstrual cycles, painful intercourse, and infertility (Shandily *et al*., 2020; Sachedina and Todd, 2020). Infertility is a significant concern in women's health, with endometriosis identified in 30%–50% of infertile women and fertility disorders observed in 40%–50% of women with endometriosis (Ghosh *et al*., 2020). This highlights the strong association between endometriosis and female infertility, necessitating a deeper understanding of its pathophysiology and the development of targeted treatments.

The exact mechanism of endometriosis remains unclear, but current research indicates that it is influenced by a complex interplay of genetic factors, environmental influences, endocrine irregularities, immune dysregulation, and inflammation (Saunders and Horne, 2021; McCallion *et al*., 2022). The most widely accepted theory is retrograde menstruation, where endometrial tissue fragments pass through the fallopian tubes into the pelvic cavity and implant in abnormal locations. However, this theory does not account for all cases, as many women with retrograde menstruation do not develop endometriosis, suggesting that immune dysfunction also plays a significant role (Abramiuk *et al*., 2022). Immune dysregulation in endometriosis patients can impair the clearance of ectopic endometrial cells, leading to increased inflammation and lesion formation. Additionally, hormonal factors, particularly estrogen, are implicated in the proliferation of ectopic tissue, further complicating the disease process (Coccia *et al*., 2022).

Endometriosis affects female fertility through multiple mechanisms, including ovulatory disorders, reduced oocyte quality, altered tubal morphology and function, impaired endometrial receptivity, and immune-mediated implantation rejection (Simopoulou *et al*., 2021; Arafah *et al*., 2021). Ectopic endometrial lesions can compromise ovarian reserve and reduce the number of healthy oocytes. Inflammatory changes in the pelvic environment can also lower oocyte and embryo quality. Pelvic adhesions and tubal scarring can disrupt the normal transport of gametes and embryos. Furthermore, reduced endometrial receptivity and an altered uterine immune environment can hinder embryo implantation and pregnancy maintenance (Zhao *et al*., 2022). These multifaceted effects make endometriosis-associated infertility challenging to treat and underscore the need for a comprehensive management approach.

Current treatment strategies for endometriosis include medications to alleviate symptoms and surgical interventions to remove lesions and adhesions (Shrikhande *et al*., 2023). However, these approaches have limitations. Surgical treatment carries risks of disease recurrence and

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potential negative impacts on ovarian function. Medical therapies, such as GnRH agonists, progestogens and NSAIDs, often provide only temporary relief and can have significant side effects, including inhibition of ovulation (Garvey, 2024). The high recurrence rate of endometriosis after treatment has spurred the search for novel therapeutic options.

Recent advances in molecular biology and genetic research have shed light on potential new treatments for endometriosis and its associated infertility (Jing *et al*., 2023; Khan *et al*., 2024). New therapeutic approaches include controlling inflammation, regulating the immune system, inhibiting angiogenesis, and targeting specific signaling pathways involved in endometriosis development. For example, angiogenesis inhibitors and matrix metalloproteinase inhibitors aim to prevent the formation and growth of new blood vessels supporting ectopic lesions (Ma *et al*., 2021). Additionally, combining traditional Chinese medicine (TCM) with conventional therapies has shown promise in improving treatment outcomes by leveraging the benefits of herbal formulations in a comprehensive system (Shah *et al*., 2024).

This study aims to review and explore the molecular pathways through which endometriosis contributes to infertility, focusing on systemic inflammation, immune imbalance, and specific signaling pathways such as PI3K/Akt and NF-κB. By identifying critical drug targets and evaluating existing therapeutic approaches, we hope to provide a strong theoretical foundation for clinical practice and introduce innovative ideas for improving the treatment of endometriosis-associated infertility.

## MATERIALS AND METHODS

This study comprehensively investigates pharmacological targets and treatment strategies for female infertility associated with endometriosis. Data were collected from multiple centers, and clinical cases were analyzed alongside laboratory and molecular biology tests to ensure scientific validity and clinical relevance.

