A COMPREHENSIVE ANALYSIS OF RISK FACTORS FOR RECURRENCE OF ENDOMETRIOD CYST AND FERTILITY-SAVING TREATMENT STRATEGIES

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Annotation: Endometrioid ovarian cysts are a common form of endometriosis, with recurrence rates of 12–30% within 2–5 years despite surgical treatment. Identifying factors associated with recurrence helps predict disease course and improve preventive strategies. This paper reviews current therapeutic approaches and evaluates the role of assisted reproductive technologies in preserving and restoring ovarian function.

Keywords: endometrioid cyst, recurrence, risk factors, ovarian reserve; infertility; in vitro fertilization; prevention .

Endometriosis is a common gynecological disease in women of reproductive and perimenopausal age, caused by the formation of ectopic endometrial tissue [1,2]. It affects up to 10% of women of reproductive age and is more frequent in women with infertility (30%) or chronic pelvic pain (45%) [2]. Endometrioid ovarian cysts are the most common manifestation of endometriosis and are found in 10–14% of women undergoing pelvic surgery. Recurrence rates after surgery range from 12–30% within 2–5 years and are higher in widespread or infiltrative forms of the disease [1]. Understanding the factors and course of endometriosis helps predict the risk of cyst recurrence and guide clinical management.

Patients with recurrent endometrioid cysts often have long-term infertility, miscarriages, therapeutic abortions, and other gynecological disorders, reflecting shared factors such as hyperestrogenism, progesterone resistance, and chronic inflammation [3,11]. Menstrual blood reflux into the abdominal cavity weakens immunity and promotes recurrence. Family history of benign or malignant tumors, especially maternal, indicates genetic predisposition [4]. Overexpression

of SF-1 and ER-β in endometrial stem cells enhances estradiol and COX-2-mediated PGE2 production, driving inflammation and cyst recurrence; ER-β also reduces progesterone receptor expression, contributing to resistance [5].

Diagnosis is challenging, with delays averaging 7 years and up to 30, reducing reproductive potential and sometimes leading to widespread extragenital disease [6]. Laparoscopy is standard, while tumor markers like CA-125 show high specificity but low sensitivity [6,7]. Hereditary predisposition is ~50% [8]. GWAS studies associate SNPs in WNT4, VEZT, ID4, NFE2L3, CDKN2BAS1, GREB1, IL1A, ETAA1, FN1, and RND3 with higher risk [8]. Suppression of tumor suppressors (CDKN2A/B, ARF) and activation of early developmental genes (HOXA, HOXB, WNT4) enable endometrial metaplasia and peritoneal implantation, while inflammation hyperactivates estrogen genes and disrupts progesterone signaling [7,8].

Immunological factors: Recent studies confirm that immune system dysfunction plays a key role in endometriosis development [9]. Patients show increased numbers of peritoneal macrophages with functional deficiencies, which normally recognize and lyse damaged tissues and ectopic endometrial cells. Higher macrophage content in lesions correlates with disease severity and macrophage reactivity in peritoneal fluid [8,9].

Activated macrophages produce TNF-α, IL-1β, IL-6, and IL-8, while VEGF, FGF, IGF-1, and TGF-β promote angiogenesis in the peritoneal fluid [7,9]. Leukocyte infiltration and inflammation, driven by prostaglandins, metalloproteinases, cytokines, and chemokines, are essential for endometriotic implant development [5].

Cytokines, produced by monocytes/macrophages, granulocytes, lymphocytes, fibroblasts, endothelial and stromal cells, regulate proliferation, differentiation, and immune responses [4]. Proinflammatory cytokines include IL-1, IL-2, IL-6, IL-8, IL-12b, IL-17, IL-18, IFN-α/β/γ, and TNF-α/β, while anti-inflammatory cytokines include IL-4, IL-10, IL-13, and TGF-β [7]. Changes in the balance

between pro- and anti-inflammatory cytokines favor implantation and survival of ectopic endometrial tissue [2].

Infectious and extragenital factors, and clinical course: Patients with recurrent ovarian endometriosis often have histories of chronic infections, such as tonsillitis, measles, or scarlet fever, which indirectly damage the reproductive system and predispose to metabolic disorders [10]. Extragenital pathology is more pronounced in these patients, including cardiovascular (17.3%), thyroid (16.3%), gastrointestinal (14.5%), hepatobiliary (14.5%), and CNS disorders (0.9%) [10]. Chronic gastrointestinal and hepatobiliary diseases can slow metabolism, impair immune responses, and promote hyperestrogenism, contributing to ovarian dyshormonal changes. Obesity and diabetes exacerbate insulin resistance and hyperinsulinemia, reducing sex hormone-binding globulin and increasing aromatase activity, thus promoting hyperestrogenism [7,10].

Clinically, recurrent endometrioid cysts show more severe symptoms: hyperpolymenorrhea (65.1%), dysmenorrhea (82.6%), and dyspareunia (82.6%), compared to non-recurrent cases (8.2%, 7.1%, 15.3%) [2,7]. Symptom severity correlates with vascular disorders, infiltrative endometriosis, and pelvic adhesions. Recurrence is often signaled by pain resumption and elevated CA-125 levels. Preoperative assessment using patient complaints, ultrasound with color Doppler mapping, and CA-125 can help predict morphological variants: glandular-cystic forms have higher CA-125 (~149.2) versus cystic forms (~26.5) [2,10].

Conservative treatment: Conservative therapy for endometriosis focuses on suppressing estrogen locally or systemically or acting hormonally on endometrioid lesions [8]. Common drugs include progestins (dienogest 2–4 mg), combined oral contraceptives (COCs), and GnRH agonists, which induce a hypoestrogenic state but are limited by side effects and rebound after discontinuation [8–11]. Analgesics like NSAIDs relieve pain but are generally ineffective for disease control [5].

Drug therapy alone fails in 11–24% of patients, and symptoms recur in 17–34% after stopping treatment [10,11]. Combining hormonal therapy with surgery is often most effective [11]. Postoperative hormonal therapy should consider reproductive plans [1]. GnRH agonists protect ovarian reserve, restore fertility, and may avoid radical surgery [14,15]. COCs should be used continuously to prevent estrogen peaks, and adjuncts like Diosmin may reduce hormone-dependent pain [1].

Surgical treatment of endometriomas: Surgical management of endometriomas is controversial. Women with endometriomas show a faster decline in serum AMH compared to healthy peers, highlighting the importance of early diagnosis and treatment to preserve ovarian reserve [5]. However, cystectomy may further reduce ovarian reserve, with AMH declining by 39.5% (unilateral) and 57% (bilateral) 9–12 months postoperatively [11].

Factors influencing AMH decline include preoperative AMH levels and bilaterality of the endometriomas [10]. Age appears less important. High baseline AMH may allow better postoperative reserve despite greater follicle loss. Recurrent or repeat surgeries are more damaging than primary cystectomy, significantly reducing antral follicle count in the re-operated ovary [2].

Conclusion. Recurrent ovarian endometriosis is a multifactorial disease driven by hormonal, genetic, immunological, and metabolic factors. Immune dysregulation and chronic inflammation support implantation and survival of ectopic tissue, while hyperestrogenism and obesity worsen disease progression. Conservative hormonal therapy can relieve symptoms and preserve fertility, but recurrence is common, and surgery may reduce ovarian reserve, particularly in bilateral or repeat cases. Optimal management requires early diagnosis and an individualized combination of medical and, when necessary, surgical treatment to balance symptom control and fertility preservation.

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