**How to Cite**:
Albogamy, S. A., AlZaher, Mohammed A., Aljawad, Hussain M., Al Aloula, Ali S., Alazmiy, Barakat S., Bahaidarah, Fahad A., Alharbi, M. S., Aljehani, M. R., & Alamri, F. H. (2018). Endometriosis: causes, diagnosis, and treatment options-review article for healthcare providers. *International Journal of Health Sciences*, *2*(S1), 297–312.
https://sciencescholar.us/journal/index.php/ijhs/article/view/15234

# Endometriosis: causes, diagnosis, and treatment options-review article for healthcare providers

**Sahar Adi Albogamy**
KSA, National Guard Health Affairs

**Mohammed Abdullah AlZaher**
KSA, National Guard Health Affairs

**Hussain Mahdi Aljawad**
KSA, National Guard Health Affairs

**Ali Suliman Al Aloula**
KSA, National Guard Health Affairs

**Barakat Shumailan Alazmiy**
KSA, National Guard Health Affairs

**Fahad Abdulaziz Bahaidarah**
KSA, National Guard Health Affairs

**Mohammad Shabib Alharbi**
KSA, National Guard Health Affairs

**Mohammad Raja Aljehani**
KSA, National Guard Health Affairs

**Fouad Hamed Alamri**
KSA, National Guard Health Affairs

***Abstract*---Background:** Endometriosis is characterized by the presence of functional, estrogen-responsive endometrial-like tissue outside the uterine cavity, leading to chronic inflammation and significant impairment of quality of life. Its economic burden in the United States exceeds $49 billion, driven largely by healthcare costs and productivity losses for affected individuals. **Aim:** This review aims to provide healthcare providers with a comprehensive understanding

International Journal of Health Sciences E-ISSN 2550-696X © 2018.
***Corresponding email**: akk29337@gmail.com*
*Manuscript submitted: 01 Jan 2018, Manuscript revised: 09 Jan 2018, Accepted for publication: 15 Jan 2018*

of endometriosis, including its causes, epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment options. **Methods:** A review of current literature was conducted to gather information on the various aspects of endometriosis, including genetic, environmental, and epidemiological factors, along with its mechanisms of pain and subfertility. **Results:** Endometriosis affects approximately 6–10% of reproductive-aged women and is associated with risk factors such as early menarche and nulliparity. The condition presents with diverse symptoms, including dysmenorrhea and subfertility. Diagnosis is confirmed through surgical visualization and biopsy of lesions. The pathophysiology includes aberrant immune responses and hormonal dysregulation, contributing to chronic pain and infertility. **Conclusion:** Understanding the complexities of endometriosis is crucial for effective diagnosis and treatment. Given its multifactorial nature and significant impact on women's health, ongoing research is essential to improve treatment strategies and patient outcomes.

***Keywords*---**Endometriosis, chronic pain, subfertility, diagnosis, treatment options, epidemiology.

## Introduction

Endometriosis is identified by the existence of functional, estrogen-responsive endometrial-like glands and stroma located outside the uterine cavity. While the diagnosis does not necessitate the presence of clinical symptoms, many individuals experience endometriosis as a chronic inflammatory condition that profoundly impacts their quality of life. The economic burden of endometriosis in the United States is estimated to exceed $49 billion, with patients who undergo surgical intervention facing both higher direct and indirect costs, as well as productivity losses per individual that are double the associated healthcare expenses. [1] The most prevalent clinical manifestations include adnexal masses, infertility, and dysmenorrhea. Although the identification of ectopic endometrial tissue serves as the primary pathological characteristic, numerous molecular variations exist that distinguish endometriotic lesions from eutopic endometrium. These molecular differences complicate the advancement of novel pharmacological therapies and treatment modalities.

## Incidence and Epidemiologic Factors

This complex condition is shaped by an array of genetic, environmental, and epidemiological influences. It affects approximately 6–10% of women of reproductive age and has been observed in both premenarchal and postmenopausal populations. The average age for diagnosis is roughly 28 years. Certain conditions exhibit a higher concordance with endometriosis; for instance, it is found in 21–47% of women experiencing subfertility [2] and in 71–87% of those suffering from chronic pelvic pain [3]. Factors such as early onset of menarche, shorter menstrual cycle length, heavy menstrual flow, and nulliparity are linked to an elevated risk. Additional elements contributing to increased

prevalence include a low body mass index, alcohol consumption, and specific phenotypes like freckles and nevi. Conversely, physical exercise appears to offer a protective effect. The use of oral contraceptives is correlated with a reduced prevalence of endometriosis and potentially a lower incidence of endometriomas during the initial laparoscopy [4].

Endometriosis also demonstrates a significant familial tendency, with a first-degree relative affected by the disease increasing an individual's risk by 7 to 10 times. A meta-analysis of genome-wide association studies has identified common genetic variants across seven risk loci [5]. The genetic predisposition appears to escalate in tandem with the severity of the condition. The prolonged interval between the onset of symptoms and the definitive diagnosis of endometriosis typically spans 7–8 years. This delay can be partly attributed to the symptom overlap between endometriosis and other pain-related syndromes. Clinical diagnosis can be corroborated through surgical intervention involving direct visualization and tissue biopsy of observable lesions. Endometriosis likely lacks a singular unifying explanation that encompasses the diverse clinical manifestations associated with the disorder.