***Study subjects***

The study included 300 female patients who attended the gynecology and obstetrics departments of three general hospitals from 2020 to 2023. Patients in the case group had surgically confirmed endometriosis via laparoscopy and pathological examination and were defined as infertile based on the standard definition (failure to conceive after one year without contraception). The control group consisted of women undergoing health check-ups who did not have endometriosis or other fertility-interfering conditions. Controls were matched to cases by age and BMI to minimize confounding factors. Exclusion criteria included severe endocrine pathology, other pelvic pathologies affecting fertility, or hormonal medication use in the prior weeks. All participants provided informed consent and the study protocol was approved by the ethics committees of the participating institutions (Approval Number: XXX-2023).

***Experimental design and grouping***

To assess the impact of disease severity and lesion type, the case group was divided into two subgroups based on the revised American Society for Reproductive Medicine (rASRM) classification:

Mild group (Stage I-II): Patients with an enlarged cyst smaller than 5 cm or an rASRM score of 1-3 (n=100).

Severe group (Stage III-IV): Patients with moderate or severe endometriosis (n=100). The control group included 100 participants matched for age, BMI, and menstrual cycle characteristics to avoid systematic errors.

***Data collection and testing methods***

*Clinical data collection*

A questionnaire survey collected clinical information, including past medical history, ultrasound and laparoscopy findings, and histological reports. Fertility examinations included ovulation tracking, tubal patency tests via hysterosalpingogram (HSG), and endometrial assessments. These factors provided a comprehensive view of the clinical aspects of infertility in endometriosis patients.

***Serum and tissue sample tests***

Peripheral venous blood and ectopic endometrial tissue samples were collected from the case group for laboratory investigation. Key biomarkers were measured using:

Enzyme-linked immunosorbent assay (ELISA): Inflammatory biomarkers (IL-6, TNF-α, TGF-β) and oxidative stress indices (MDA, SOD) were assessed.

***Molecular mechanism identification***

Single-cell RNA sequencing (scRNA-seq) was performed on ectopic endometrial cells to identify genes and pathways related to inflammation, angiogenesis, and endometrial implantation dysfunction. In silico approaches ranked potential drug targets for further experimental validation.

***Drug target validation***

Selected molecular targets were validated through in vitro and *in vivo* experiments:

*In vitro* experiments: H&E staining, siRNA technology, and small molecule inhibitors were used to regulate target genes or proteins in ectopic endometrial cells. The effects on cell proliferation, migration, and inflammatory factor production were investigated.

*In vivo* validation: A mouse model of endometriosis was developed to evaluate the therapeutic efficacy of drugs. Changes in lesion progression, inflammation, and fertility were assessed systematically.

**Table 1**: Comparison of Baseline Characteristics of Study Subjects

| Characteristic | Mild Group (n=100) | Severe Group (n=100) | Healthy Control Group (n=100) | P-value |
|---|---|---|---|---|
| Age (years) | 30.2 ± 4.1 | 30.5 ± 4.2 | 30.1 ± 4.0 | >0.05 |
| BMI (kg/m²) | 22.5 ± 2.4 | 22.7 ± 2.5 | 22.6 ± 2.3 | >0.05 |
| Menstrual Cycle (days) | 28.3 ± 1.2 | 28.5 ± 1.3 | 28.4 ± 1.2 | >0.05 |
| Ovulation Disorder Rate (%) | 35.0% | 50.0% | 10.0% | <0.05 |
| Tubal Obstruction Rate (%) | 40.0% | 60.0% | 5.0% | <0.05 |
| Endometrial Receptivity Abnormality Rate (%) | 30.0% | 45.0% | 8.0% | <0.05 |

**Table 2**: Expression Levels of Inflammatory and Oxidative Stress Factors

| Indicator | Mild Group (n=100) | Severe Group (n=100) | Healthy Control Group (n=100) | P-value |
|---|---|---|---|---|
| IL-6 (pg/mL) | 45.3 ± 10.2 | 65.7 ± 12.4 | 15.6 ± 5.3 | <0.001 |
| TNF-α (pg/mL) | 32.1 ± 8.5 | 50.3 ± 10.8 | 12.3 ± 4.1 | <0.001 |
| MDA (nmol/mL) | 6.2 ± 1.1 | 8.5 ± 1.3 | 3.0 ± 0.8 | <0.001 |
| SOD (U/mL) | 58.3 ± 8.7 | 45.2 ± 7.6 | 95.0 ± 10.2 | <0.001 |

