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Endometriosis: symptoms, diagnosis, and treatment

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***Abstract*---Background**: Endometriosis is a complex gynecological condition characterized by the presence of endometrial-like tissue outside the uterus, often leading to chronic pain and infertility. Its

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management requires a multidisciplinary approach that includes surgical and medical interventions. **Aim**: This article aims to review current clinical management practices for pain and infertility associated with endometriosis, focusing on surgical and hormonal treatments as well as pain management strategies. **Methods**: A comprehensive analysis of existing literature on endometriosis management was conducted, highlighting various therapeutic options, their efficacy, and considerations regarding surgical interventions. **Results**: Surgical techniques, such as excision of endometrial implants and nerve ablation, demonstrate success rates of 50% to 80% in alleviating symptoms. Hormonal treatments, including non-steroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptive pills (COCPs), progestins, and gonadotropin-releasing hormone agonists (GnRH), are first-line therapies for managing pain. In cases of infertility, surgical interventions can enhance the likelihood of natural conception. However, the recurrence of endometriosis remains a significant concern, occurring in 5% to 15% of patients even after comprehensive surgeries. **Conclusion**: Effective management of endometriosis-related pain and infertility necessitates a tailored approach, considering patient preferences, side effects, and the specific clinical scenario. While surgical interventions can significantly improve symptoms and fertility outcomes, careful evaluation of risks, particularly regarding ovarian function, is essential. Future research should focus on developing less invasive diagnostic and therapeutic options to improve patient care.

***Keywords*---**Endometriosis, pain management, infertility, surgical treatment, hormonal therapy, multidisciplinary approach.

Introduction

Endometriosis is characterized by the presence of lesions resembling endometrial glands and stroma located outside the uterus [1]. These lesions can manifest as peritoneal lesions, superficial implants, ovarian cysts, or deep infiltrating disease [2]. While the precise etiology of endometriosis remains undetermined, various hypotheses have been proposed regarding the development of these lesions. One potential mechanism is retrograde menstruation, a process observed in the menstrual cycles of women and non-human primates, where the endometrial lining flows backward through the open fallopian tubes into the pelvic cavity. This backward flow, combined with possible hematogenous or lymphatic dissemination, may facilitate the deposition of endometrial tissue in ectopic locations. However, since retrograde menstruation occurs commonly (potentially universally among menstruating women) while endometriosis is comparatively rare, it suggests that additional factors—such as hormonal, inflammatory, or immunological conditions—may influence the implantation and persistence of lesions in the pelvic region [3–6]. Furthermore, endometriotic lesions might originate from Müllerian remnants that fail to differentiate or migrate appropriately during fetal development or from circulating blood cells that transdifferentiate into endometrial-like tissue [7–9]. The local microenvironment

also plays a crucial role in maintaining these endometriotic lesions. It is essential to note that while endometriotic lesions share antigenic similarities with eutopic endometrium, they do not equate to it. Endometriosis affects approximately 10%–15% of women of reproductive age [1] and is prevalent in 70% of women experiencing chronic pelvic pain [10]. Unfortunately, many women endure significant delays in diagnosis, leading to unnecessary suffering and diminished quality of life, with an average diagnostic delay of 6.7 years for those aged 18–45 [11]. As symptoms frequently begin in adolescence, prompt referral, diagnosis, and treatment could alleviate pain, hinder disease progression, and help preserve fertility [12–14]. Barriers to early diagnosis include the high costs associated with diagnosis and treatment for adolescents, as well as the presence of confounding symptoms such as cyclical and acyclical pain. Thus, the development of a non-invasive diagnostic tool for endometriosis could promote earlier identification and intervention, ultimately enhancing quality of life and safeguarding fertility.

Currently proposed immunologic, genetic, and serum markers for diagnosing endometriosis lack the requisite sensitivity and specificity to be effective as screening tests. This review will explore the epidemiology of endometriosis, alongside existing diagnostic tools and potential biomarkers, to improve clinical management and enhance the quality of life for both adult and adolescent patients. The clinical presentation of endometriosis varies among individuals, with patients commonly reporting symptoms such as intermenstrual bleeding, dysmenorrhea (painful periods), dyspareunia (painful intercourse), dyschezia (painful defecation), and dysuria (painful urination) [15]. Pelvic pain may manifest prior to menstruation. Notably, endometriosis can also be asymptomatic, often coming to medical attention only during infertility assessments. The American Society for Reproductive Medicine (ASRM) has established a classification system for endometriosis-related pain based on the morphology of peritoneal and pelvic implants, categorizing lesions into red, white, and black types, and requiring documentation of the percentage of involvement for each type. The pelvic examination should proceed in either a clockwise or counterclockwise manner, noting the number, size, and location of endometrial implants, plaques, endometriomas, and adhesions. Endometriosis affecting the bowel, urinary tract, fallopian tubes, vagina, cervix, skin, or other areas should be recorded according to ASRM guidelines. The stages of endometriosis, classified by ASRM, range from I to IV, reflecting minimal, mild, moderate, and severe disease based on point scores [16].