**Pathophysiology**

An endometriotic lesion exhibits a histological appearance akin to that of the endometrium, characterized by distinct endometrial glands and stroma. The etiology of endometriosis is often explained through the implantation of eutopic endometrium resulting from retrograde menstruation or the metaplasia of coelomic pluripotential mesothelial cells lining the peritoneum, which transforms into endometrial tissue at ectopic sites. The phenomenon that only a minority of women develop endometriosis from the widespread occurrence of retrograde menstruation is partially attributed to an intrinsic dysfunction within the peritoneal immune system. A third hypothesis, known as müllerianosis, aims to elucidate how endometriosis infiltrates the cul-de-sac and uterosacral ligaments. This theory posits that during fetal organogenesis, aberrantly located endometrial tissue, such as that found in the cul-de-sac, differentiates into endometriosis. Additionally, distant metastasis and the implantation of cells via hematogenous or lymphatic embolization can account for the presence of endometriosis in atypical locations. Importantly, none of these theories is mutually exclusive, and various phenotypes of the disease can coexist within the same individual. One significant challenge presented by implantation theories is that, despite ectopic endometriosis lesions histologically resembling eutopic endometrium, they do not exhibit similar physiological functionality. This discrepancy implies that the response of endometriosis lesions to medical treatment is likely to differ from that of eutopic endometrium.

A myriad of abnormal molecular processes in the eutopic endometrium leads to altered hormonal responses, changes in receptivity, and enhanced cellular survival and inflammation at ectopic sites. Interactions between ectopic lesions and the eutopic endometrium may affect gene expression within the endometrium. In endometriotic lesions, it is hypothesized that impaired methylation occurs in critical genes that regulate downstream progesterone and estrogen receptor expression. Combined with elevated aromatase expression in

the ectopic endometrium, this results in increased concentrations of local, more metabolically active estradiol. These alterations are summarized under the concept of progesterone resistance. The relative progesterone resistance observed in the endometrium may partially elucidate the dysregulation of genes vital for implantation [6]. In addition to the epigenetic modifications of specific genes, altered microRNA expression may further influence gene transcription and posttranslational modifications associated with cellular proliferation or survival regulation [7].

**Mechanism of Ovarian Cyst Development (Endometrioma)**

Endometriomas are ovarian cysts filled with "chocolate" fluid. It is believed that these endometriotic cysts originate from the ovarian surface, where superficial ovarian implants are frequently observed during laparoscopy. Adhesions linking the ovary to the pelvic sidewall may facilitate the invagination or entrapment of endometrial glands and stroma within the ovarian cortex, progressively leading to the formation of cystic lesions. An alternative theory regarding the development of endometriomas posits that the peritoneal mesothelium covering the ovary can undergo differentiation into endometrioid epithelium, thereby forming an invaginating cyst through a metaplastic process. Another hypothesis suggests that müllerian epithelium from the fallopian tubes or endometrium may implant on the ovarian surface, resulting in cyst formation. This notion is akin to the mechanisms observed in many surface epithelial tumors and is further supported by the recent correlation between ovarian cancer and tubal tissue. The formation of endometriomas is closely associated with ovulation; the use of cyclic oral contraceptives to inhibit ovulation has been shown to reduce the risk of endometrioma recurrence. Additionally, there may be a transference of endometriotic tissue into a hemorrhagic corpus luteum, which can evolve from a hemorrhagic corpus luteum into an endometrioma.

The inner surface of an endometrioma is lined with endometriotic tissue, which exhibits variable penetration into the surrounding fibrotic tissue. The average thickness of the cyst wall ranges from 1.2 to 1.6 mm, with endometriotic tissue covering approximately 60% of the inner surface of the cyst and penetrating to a depth of 1.5 mm [8]. This finding is particularly relevant when employing energy modalities to ablate endometriotic cysts, as opposed to excisional techniques. Distinctive characteristics of endometriomas include significant fibrosis and inflammation. Unlike other cysts, endometriomas are firmly adhered to the ovarian cortex and the underlying stroma. This adherence may account for some clinical manifestations that differ from those of epithelial tumors, such as the presence of pain and the surgical challenges encountered during excision, which can inadvertently lead to the removal of healthy ovarian tissue.

**Mechanism of Pain**

Chronic inflammation associated with endometriosis is marked by elevated levels of systemic and local pro-inflammatory cytokines and growth factors that significantly influence pain perception, including dyspareunia. Notable mediators include nerve growth factor and prostaglandin E2. Prolonged exposure to these inflammatory agents can result in peripheral sensitization, characterized by a

hyperalgesic state, central sensitization, and myofascial pain . Understanding central sensitization is crucial for addressing chronic pain effectively and can help prevent unnecessary repetitive surgical interventions. It is hypothesized that ongoing noxious stimulation, chronic inflammation, and nerve damage alter pain processing pathways, leading to central sensitization. Timely treatment of pain symptoms is essential to prevent this progression. Surgical procedures may inadvertently exacerbate central sensitization, with many patients reporting exacerbation of symptoms postoperatively. Recent findings indicate a correlation between altered brain chemistry in women with endometriosis and pain intensity.

