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Endometriosis as a cause of chronic pain and deterioration of women's quality of life - etiology, symptoms and treatment method

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ABSTRACT

Introduction, purpose

Endometriosis is a chronic inflammatory condition that primarily affects pelvic tissues, including the ovaries, and is the most common cause of chronic pelvic pain, significantly impacting the quality of life of women of reproductive age. It is currently estimated that up to 10% of women may be affected by this condition. However, diagnosing endometriosis is challenging and often delayed due to frequent misdiagnoses as well as the relatively common occurrence of asymptomatic cases. Several factors may contribute to the development of endometriosis, including anatomical, genetic, and immunological factors. Additionally, it is believed that diet and lifestyle may influence the course of the disease. It is important to remember that beyond reducing overall quality of life and causing chronic pain, endometriosis may also contribute to the development of depressive and anxiety disorders, making it an interdisciplinary health issue.

Materials and methods

A systematic literature review was conducted using the PubMed database to explore the current state of knowledge regarding endometriosis, with particular focus on its etiological factors, clinical manifestations, and treatment options.

Conclusions

Endometriosis remains a mystery and a challenge for modern medicine. There are various theories explaining the etiology of endometriosis; however, none of them is universal, nor do they fully account for the development of the disease in every case. In addition to medications and invasive treatment methods, one must not forget the beneficial impact of a proper diet and an active lifestyle on the progression of the disease and the alleviation of its burdensome symptoms. Patients struggling with this condition should be provided with comprehensive, interdisciplinary medical care.

Keywords: endometriosis, chronic pelvic pain, inflammation, women, laparoscopy

Introduction

Endometriosis is the most common cause of chronic pelvic pain in women of reproductive age and is closely associated with persistent episodes of ovulation, menstruation, and cyclical hormonal changes. It is a complex clinical syndrome characterized by an estrogen-dependent chronic inflammatory process that primarily affects pelvic tissues,

including the ovaries. **[1][2]** According to the classical definition, the hallmark of the disease is the presence of endometrial-like tissue outside the uterine cavity, most commonly found in the pelvic cavity but also potentially in the ovaries, fallopian tubes, sigmoid colon, appendix, upper abdomen, and other locations. **[3]** It is estimated that endometriosis currently affects 5–10% of women of reproductive age; however, accurately determining its prevalence is challenging due to delayed diagnosis, difficulties in obtaining a definitive diagnosis, and the relatively frequent occurrence of asymptomatic cases, which can lead to deterioration in patients' health over time. **[4]** The peak age of patients is estimated to fall between 25 and 45 years, and it usually takes 8 to 10 years to receive a diagnosis. **[5]** Stigmata of endometriosis include painful menstruation, dyspareunia, chronic pelvic pain, irregular uterine bleeding, dyschezia, and hematochezia. **[6]** However, a key source of stress related to endometriosis appears to be the potential threat to current or future fertility. Moreover, the symptoms that patients deal with daily can interfere with both daily life and professional functioning. Additionally, living with severe cyclical or constant pelvic pain—or the fear of its recurrence—often for decades, can also lead to anxiety and depression. **[7]** Significant individual and public health concerns associated with endometriosis highlight the importance of understanding its pathogenesis and pathophysiology in order to prevent it and to develop sensitive, non-surgical diagnostic tests, and most importantly, effective treatment methods.
In recent decades, substantial progress has been made in unraveling the mysteries of this disorder. **[8]**

What are the hypothetical causes of endometriosis development?

The etiology and pathogenesis of endometriosis remain unclear, and the condition continues to be a mystery to modern medicine. However, several theories attempt to explain the origin and causes of endometriosis, and understanding them can be helpful in choosing effective treatment and improving the quality of life for women suffering from this disease. One of the most well-known is the **retrograde menstruation theory**, also known as **Sampson's theory**. It was first described in 1925. The central idea is that menstrual blood containing endometrial cells flows backward through the patent fallopian tubes into the peritoneal cavity, where implantation of these cells may occur. **[9]** The development of these cells is then supported by **angiogenesis [10]**, which is possible thanks to angiogenic factors produced by activated peritoneal macrophages, such as the well-known **VEGF**. **[11]**
A limitation of Sampson's theory is that, while it explains ovarian or superficial peritoneal endometriosis well, it does not account for the presence of endometriosis outside the

peritoneal cavity. Moreover, several studies show that menstrual blood reflux may be physiological in women with patent fallopian tubes, and in most of them, despite retrograde menstruation, endometriosis does not develop. **[10]**