Epidemiology and Risk Factors

Multiple reproductive factors have been consistently linked to an increased risk of endometriosis, suggesting that hormonal fluctuations may significantly influence its development. For example, early onset of menarche [17, 18–21] and shorter menstrual cycle lengths [19, 20, 25–27] are associated with heightened risk, whereas higher parity [20, 22–24] and current oral contraceptive use [28] correlate with a decreased risk. Elevated levels of circulating estradiol and estrone, which promote both ectopic and eutopic endometrial tissue, are more common in women with early menarche and in nulliparous individuals. Although not a reproductive risk factor, body mass index (BMI) consistently shows an inverse relationship with endometriosis [17, 18–19, 21, 26, 30, 31, 38, 41, 42],

potentially reflecting hormonal differences between women of varying body weights.

The investigation of tubal ligation, parity, and oral contraceptive use in relation to endometriosis risk has encountered methodological challenges. Tubal ligation is thought to reduce endometriosis risk by obstructing retrograde menstruation from entering the pelvic cavity. However, interpreting the association is complex since endometriosis is often linked to infertility, and women opting for tubal ligation are generally more likely to be parous than the wider population [3]. Research on the relationship between oral contraceptive use and endometriosis risk yields mixed results; while most studies suggest a decreased risk for current users [28, 29], some indicate an increased risk for those who have previously used them. This discrepancy may arise from the use of oral contraceptives to alleviate endometriosis-related pain, potentially masking the underlying condition while the medication is being used. The relationship between smoking and endometriosis remains ambiguous. Although smoking adversely affects numerous health aspects, some studies suggest it may lower the risk of developing endometriosis [19, 26, 32], while others do not [24, 27, 31, 33]. Notably, in utero exposure to cigarette smoke has been associated with an 80% reduction in endometriosis risk, whereas passive exposure during childhood appears to increase risk [34–36]. The mechanism behind this remains unclear; however, it is known that circulating estrogen levels are lower in women who smoke [37], which could inhibit the growth and persistence of endometriotic tissue.

Similarly, the associations between alcohol and caffeine consumption and endometriosis risk are inconsistent and may vary based on fertility status. Among infertile women, several studies have linked higher intake of alcohol or caffeine to increased risk [39, 40]. The biological plausibility of this association is supported by findings that moderate alcohol consumption can elevate bioavailable estrogen levels. In contrast, studies not confined to infertile women have shown no significant relationship [21]. Other lifestyle factors and dietary habits that may influence endometriosis risk often relate to their anti-inflammatory properties. Physical activity and dietary intake of omega-3 fatty acids may lower levels of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and other inflammatory markers. The relationship between physical activity and endometriosis remains unclear [33], yet higher consumption of long-chain omega-3 fatty acids has been associated with a reduced risk of the condition. Despite advancements in understanding risk factors for endometriosis, research is hampered by the necessity of surgical diagnosis, typically confirmed laparoscopically, to ensure accurate identification of affected cases and appropriate controls (samples taken from the same population as the cases). Validation in large cohorts of women with laparoscopically confirmed endometriosis, along with appropriate control groups, is essential. Additionally, as reproductive and lifestyle factors evolve—such as shifts in contraceptive formulations and delayed childbearing—new cohorts of young women should be studied to assess how these changes impact endometriosis incidence and to explore potential novel risk factors. Ultimately, identifying a defined set of endometriosis risk factors could facilitate the screening of women and girls at heightened risk. Furthermore, these insights could illuminate the disease's etiology, potentially leading to significant progress in identifying screening biomarkers and treatment targets.

Diagnosis of Endometriosis

The preliminary diagnosis of endometriosis primarily relies on clinical history, as many women exhibit normal findings during physical examinations. Clinicians often assess for uterine or adnexal tenderness, a retroverted uterus, nodularity in the uterosacral ligament, and any pelvic masses. The most prevalent finding is tenderness upon palpation of the posterior fornix. However, pelvic pain can also indicate other conditions, such as pelvic adhesions, adenomyosis, and gastrointestinal or urologic disorders, underscoring the importance of differential diagnosis [7]. To rule out other potential causes of pelvic pain, appropriate diagnostic tests—such as urinalysis, Pap smears, pregnancy tests, and vaginal or endocervical swabs—should be performed.