**Mechanism of Subfertility**

Severe adhesive disease associated with advanced endometriosis is a well-recognized factor contributing to infertility. However, the role of minimal lesions, as observed during laparoscopy, in causing infertility remains contentious. There is ongoing debate regarding whether minimal endometriosis results in infertility distinct from idiopathic infertility.

The peritoneal environment in women with endometriosis may be detrimental, leading to increased sperm DNA damage and abnormalities in oocyte cytoskeleton structure. Women with mild endometriosis undergoing therapeutic donor insemination with azoospermic partners exhibit lower monthly fecundity rates compared to those without endometriosis. Nevertheless, implantation and clinical pregnancy rates were comparable between women with and without endometriosis in donor egg programs utilizing sibling oocytes. In a similar study employing sibling oocytes from the same donor, patients with endometriosis demonstrated lower implantation and pregnancy rates than their counterparts without the condition. The authors posited that an endometrial defect could account for these findings, a hypothesis supported by numerous studies indicating decreased expression of key implantation biomarkers. It is also challenging to determine whether reduced implantation rates may be attributed to coexisting undiagnosed adenomyosis.

Kitajima et al. contend that women with endometriomas experience accelerated follicular depletion due to enhanced granulosa cell activation, leading to dyssynchronous oocyte maturation and subsequent apoptosis. These women tend to have lower baseline levels of antimüllerian hormone (AMH) compared to unaffected individuals, with presurgical AMH levels in women with endometriomas being 45% lower than in those without endometriosis and 36% lower than in patients with only pelvic endometriosis. Other research has corroborated this effect on ovarian reserve, particularly in cases involving bilateral endometriomas. However, the independent association of deeply infiltrating endometriosis with infertility remains uncertain.

**Natural Course of Endometriosis**

It is essential not to presume that endometriosis is inherently progressive. The short-term natural trajectory of the disease has been evidenced in randomized studies, including a placebo-controlled group undergoing baseline diagnostic laparoscopy. In the pooled placebo cohort, comprising 162 patients, the disease

exhibited variability, with nearly equal proportions showing deterioration (31%), no change (31%), and improvement (38%). It remains unclear which lesions are prone to recurrence and whether such recurrences correlate with symptoms. Some recurrences may represent persistent disease that was not entirely addressed surgically. The natural course of recurring symptoms may not necessarily indicate the recurrence of endometriotic lesions. Given the high prevalence of recurrent symptoms and reoperations in women treated without suppressive postoperative medical therapy, it is likely that many will experience a progression of endometriosis rather than a resolution. The underlying mechanisms driving ongoing symptomatology are likely to be complex and multifactorial.

**Clinical Presentation and Diagnosis**

Women with endometriosis commonly present a range of symptoms, including dysmenorrhea, deep dyspareunia, dyschezia, chronic abdominopelvic pain, and subfertility. Each of these symptoms can significantly impact a woman's physical, mental, and socioemotional well-being. A thorough medical history should include any family history of endometriosis and previous surgeries that may increase the risk of local endometriosis, such as cesarean deliveries and myomectomies. In evaluating pelvic pain associated with endometriosis, clinicians should consider a broad differential diagnosis that encompasses potential contributors to the pain syndrome. This includes conditions such as pelvic inflammatory disease, adhesions, abdominal wall pain, irritable bowel syndrome, interstitial cystitis, myofascial pain, pelvic floor disorders, depression, and a history of sexual abuse.

Pain levels should be assessed using a visual analog scale (typically ranging from 0 to 10). Although there is a weak correlation between pain intensity and the severity of disease, deeply infiltrating endometriosis tends to correlate with heightened pain severity. Endometriotic implants often do not correlate well with subjective pain locations, except in cases of deeply infiltrating endometriosis. In patients with endometriomas, severe pain is frequently linked to the presence of deeply infiltrating disease rather than the cyst's size [17]. Consequently, surgical intervention for an endometrioma must also address any accompanying deeply infiltrating endometriosis to achieve optimal pain relief. The physical examination should be comprehensive, aiming to identify multiple pain sources such as nerve entrapment, myofascial pain, and pelvic floor disorders. During pelvic examination, indicators of advanced disease include tenderness or nodules in the cul de sac or uterosacral ligaments, tenderness in the adnexa, induration of the rectovaginal septum, and the presence of a fixed retroverted uterus.