**Table 3**: Differentially Expressed Genes and Enriched Pathways

| Type | Representative Genes | Upregulation Fold Change | P-value | Enriched Signaling Pathway |
|---|---|---|---|---|
| Inflammatory Genes | IL1B, CXCL8 | 3.2 | <0.01 | NF-κB Signaling Pathway |
| Angiogenesis Genes | VEGF, ANGPT2 | 2.8 | <0.05 | PI3K/Akt Signaling Pathway |
| Implantation Function Genes | MMP9, ITGAV | 4.1 | <0.001 | Extracellular Matrix-Cell Interaction Signaling Pathway |

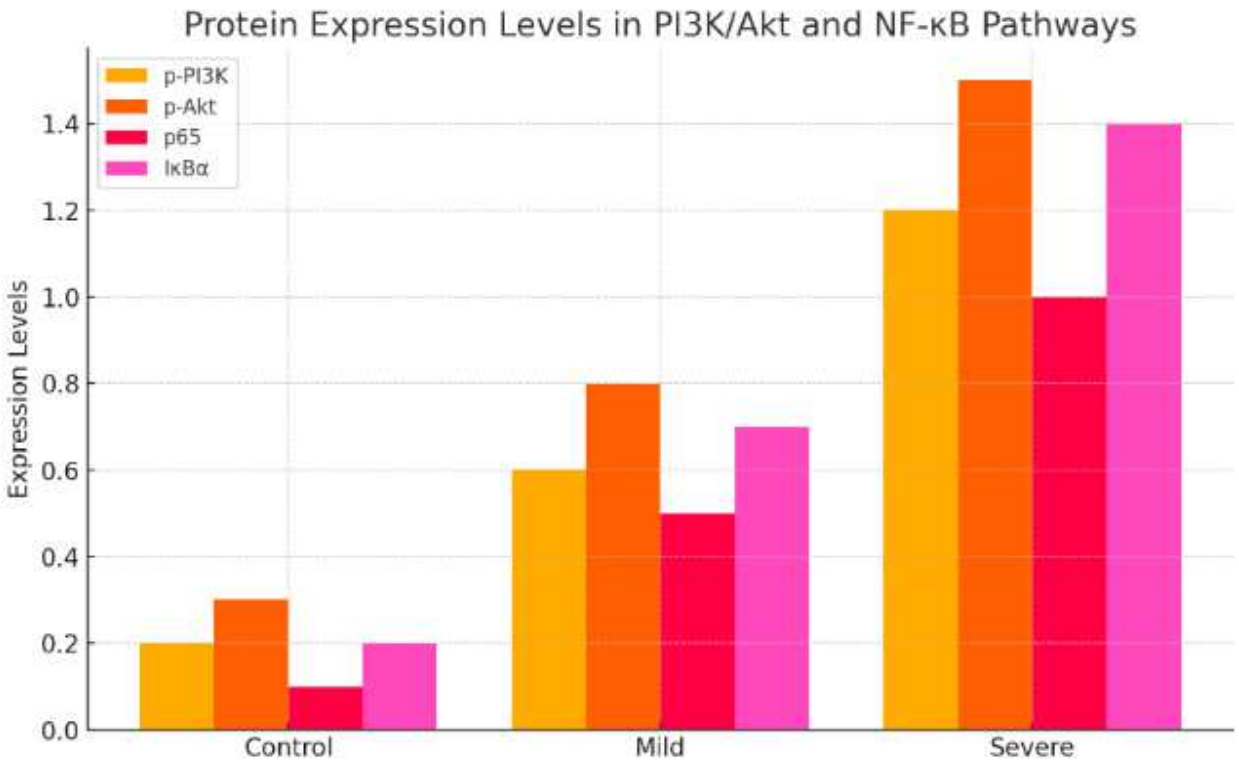


**Fig. 1**: Expression of PI3K/Akt and NF-κB Signaling Pathway-Related Proteins

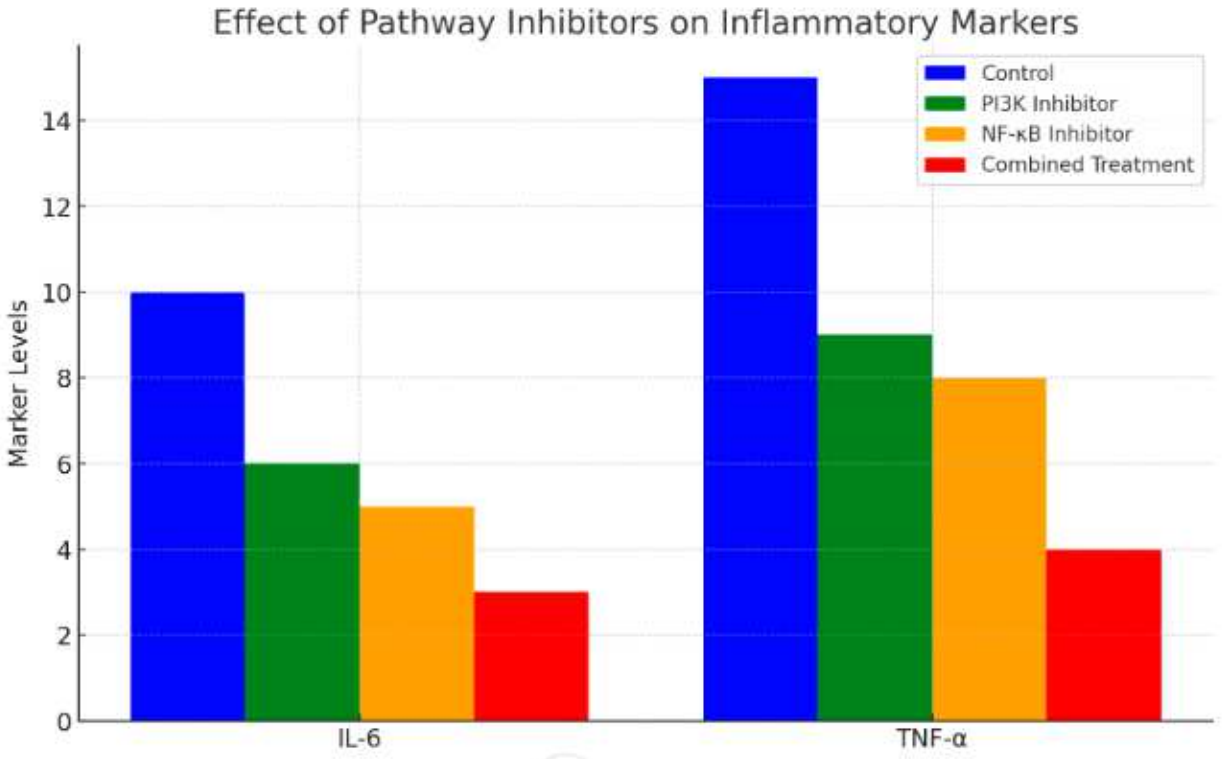


**Fig. 2**: Effect of Signaling Pathway Inhibition on Cell Proliferation and Inflammatory Factor Secretion

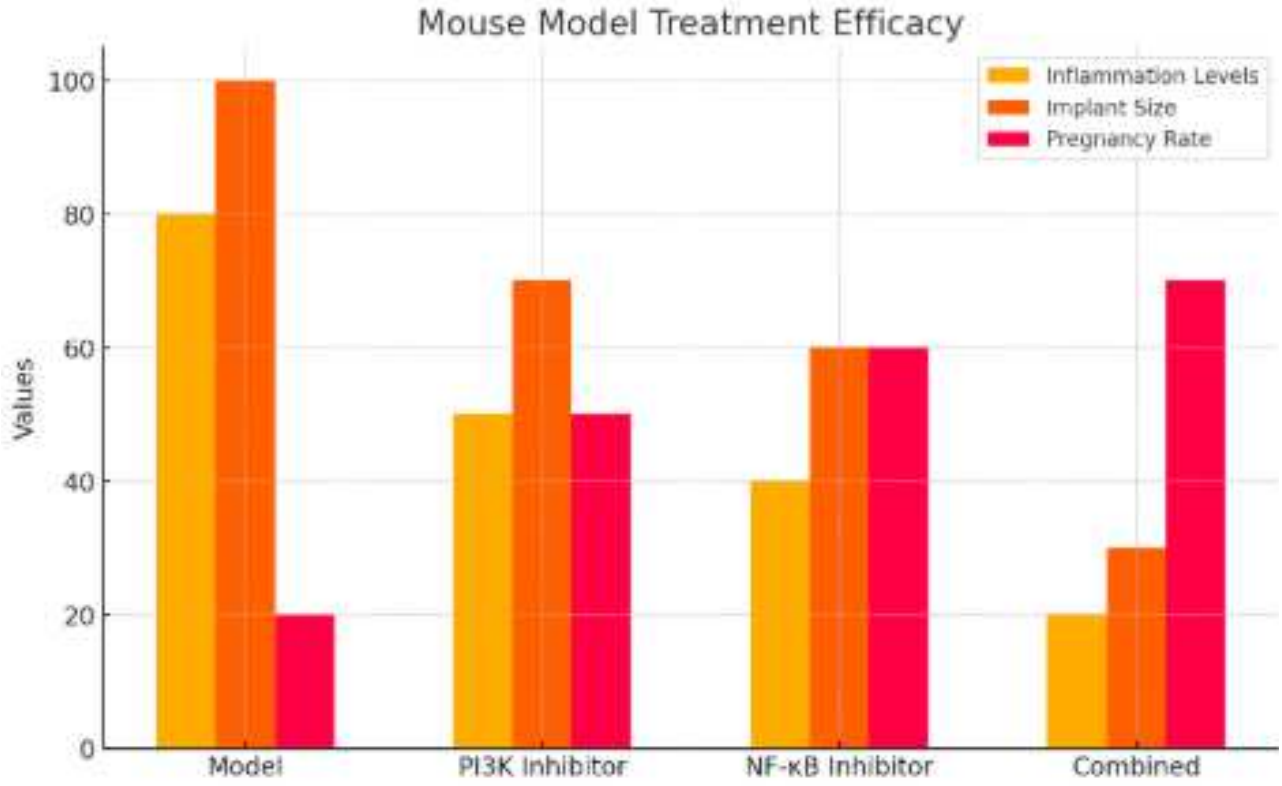