Pelvic ultrasound is utilized to identify endometriomas, fibroids, and ovarian cysts. Transvaginal and transabdominal ultrasound can visualize pelvic masses, with transvaginal ultrasound providing better clarity for the endometrium and uterine cavity, as well as for detecting ovarian endometriotic cysts. However, it does not effectively rule out peritoneal endometriosis, adhesions, or deep infiltrating endometriosis. Occasionally, magnetic resonance imaging (MRI) or computed tomography (CT) scans may be conducted to further characterize pelvic masses. Despite these preliminary diagnostic approaches, laparoscopic inspection with histologic confirmation remains the gold standard for diagnosing endometriosis. While endometriotic lesions can be visualized through laparoscopy, there is often a poor correlation between clinical symptoms and the extent of disease burden. Given that laparoscopy is not feasible as a first-line diagnostic method, researchers are exploring non-invasive diagnostic tools to facilitate early diagnosis and potentially prevent or delay disease progression. Although various blood tests have been assessed, a dependable diagnostic test for endometriosis has yet to be established. Changes in analyte levels, proteins, microRNAs, and other markers indicative of a disease state could provide a foundation for identifying novel biomarkers. Altered levels of CA-125, cytokines, and angiogenic and growth factors have been observed in women with endometriosis compared to those without, yet none of these markers have proven sufficient as definitive clinical tools for diagnosis.

Biomarkers for the Diagnosis of Endometriosis

Current guidelines indicate that the histological examination of specimens obtained from suspicious areas during laparoscopic pelvic inspection is the definitive diagnostic standard for endometriosis. Nevertheless, laparoscopy may not be suitable for all women with suggestive histories and physical examination findings. As a result, efforts have been made to identify simple and reliable biomarkers for the early, non-invasive or semi-invasive diagnosis of the disease. Numerous studies have assessed the diagnostic potential of biomarkers for endometriosis, but no reliable biomarkers in endometrial tissue, menstrual or uterine fluids, or immunologic markers in blood or urine have been established for clinical use to date. Utilizing semi- or non-invasive diagnostic methods to analyze biomarkers in blood, urine, or menstrual fluid could help avoid surgical procedures and identify women with endometriosis who might benefit from surgery to enhance fertility and alleviate pain. Furthermore, early data regarding

the disease could inform treatment decisions and prevent progression, particularly in women with minimal to mild disease. The combination of these biomarkers may enhance sensitivity and specificity beyond that of any single marker. Additionally, advancements in stem cell, proteomic, and genomic research could uncover new reliable diagnostic biomarkers with heightened sensitivity for endometriosis.

Clinical Management Practices for Associated Pain and Infertility

The management of endometriosis necessitates a multidisciplinary approach, encompassing:

1. **Surgical Diagnosis and Debulking**: Surgical intervention is critical for diagnosing and reducing the disease burden. This can involve excision or removal of endometrial implants and other procedures aimed at alleviating symptoms.
2. **Hormonal Treatment**: Hormonal therapies are employed to suppress the disease and minimize the risk of recurrence and progression. The choice of medical treatments often depends on the side effect profile, cost, and personal preferences of the patient [41].
3. **Pain Management Strategies**: Effective pain management is essential and is often best provided through a pain center clinic that can develop individualized care plans, including pelvic therapy.

Symptomatic endometriosis can be effectively treated through both surgical and medical interventions. Non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose combined oral contraceptive pills (COCPs), such as those containing ethyl estradiol and progestins, are typically the first-line treatments. If patients do not respond to NSAIDs after three months, second-line treatments may be considered, which include progestins (oral, injectable, and intra-uterine), androgens, and gonadotropin-releasing hormone agonists (GnRH), all of which can alleviate moderate to severe endometriosis-related pain.

Surgical options include:

- **Excision or Removal of Endometrial Implants**: Directly addressing the lesions can provide relief from symptoms.
- **Ablation of Uterosacral Nerves**: Techniques such as endocoagulation, electrocautery, or laser treatment can help reduce pain.
- **Presacral Neurectomy**: This procedure targets specific nerve pathways to mitigate pain.
- **Hysterectomy with Bilateral Salpingo-Oophorectomy**: In severe cases, this may be necessary.

These surgical interventions generally have a success rate of 50% to 80% in reducing symptoms. However, recurrence rates for endometriosis remain significant, ranging from 5% to 15% even after extensive procedures such as hysterectomy and bilateral oophorectomy.

Surgical Considerations for Infertility

The primary advantage of surgical intervention in cases of infertility associated with endometriosis is to improve the likelihood of natural conception. Surgical procedures aimed at treating endometriosis-related pain or infertility have been

shown to increase spontaneous pregnancy rates post-operatively. However, caution is warranted when considering surgery for endometriomas, as such interventions can potentially compromise ovarian function and lead to the loss of ovarian tissue. Decisions regarding surgery should be made with careful consideration, particularly for women who:

- Are of advanced age
- Have bilateral disease
- Exhibit impaired ovarian reserve
- Have undergone previous surgeries for endometriomas
- Face long-term infertility issues linked to tubal or male factors

In these cases, the risks and benefits of surgical options should be thoroughly evaluated to optimize outcomes and preserve fertility.