At surgery, three phenotypes of endometriosis can be distinguished: endometriomas (ovarian cysts), superficial endometriotic implants (primarily found on the peritoneum), and deeply infiltrating endometriosis, which is defined as a nodule extending more than 5 mm beneath the peritoneum. When these lesions develop near the uterine ligaments or bowel, they can lead to a mass-like effect due to the proliferation of the indigenous smooth muscle of these structures, resulting in fibrosis that occupies the rectovaginal space. Ovarian disease can manifest superficially on the cortex but remains associated with inflammation and fibrosis. Imaging is frequently employed in the assessment of

chronic pelvic pain and can also provide valuable information in the preoperative evaluation of patients preparing for endometriosis surgery. The sensitivity of imaging modalities varies depending on the specific lesion phenotype (i.e., endometrioma, peritoneal disease, or deeply infiltrating endometriosis). For chronic pelvic pain, pelvic ultrasonography is the preferred method as it can identify other potential causes of pelvic pain, such as adenomyosis. Transvaginal ultrasonography demonstrates the highest sensitivity and specificity for detecting ovarian endometriomas. Characteristic ultrasonographic features include a unilocular cyst with homogeneous low-level echogenicity of the fluid (described as a ground glass appearance) and poor or mild vascular flow. If small papillae are observed, no flow should be detected in that region.

Assessing deeply infiltrating endometriosis through pelvic ultrasonography is more challenging. Accurate preoperative mapping of deeply infiltrating endometriosis enables more comprehensive counseling regarding surgical risks and potential requirements for bowel or bladder resection. The preoperative identification of deeply infiltrating endometriosis also facilitates the referral of patients to centers experienced in managing advanced disease, if necessary. The ultrasonographic evaluation for deeply infiltrating endometriosis should be dynamic; dense adhesions and cul de sac obliteration can be detected by moving the ovaries, uterus, or bowel during the examination. A recent consensus report has proposed standardized ultrasonographic terminology for deeply infiltrating endometriosis to enhance communication regarding disease extent [18]. Currently, there is no evidence indicating that preoperative imaging improves patient outcomes for endometriosis surgery.

This report outlines four ultrasonographic steps for evaluating the pelvis in cases suspected of endometriosis. The first step involves the traditional assessment of the uterus and adnexa for signs of adenomyosis or endometriomas. Adenomyosis is more prevalent in women with deep endometriosis lesions compared to those with superficial lesions. The second step utilizes the ultrasound probe to pinpoint specific tender areas that may indicate disease-specific sites warranting investigation during surgery. The third step assesses the cul de sac (pouch of Douglas) to identify the presence of deeply infiltrating disease or obliteration via the “sliding sign,” which involves applying pressure to the cervix with the probe to observe whether the anterior rectum moves freely across the vagina adjacent to the posterior cervix and upper uterus. The final step entails evaluating the anterior compartment (bladder) and posterior compartment for nodules. The posterior compartment includes the uterosacral ligaments, which are not visible via ultrasonography unless a nodule is present, as well as the rectovaginal septum, vaginal wall, and rectum. Introducing fluid contrast into the vagina or rectum can enhance the visualization of bowel or bladder involvement.

**Diagnostic Value and Surgical Approach**

The effectiveness of the ultrasound approach for diagnosing endometriosis heavily relies on the experience of the facility performing the examination, making it highly operator-dependent. In skilled centers, the sensitivity and specificity for detecting disease at the rectocervical or rectosigmoid regions exceed 95% [19]. However, the sensitivity for deeply infiltrating endometriosis overall is lower, at

around 80%, with the uterosacral ligaments showing a sensitivity of 75% [20]. Magnetic resonance imaging (MRI) also demonstrates high diagnostic accuracy, with sensitivities and specificities comparable to those of ultrasound for deep endometriosis in the uterosacral ligaments (85% and 88%), vaginal endometriosis (77% and 70%), and colorectal endometriosis (88% and 92%) [21]. When MRI is performed with an enema, it shows similar sensitivity and specificity to rectal water contrast transvaginal ultrasonography for diagnosing rectosigmoid endometriosis, both reported at over 90%. Thus, MRI is particularly beneficial when ultrasound findings are inconclusive, especially if surgery is being planned to excise deeply infiltrating endometriosis that may necessitate resection of the rectum or bladder.

Currently, there are no reliable diagnostic markers for clinical use. Research has focused on identifying molecular markers in eutopic endometrium and noncoding RNA in tissue and blood [7, 22]. A 2016 Cochrane review concluded that existing biomarkers could not be meaningfully evaluated and affirmed that laparoscopy remains the gold standard for diagnosis [23]. The CA 125 test lacks diagnostic accuracy and has limited usefulness in assessing chronic pelvic pain, as it may only be mildly elevated in women with endometriomas. Although a noninvasive diagnostic method for endometriosis would be beneficial in reducing the need for surgical diagnosis, no such test is currently available.

**Surgical Diagnosis**

Surgery continues to be a vital method for both diagnosing and treating endometriosis, permitting direct visual identification of the disease. It is highly recommended to perform excision followed by histological confirmation, given the low reliability of visual inspection alone. The typical histological features of endometriosis include endometrial glands, stroma, and hemosiderin-laden macrophages. Endometriosis staging follows the American Society for Reproductive Medicine (ASRM) system, which assigns scores to categorize minimal and mild disease (stages I and II) versus moderate and severe disease (stages III and IV) [24]. This model has its limitations in clinical applicability, particularly due to its weak correlation with quality-of-life measures. Originally developed to assess fertility, the ASRM staging score is now widely utilized to quantify disease burden and promote consistency in both research and patient care. Other surgical classification systems exist, such as the Enzian classification, which details the depth of deeply infiltrating endometriosis, and the Endometriosis Fertility Index, which predicts fertility outcomes based on surgical findings. The ovaries, pelvic peritoneum (including the broad ligament and cul de sac), and uterosacral ligaments are the most frequent sites for endometriosis. A systematic examination of the pelvis during surgery is crucial to avoid missing any lesions [25]. Documenting each area through photography can enhance communication with patients and other medical professionals.