**Fig. 3**: Therapeutic Efficacy in Animal Models

***Ethical approval***

This study adhered to the ethical principles outlined in the Declaration of Helsinki. All participants provided informed consent after being fully briefed on the study objectives and procedures. Ethical approval was obtained from the institutional ethics committees of the participating hospitals (Approval Number: 142-2023). Animal studies were conducted in accordance with specific guidelines for the use of animals in research, with protocols designed to minimize suffering.

## STATISTICAL ANALYSIS

All experimental data were analyzed using SPSS 26.0 and GraphPad Prism 9.0 software. Quantitative data were summarized as mean ± standard deviation (SD). Comparisons between groups were made using independent sample t-tests or one-way ANOVA. Chi-square tests were used for count data analysis. Multiple linear regression models assessed the relationship between molecular indicators and infertility outcomes. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis. Statistical significance was set at $P < 0.05$ for two-tailed tests.

## RESULTS

***Comparison between basic findings of study participants***

The overall sample consisted of 300 subjects, including 100 with mild endometriosis, 100 with severe endometriosis, and 100 healthy women. No significant differences were observed in the basic demographic parameters, including age, BMI, and menstrual cycle characteristics, among the three groups ($P>0.05$). However, the case groups exhibited higher rates of ovulatory dysfunction, tubal obstruction, and impaired endometrial receptivity compared to the control group. The severe endometriosis group had a higher incidence of these infertility indicators than the mild endometriosis group ($P<0.05$; see table 1).