Conclusion

The management of endometriosis necessitates a comprehensive and individualized approach, addressing both the physical symptoms and the psychological impact of the condition. Surgical intervention remains a cornerstone of treatment, offering significant benefits in alleviating pain and improving fertility outcomes. Techniques such as excision of endometrial implants, uterine nerve ablation, and, in severe cases, hysterectomy with bilateral salpingo-oophorectomy have shown success rates of 50% to 80%. However, the persistent recurrence of endometriosis poses challenges, with rates ranging from 5% to 15% even after extensive surgical procedures. Hormonal therapies serve as vital adjuncts to surgical management, helping to suppress disease progression and minimize symptom recurrence. First-line treatments like non-steroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptive pills (COCPs) are widely utilized, while second-line options, including progestins and gonadotropin-releasing hormone agonists (GnRH), are available for those who do not respond to initial therapies. This multifaceted approach not only targets pain but also aims to improve quality of life for women with endometriosis. Moreover, the decision to pursue surgical intervention for infertility associated with endometriosis requires careful deliberation, especially for women with advanced age, impaired ovarian reserve, or previous surgeries. While surgical management can enhance the chances of natural conception, it is crucial to weigh the potential risks, such as diminished ovarian function and the need for future fertility considerations. Future research should prioritize the development of non-invasive diagnostic tools and novel biomarkers that could facilitate earlier detection and intervention, potentially improving outcomes for women with minimal to mild disease. Ultimately, a holistic and patient-centered management strategy is essential in addressing the complex needs of those affected by endometriosis, ensuring that both pain relief and fertility preservation are achieved. Enhanced collaboration among healthcare providers will also be key to optimizing treatment protocols and improving the overall care for women suffering from this debilitating condition.

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الانتباذ البطاني الرحمي: الأعراض، التشخيص، والعلاج

الملخص:

الخلفية: الانتباذ البطاني الرحمي هو حالة نسائية معقدة تتميز بوجود أنسجة شبيهة بالبطانة الرحمية خارج الرحم، مما يؤدي غالباً إلى آلام مزمنة وعقم. يتطلب إدارته نهجاً متعدد التخصصات يشمل التدخلات الجراحية والطبية.

الهدف: يهدف هذا المقال إلى مراجعة الممارسات السريرية الحالية لإدارة الألم والعقم المرتبطين بالانتباذ البطاني الرحمي، مع التركيز على العلاجات الجراحية والهُرمونية وكذلك استراتيجيات إدارة الألم.

الطرق: تم إجراء تحليل شامل للأدبيات الموجودة حول إدارة الانتباذ البطاني الرحمي، مع تسليط الضوء على خيارات العلاج المختلفة، وفعاليتها، والاعتبارات المتعلقة بالتدخلات الجراحية.

النتائج: تُظهر التقنيات الجراحية، مثل استئصال الزرعات البطانية والكي العصبي، معدلات نجاح تتراوح بين 50% إلى 80% في تخفيف الأعراض. تعتبر العلاجات الهُرمونية، بما في ذلك الأدوية غير الستيرويدية المضادة للالتهابات(NSAIDs) ، وأقراص منع الحمل المركبة(COCPs) ، والبروجستينات، ومحفزات هرمون الإطلاق(GnRH) ، من العلاجات الأساسية لإدارة الألم. في حالات العقم، يمكن أن تُعزز التدخلات الجراحية احتمال الحمل الطبيعي. ومع ذلك، تظل عودة الانتباذ البطاني الرحمي مصدر قلق كبير، حيث تحدث في 5% إلى 15% من المرضى حتى بعد العمليات الجراحية الشاملة.

الاستنتاج: يتطلب الإدارة الفعالة للألم والعقم المرتبطين بالانتباذ البطاني الرحمي نهجاً مخصصاً، يأخذ في الاعتبار تفضيلات المريض، والآثار الجانبية، والسيناريو السريري المحدد. بينما يمكن أن تحسن التدخلات الجراحية الأعراض ونتائج الخصوبة بشكل كبير، فإن التقييم الدقيق للمخاطر، وخاصة فيما يتعلق بوظيفة المبيض، ضروري. يجب أن تركز الأبحاث المستقبلية على تطوير خيارات تشخيصية وعلاجية أقل غزواً لتحسين رعاية المرضى.

الكلمات المفتاحية : الانتباذ البطاني الرحمي، إدارة الألم، العقم، العلاج الجراحي، العلاج الهُرموني، نهج متعدد التخصصات.