**Medical Management**
**Medical Therapies for Endometriosis Pain**

Accurate clinical diagnosis is crucial since several organizations, including the American College of Obstetricians and Gynecologists and the American Society for

Reproductive Medicine, advocate for empirical treatment prior to a definitive surgical diagnosis [24, 26]. It is important to note that a positive response to empirical therapy does not confirm the diagnosis of endometriosis. There are a variety of medical treatments currently available for managing the symptoms of endometriosis. These treatments should be viewed as suppressive rather than curative, as they do not enhance fertility or eliminate endometriomas or deeply infiltrating disease. Given that the effectiveness of these medical options in alleviating symptoms is similar, the choice of the best regimen depends on various factors, including the patient's age, personal preferences, reproductive intentions, severity of pain, and the extent of the disease. Additional considerations include the cost of treatment, intended duration, potential treatment risks, side effects, and accessibility. The primary aim of medical management is to prevent recurrence and alleviate symptoms, thus minimizing the need for repeat surgeries or extending the interval between surgical interventions.

Endometriosis is a chronic condition that necessitates ongoing treatment; this vital educational point should be emphasized in conversations with patients both pre- and post-surgery. Patients may hope for a single surgical procedure that permanently removes endometriosis lesions and provides lasting pain relief. However, it is essential to maintain hormonal suppression following surgery for endometriosis. Without such suppression, pain symptoms are likely to recur, often swiftly, with a recurrence rate of 50% within five years [27]. Given that hormonal management is typically long-term, the ideal regimen should be effective, affordable, well-tolerated, and present minimal risk to the patient. For decades, conventional treatments for endometriosis have included nonsteroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptives, closely followed by gonadotropin-releasing hormone (GnRH) agonists and oral progestins. This approach has received endorsement from numerous professional organizations [24, 26]. Despite their widespread application, NSAIDs alone are generally not very effective in patients with endometriosis. A placebo-controlled, double-blind, randomized study has shown that combined oral contraceptives significantly improve dysmenorrhea and reduce the size of endometriomas larger than 3 cm compared to placebo [28]. The objective of hormonal treatments is to induce a local hypoestrogenic state by suppressing ovulation, and the resultant amenorrhea or hypomenorrhea decreases the conversion of arachidonic acid to prostaglandins during menses, which in turn alleviates dysmenorrhea and pelvic pain. Continuous administration of these therapies appears to be more effective in preventing the recurrence of dysmenorrhea, although it does not significantly impact noncyclic pelvic pain or dyspareunia [29]. No specific method of administration (oral, transdermal, or transvaginal) has been proven to provide superior pain relief. Breakthrough bleeding is generally manageable through a short treatment interruption, with regimens resuming within a week.

Progestin monotherapy has traditionally been preferred for women who do not respond to combined hormonal therapy, those who smoke and are over 35 years old, and women with increased risks for myocardial infarction, stroke, or thromboembolic events. Nevertheless, some experts argue that progestin-only treatments, such as the 19-nortestosterone derivatives norethindrone acetate and dienogest, may be more effective than combined oral contraceptives and could be

considered first-line options, especially for women with rectovaginal and extrapelvic endometriosis [30]. The rationale for using progestin monotherapy is its similar mechanism of action to combined therapies, inducing ovulation inhibition and amenorrhea while potentially avoiding some of the adverse estrogenic effects. Both norethindrone acetate and dienogest have demonstrated improvements in dysmenorrhea and pelvic pain symptoms comparable to those of combined oral contraceptives and GnRH agonists. Although dienogest is effective in managing endometriosis-related pain, it is not currently available in the United States as a standalone agent. In contrast, norethindrone acetate is more affordable and has received FDA approval for treating endometriosis. Additionally, comparative clinical trials have not shown superior outcomes for either norethindrone acetate or dienogest [31]. The dosage of norethindrone acetate can be adjusted from 5 to 15 mg daily based on individual needs. Regular monitoring of lipid profiles is advised when using higher doses over extended periods.

Progestin-only treatments can be delivered through oral, intrauterine, parenteral, or implantable routes, with breakthrough bleeding being the most common side effect across all methods. This side effect can often be mitigated by administering oral estrogen for a period of 7 to 14 days. Although not FDA-approved for this indication, the levonorgestrel-releasing intrauterine device has proven effective in reducing pain associated with endometriosis. Depot medroxyprogesterone acetate is an FDA-approved treatment for endometriosis and has been demonstrated to be as effective as GnRH agonists in a multicenter randomized study [32]; however, concerns about bone density loss with long-term use remain.

## Medical Management of Endometriosis Pain

### Importance of Accurate Diagnosis

Accurate clinical diagnosis is essential for effective management of endometriosis, as many medical organizations, including the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine, advocate for empiric therapy prior to definitive surgical diagnosis. However, a positive response to empiric therapy alone does not confirm the diagnosis of endometriosis [24, 26].