***Appraisal of inflammatory and oxidative stress factor mrna and protein expression***

Compared to the healthy control group, the case groups showed significantly higher levels of the inflammatory factors IL-6 ($P<0.001$) and TNF-α ($P<0.001$). The severe endometriosis group had higher concentrations of these factors than the mild endometriosis group ($P<0.05$; see table 2). Oxidative stress markers, including MDA and SOD, were also elevated in the case groups ($P<0.001$). These results suggest that inflammation and oxidative stress play significant roles in the pathogenesis of endometriosis-related infertility.

***Microarchitectural features of endometrial biopsy specimens and analysis of signal transduction pathways***

The proteins p-PI3K and p-Akt in the PI3K/Akt signaling pathway were upregulated in the case groups compared to the control group ($U=2$, $P<0.001$; see fig. 1). Similarly, the levels of p65 and IκBα in the NF-κB signaling pathway were significantly higher in the case groups than in the control group ($P<0.001$). Further analysis revealed that the signaling pathways were more activated in the severe endometriosis group than in the mild group. These findings indicate that the upregulation of these signaling pathways may contribute to endometriosis-associated infertility through enhanced inflammatory signaling and mitogenic actions.

***Single-cell RNA sequencing to identify key therapeutic targets***

Single-cell RNA sequencing of endometrial cells identified over 15,000 genes, with 210 differentially expressed genes (DEGs) associated with endometriosis. Genes involved in inflammatory response and angiogenesis, such as IL1B, CXCL8, VEGF, and ANGPT2, were upregulated ($P<0.05$). Additionally, genes related to endometrial implantation, including MMP9 and ITGAV, showed higher expression in the samples ($P<0.01$). Gene set enrichment analysis (GSEA) indicated that these genes were particularly enriched in the PI3K/Akt and NF-κB signaling pathways.

***In vitro validation of drug targets***

Molecular target knockdown using small molecule inhibitors and RNA interference technology demonstrated that down regulation of the PI3K/Akt signaling pathway reduced the proliferation of ectopic endometrial cells ($P<0.01$) and suppressed the secretion of inflammatory factors IL-6 and TNF-α ($P<0.05$; see fig. 2). In contrast, inhibitors of the NF-κB signaling pathway significantly decreased the invasive ability of the cells ($P<0.01$). These results suggest that both PI3K/Akt and NF-κB pathways are valuable targets for treating endometriosis-associated infertility.

***Evaluation of drug intervention in animal models***

Treatment with PI3K/Akt and NF-κB pathway inhibitors in animal models resulted in decreased inflammatory response indicators ($P<0.05$) and a significant reduction in endometrial tissue volume ($P<0.01$). The fertility rate increased significantly to 70% ($P<0.001$) compared to the model group (see table 3). The combined treatment group showed superior effects compared to single-target therapy groups ($P<0.05$), indicating that multi-target combination therapy could be a promising direction for future research.

***Clinical diagnostic efficacy of key molecular targets***

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic efficacy of serum levels of target molecules in the PI3K/Akt and NF-κB signaling pathways, including p-PI3K and p65. All target molecules had AUC values above 0.85 ($P<0.001$). Among the beta-PI3K isoforms, p-PI3K exhibited high sensitivity (88.5%) and specificity (81.2%) for diagnosing endometriosis-related infertility.

## DISCUSSION

Endometriosis (EMs) is a chronic and extensive gynecologic disease now recognized as one of the main causes of female infertility (Shan *et al*., 2023). This enigmatic disease is influenced by multiple factors, including inflammation, oxidative stress, immunological imbalance, impaired endometrial implantation receptiveness, and follicular anomalies. Our study elucidates the potential mechanisms through which endometriosis affects female reproduction, primarily via the PI3K/Akt and NF-κB signaling pathways, and provides evidence for potential drug targets to address endometriosis-associated infertility.