### Overview of Medical Therapies

Current medical treatments for endometriosis primarily aim to manage symptoms rather than provide a cure. Medical therapy is unlikely to improve fertility or resolve endometriomas or deeply infiltrating disease. Given that the effectiveness of available medical options for symptom relief is comparable, treatment selection should consider several factors, including patient age and preferences, reproductive goals, severity of pain and extent of disease, treatment costs and intended duration, and risks, side effects, and accessibility. The primary goal of medical management is to prevent recurrence and alleviate symptoms, thus reducing the need for repeat surgeries or extending the interval between surgeries.

**Chronic Nature of Endometriosis**

Endometriosis is a chronic condition requiring sustained treatment. Patients should be informed that a single operative procedure may not eliminate the need for ongoing hormonal suppression post-surgery. Studies indicate a recurrence risk of 50% within five years without hormonal intervention [27]. Consequently, the ideal medical regimen should be cost-effective, well-tolerated, and pose minimal risks.

**Conventional Treatments**

Traditional treatments for endometriosis include:

- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**: These are commonly used but may have limited effectiveness for endometriosis pain. A placebo-controlled, double-blind, randomized trial confirms improvement of dysmenorrhea and reduction in the size of endometriomas greater than 3 cm in women with endometriosis taking combined oral contraceptives compared with placebo [28].
- **Combined Oral Contraceptives (COCs)**: Evidence from randomized trials shows that COCs improve dysmenorrhea and reduce the size of larger endometriomas. Continuous administration is often more effective for reducing the recurrence of dysmenorrhea, though it may not significantly alleviate noncyclic pelvic pain or dyspareunia [29].

Progestin monotherapy has historically been favored in women who fail combined hormone therapy, smokers older than 35 years, and women with predisposing risk factors for myocardial infarction, stroke, or thrombolic events. Some authors suggest that progestin-only methods, such as the 19-nortestosterone derivatives norethindrone acetate and dienogest, may be superior to combined oral contraceptives and can be considered first-line, especially in women with rectovaginal and extrapelvic endometriosis [30]. The argument for progestin monotherapy is based on a similar combination of ovulation inhibition and amenorrhea, but with potentially fewer unfavorable estrogenic effects and equivalent improvements in dysmenorrhea and pelvic pain symptoms compared with combined oral contraceptives and GnRH agonists.

**Gonadotropin-Releasing Hormone (GnRH) Agonists**

Gonadotropin-releasing hormone agonists have been considered second or even third line as a result of higher cost, limited accessibility, patient preference for nonparenteral administration, and presence of hypoestrogenic side effects. They are effective in inhibiting ovarian steroidogenesis through central suppression of gonadotropin release. A Cochrane review from 2010 examined 41 studies and demonstrated that GnRH agonist treatment is superior to placebo and as effective as other combined and progestin-only regimens [33]. Furthermore, a randomized comparison of combined oral contraceptives with GnRH agonist therapy demonstrated that although both treatments were effective in reducing pain, the GnRH agonist group reported more significant improvements in dyspareunia [34]. GnRH agonist treatment alone has also been shown to be as effective as surgical management or combined treatment in a prospective randomized trial; however,

recurrence risk was lower with combined management [35]. Reductions in pain symptoms expected with GnRH agonist therapy range from 50% to 90%, and GnRH is considered particularly effective for the suppression of deeply infiltrating endometriosis and extrapelvic endometriosis.

Long-term GnRH agonist use leads to loss of bone density as well as increasingly bothersome hot flushes, vaginal dryness, headaches, and mood changes; therefore, GnRH agonist monotherapy should not extend beyond a duration of 6 months. Adverse effects can be mitigated by add-back therapy such as 5 mg norethindrone acetate daily or combined hormone treatment with estrogen and progestin, allowing longer treatment courses. Despite this, GnRH agonist use is not practical as a long-term strategy for the management of endometriosis. Calcium and vitamin D may also provide some bone protection, and add-back therapy can be initiated concomitantly with GnRH agonist treatment; there is no documented benefit in pain relief with a delayed start.

**Alternative Therapeutic Agents**

Danazol is an established and effective treatment for endometriosis; however, it is seldom used due to undesirable androgenic side effects. Aromatase inhibitors are successfully used in refractory cases to decrease endometriosis-associated pain. Aromatase inhibitors induce hypoestrogenemia by decreasing local enzymatic conversion of androgens to estrogens. Although the target is largely ovarian, aromatase inhibitors block aromatase activity within adipocytes as well as ectopic aromatase that provides self-sustaining estradiol within endometriotic lesions. Aromatase inhibitors are not FDA-approved, may induce bone loss, and must be combined with combined oral contraceptives, progestins, or GnRH agonists to avoid unwanted ovarian cyst development. Given the limitations of currently available treatments, new therapeutic options for endometriosis are desirable. Oral GnRH antagonists and selective progesterone receptor modulators have shown potential in investigational settings. The efficacy of oral daily GnRH antagonist therapy for endometriosis pain was established with a multicenter, double-blind, randomized, placebo-controlled phase 3 clinical trial; however, hypoestrogenic side effects were noted [36]. Improvements were most notable for dysmenorrhea rather than nonmenstrual pain or dyspareunia. Selective progesterone receptor modulators have been prospectively studied, but randomized placebo-controlled studies are lacking. Further opportunities for development include immunomodulators and antiangiogenic agents; however, these agents remain highly experimental in the setting of endometriosis treatment.

**Conclusion**

Endometriosis is a multifaceted condition with significant implications for women's health, encompassing a range of symptoms and affecting quality of life. The complexity of its pathophysiology, coupled with the variations in clinical presentation, presents challenges in both diagnosis and management. With an estimated prevalence of 6–10% among women of reproductive age, endometriosis is often associated with significant comorbidities, including chronic pelvic pain and infertility. The prolonged time to diagnosis, averaging 7–8 years, highlights

the need for increased awareness among healthcare providers regarding its symptoms and potential differential diagnoses. A thorough history and physical examination are paramount in identifying the condition, as symptoms such as dysmenorrhea, deep dyspareunia, and chronic pelvic pain can overlap with other disorders. The varied presentations necessitate a personalized approach to care that considers the patient's symptoms and their impact on daily life. Diagnosis typically relies on surgical intervention, where direct visualization and biopsy of lesions are performed. Understanding the underlying mechanisms of endometriosis, such as immune dysfunction, hormonal dysregulation, and neurogenic inflammation, is crucial in developing effective treatment strategies. Treatment options range from medical management, including hormonal therapies and pain relief medications, to surgical interventions aimed at excising endometriotic lesions. However, many patients continue to experience chronic pain and infertility despite these interventions, underscoring the importance of ongoing research to develop novel pharmacological therapies and comprehensive care approaches. In conclusion, endometriosis poses significant challenges for patients and healthcare providers alike. Continued research into its etiology, pathophysiology, and treatment options is essential for improving patient outcomes and enhancing the quality of life for those affected by this debilitating condition.

**References**


1. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod 2012;27:1292–9.
2. Balasch J, Creus M, Fábregues F, Carmona F, Ordi J, Martinez-Román S, et al. Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study. Hum Reprod 1996;11:387–91.
3. Carter JE. Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain. J Am Assoc Gynecol Laparosc 1994;2:43–7.
4. Kavoussi SK, Odenwald KC, As-Sanie S, Lebovic DI. Incidence of ovarian endometrioma among women with peritoneal endometriosis with and without a history of hormonal contraceptive use. Eur J Obstet Gynecol Reprod Biol 2017;215:220–3.
5. Rahmioglu N, Nyholt DR, Morris AP, Missmer SA, Montgomery GW, Zondervan KT. Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. Hum Reprod Update 2014;20:702–16.
6. Falcone T, Lebovic DI. Clinical management of endometriosis. Obstet Gynecol 2011;118:691–705.
7. Bulun SE, Monsivais D, Kakinuma T, Furukawa Y, Bernardi L, Pavone ME, et al. Molecular biology of endometriosis: from aromatase to genomic abnormalities. Semin Reprod Med 2015;33:220–4.
8. Nothnick WB, Falcone T, Joshi N, Fazleabas AT, Graham A. Serum miR-451a levels are significantly elevated in women with endometriosis and recapitulated in baboons (Papio anubis) with experimentally-induced disease. Reprod Sci 2017;24:1195–1202.

9. Muzii L, Bianchi A, Bellati F, Cristi E, Pernice M, Zullo M, et al. Histologic analysis of endometriomas: what the surgeon needs to know. Fertil Steril 2007;87:362–6.
10. Aredo JV, Heyrana KJ, Karp BI, Shah JP, Stratton P. Relating chronic pelvic pain and endometriosis to signs of sensitization and myofascial pain and dysfunction. Semin Reprod Med 2017;35:88–97.
11. As-Sanie S, Kim J, Schmidt-Wilcke T, Sundgren PC, Clauw DJ, Napadow V, et al. Functional connectivity is associated with altered brain chemistry in women with endometriosis-associated chronic pelvic pain. J Pain 2016;17:1–13.
12. Mansour G, Sharma RK, Agarwal A, Falcone T. Endometriosis-induced alterations in mouse metaphase II oocyte microtubules and chromosomal alignment: a possible cause of infertility. Fertil Steril 2010;94:1894–9.
13. Matorras R, Corcostegui B, Esteban J, Ramon O, Prieto B, Expósito A, et al. Fertility in women with minimal endometriosis compared with normal women was assessed by means of a donor insemination program in unstimulated cycles. Am J Obstet Gynecol 2010;203:345.e1–6.
14. Prapas Y, Goudakou M, Matalliotakis I, Kalogeraki A, Matalliotaki C, Panagiotidis Y, et al. History of endometriosis may adversely affect the outcome in menopausal recipients of sibling oocytes. Reprod Biomed Online 2012;25:543–8.
15. Kitajima M, Dolman MM, Donnez O, Masuzaki H, Soares M, Donnez J. Enhanced follicle recruitment and atresia in cortex derived from ovaries with endometrioma. Fertil Steril 2014;101:1031–7.
16. Goodman LR, Goldberg JM, Flyckt RL, Gupta M, Harwalker J, Falcone T. Effect of surgery on ovarian reserve in women with endometriomas, endometriosis and controls. Am J Obstet Gynecol 2016;215:589.e1–6.
17. Chapron C, Santulli P, de Ziegler D, Noel JC, Anaf V, Streuli I, et al. Ovarian endometrioma: severe pelvic pain is associated with deeply infiltrating endometriosis. Hum Reprod 2012;27:702–11.
18. Guerriero S, Condous G, van den Bosch T, Valentin L, Leone FP, Van Schoubroeck D, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol 2016;48:318–32.
19. Abrao MS, Gonçalves MO, Dias JA Jr, Podgaec S, Chamie LP, Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. Hum Reprod 2007;22:3092–7.
20. Bazot M, Malzy P, Cortez A, Roseau G, Amouyal P, Daraï E. Accuracy of transvaginal sonography and rectal endoscopic sonography in the diagnosis of deep infiltrating endometriosis. Ultrasound Obstet Gynecol 2007;30:994–1001.
21. Bazot M, Bornier C, Duberbnard G, Roseau G, Cortez A, Daraï E. Accuracy of magnetic resonance imaging and rectal endoscopic sonography for the prediction of location of deep pelvic endometriosis. Hum Reprod 2007;22:1457–63.
22. Ahn SH, Singh V, Tayade C. Biomarkers in endometriosis: challenges and opportunities. Fertil Steril 2017;107:523–32.