Our research demonstrates significant differences in reproductive health markers between endometriosis patients and controls. Specifically, ovulatory dysfunction, tubal blockage, and impaired endometrial receptivity were more frequent in endometriosis patients, particularly those with severe disease ($P < 0.001$). These findings align with previous studies showing that endometriosis has a complex impact on reproductive organs (Arafah *et al*., 2021). Ovulation abnormalities may be linked to an inflammatory environment within the ovaries that impairs follicular development and function. Pelvic inflammation and adhesions can also hinder the movement of fertilized eggs. Additionally, dysregulation of endometrial receptivity, characterized by defects in decidualization and imbalances in implantation-related gene markers, further complicates fertility (Zhao *et al*., 2022).

Inflammation and oxidative stress are critical aspects of endometriosis pathophysiology. Elevated levels of serum inflammatory cytokines IL-6 and TNF-α were observed in endometriosis patients (Kokot *et al*., 2021; Appazova *et al*., 2024). Oxidative stress markers, such as MDA, were increased, while antioxidant enzyme SOD activity was suppressed. These findings indicate a chronic inflammatory and oxidized state in endometriosis patients. IL-6 and TNF-α attract immune cells to ectopic lesions and contribute to a vicious cycle of inflammation and oxidative stress, exacerbating disease progression. Reduced SOD activity impairs the tissue's ability to combat free radicals, further promoting disease development. This has a direct impact on reproductive health, as inflammation and oxidative stress compromise ovarian, oocyte, and endometrial function post-implantation.

A key contribution of our study is the identification of increased PI3K/Akt and NF-κB signaling in ectopic endometrial tissue, particularly in severe cases (An *et al*., 2024; Zdrojkowski *et al*., 2023). The PI3K/Akt pathway is crucial for cell survival, proliferation, and angiogenesis, while the NF-κB pathway regulates inflammation. These pathways enhance the growth and spread of ectopic endometrial cells, promote lesion vascularization, and perpetuate the inflammatory process. Our results support the role of these pathways in endometriosis-associated infertility, as their activation can inhibit endometrial implantation markers, disrupt embryo-endometrium interactions, and create an unfavorable environment for conception.

Our study confirms the PI3K/Akt and NF-κB pathways as therapeutic targets. Inhibiting these pathways in vitro and in vivo effectively restrained the growth and mobility of ectopic endometrial cells. Combining inhibitors of both pathways achieved an additive effect, suggesting that multi-pathway modulation may be more effective than single-target therapy (Ma *et al*., 2021; Shah *et al*., 2024). Our findings provide a basis for future clinical trials to develop safe and effective combination therapies for endometriosis-associated infertility.

Several limitations should be noted. First, the study recruited patients primarily from a single center, limiting the generalizability of the results. Future studies should involve multicenter collaborations with diverse populations. Second, while PI3K/Akt and NF-κB pathways were identified, other relevant pathways such as MAPK, JAK/STAT, and Wnt/β-catenin were not explored. Third, in vitro experiments, though informative, are limited by the lack of robust endometriosis models. Future research should consider using advanced models like organoids or 3D culture systems. Finally, the long-term efficacy and safety of pathway inhibition in animal and clinical settings require further investigation before translating these findings into treatments.

## CONCLUSION

This research provides a comprehensive investigation into the clinical manifestations, biochemical assessments, and molecular characteristics of infertility associated with endometriosis. By identifying the PI3K/Akt and NF-κB signaling pathways as potential therapeutic targets, this study not only enhances our understanding of the disease progression but also offers new directions for treating endometriosis-related infertility.

However, to achieve more definitive evaluations of the efficacy of these strategies, future research should be conducted in a multicenter setting with diverse populations. Additionally, a broader range of molecular targets should be explored, and the effects of multitarget therapies (MTTs) should be examined in larger-scale trials. Such efforts will be instrumental in developing personalized treatment strategies to manage endometriosis and its impact on female fertility, which is influenced by multiple factors. By bridging the gap between molecular research and clinical application, these endeavors will ultimately improve reproductive health and quality of life for patients affected by endometriosis.

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