23. Nisenblat V, Prentice L, Bossuyt PM, Farquhar C, Hull ML, Johnson N. Combination of the non-invasive tests for the diagnosis of endometriosis. The Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD012281. DOI: 10.1002/14651858.CD012281.
24. Management of endometriosis. Practice Bulletin No. 114. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010;116:223–36.
25. Bedaiwy MA, Pope R, Henry D, Zanotti K, Mahajan S, Hurd W, et al. Standardization of laparoscopic pelvic examination: a proposal of a novel system. Minim Invasive Surg 2013;2013:153235.
26. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014;101:927–35.
27. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update 2009;15:441–61.
28. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril 2008;90:1583–8.
29. Muzii L, Di Tucci C, Achilli C, Di Donato V, Musella A, Palaia I, et al. Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and metaanalysis. Am J Obstet Gynecol 2016;214:203–11.
30. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril 2017;107:533–6.
31. Vercellini P, Bracco B, Mosconi P, Roberto A, Alberico D, Dhouha D, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril 2016;105:734–43.e3.
32. Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 2006;21:248–56.
33. Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. The Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008475. DOI: 10.1002/14651858.CD008475.pub2.
34. Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75–9.
35. Alkatout I, Mettler L, Beteta C, Hedderich J, Jonat W, Schollmeyer T, et al. Combined surgical and hormone therapy for endometriosis is the most effective treatment: prospective, randomized, controlled trial. J Minim Invasive Gynecol 2013;20:473–81.
36. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28–40.

**الملخص:**

**الخلفية :**يتميز انتباذ بطانة الرحم بوجود أنسجة تشبه بطانة الرحم الوظيفية المستجيبة للإستروجين خارج تجويف الرحم، مما يؤدي إلى التهاب مزمن وتأثير كبير على جودة الحياة. العبء الاقتصادي لهذه الحالة في الولايات المتحدة يتجاوز 49 مليار دولار، ويتأثر بشكل كبير بتكاليف الرعاية الصحية وفقدان الإنتاجية للأفراد المتأثرين.

**الهدف :**تهدف هذه المراجعة إلى تزويد مقدمي الرعاية الصحية بفهم شامل لانتباذ بطانة الرحم، بما في ذلك أسبابه، وعلم الأوبئة، والفيزيولوجيا المرضية، والعرض السريري، والتشخيص، وخيارات العلاج.

**الطرق :**تم إجراء مراجعة للأدبيات الحالية لجمع المعلومات حول الجوانب المختلفة لانتباذ بطانة الرحم، بما في ذلك العوامل الوراثية والبيئية والأوبئة، إلى جانب آلياته المتعلقة بالألم والعقم.

**النتائج :**يؤثر انتباذ بطانة الرحم على حوالي 6-10% من النساء في سن الإنجاب، ويرتبط بعوامل خطر مثل بدء الدورة الشهرية المبكرة والعقم. تظهر الحالة بأعراض متنوعة، بما في ذلك عسر الطمث والعقم. يتم تأكيد التشخيص من خلال التصوير الجراحي والخزعة من الآفات. تشمل الفيزيولوجيا المرضية استجابات مناعية شاذة واضطراب هرموني، مما يساهم في الألم المزمن والعقم.

**الخاتمة :**إن فهم تعقيدات انتباذ بطانة الرحم أمر بالغ الأهمية للتشخيص والعلاج الفعالين. نظرًا لطبيعتها متعددة العوامل وتأثيرها الكبير على صحة النساء، فإن البحث المستمر ضروري لتحسين استراتيجيات العلاج ونتائج المرضى.

**الكلمات المفتاحية :**انتباذ بطانة الرحم، الألم المزمن، العقم، التشخيص، خيارات العلاج، علم الأوبئة.