In 1927, the author of the previous theory – Sampson – suggested yet another pathogenic mechanism: the **metastatic endometriosis theory**. It assumes that small amounts of endometrial tissue can be spread through lymphatic vessels during menstruation. **[12]** A clear advantage of the benign metastasis theory is that, unlike the previous explanation, it can account for the presence of endometriosis in lymph nodes as well as in distant locations such as the lungs, given that lymphatic vessels can be found in nearly every organ. **[13]**

In 1924, **Robert Meyer** proposed the **coelomic metaplasia theory**. According to this theory, the original coelomic membrane undergoes metaplasia and forms endometrial stroma and glands. This theory is the most appropriate explanation for cases of endometriosis in men who have received high doses of estrogen during prostate cancer treatment, as well as in patients with Rokitansky–Küster–Hauser syndrome, who, due to congenital absence of the uterus and upper part of the vagina, do not have functional endometrial tissue. **[14]**
However, the process through which coelomic metaplasia occurs remains speculative. It is believed that steroid hormones or exogenous compounds may influence the differentiation of normal mesothelial cells into endometriotic cells. This theory helps explain the occurrence of endometriosis in men and in the aforementioned women who do not menstruate due to congenital conditions. Notably, an additional point supporting this theory is the prediction that endometriosis can be found anywhere mesothelium is present. The discovery of endometriotic lesions in the pleural cavity, diaphragm, brain, and several other organs lends credibility to the coelomic metaplasia theory. **[15]**

Among the branches of the metaplasia theory is the **embryonic rest theory**. According to this theory, remnants of embryonic cells originating from the Wolffian or Müllerian ducts may differentiate into endometriotic lesions. **[16]** Moreover, in the embryonic rest theory, transformation is not limited to occurring only in the mesothelium.**[17]**
The theory assumes that the spread of embryonic cells—more specifically, **primordial endometrial cells**—may occur during fetal embryogenesis as a result of changes in cellular differentiation or relocation of the Müllerian ducts. **[18]** In most cases, these cells can be found in the posterior part of the pelvic floor, where they remain inactive until puberty. With time, endometrial lesions begin to form, triggered by estrogen stimulation. **[16]**

Another theory considered helpful in explaining the causes of endometriosis is the **endometrial stem cell recruitment theory**. But what are these stem cells? They are a small population of multipotent cells characterized by high replicative potential, unlimited ability to self-renew, and the capacity to generate more differentiated cells. **[19]** Over the past few years, many studies have confirmed the presence of several stem cell populations, including epithelial, mesenchymal, and mixed populations. [**20]** To understand why stem cells are needed in the female uterus, it's important to note that they are primarily responsible for tissue remodeling, regeneration, and homeostasis, which are particularly vital during the menstrual cycle and the tissue changes it induces. A further element in the development of endometriosis linked to the presence of stem cells is their migration. Two previously discussed theories could help explain this mechanism: the first is the **retrograde menstruation theory [16]**, and the second is **abnormal cell migration during the organogenesis of the female reproductive tract**, which is associated with **aberrant expression of WNT and HOX genes**. **[20]** In addition, the passive entry of stem cells into angiolymphatic spaces during menstruation, and their subsequent movement through the circulation, is an important mechanism. **[21]**

When considered alongside the theories of cell migration, this mechanism helps to explain the full scope of the **stem cell recruitment theory** in the pathogenesis of endometriosis. A variation of the stem cell recruitment theory appears to be the bone marrow–derived stem cell theory, which suggests that stem cells from the bone marrow can integrate into the endometrium to regenerate tissue. **[20]** According to this concept, bone marrow cells, once released into circulation and transported via blood vessels, may become abnormally lodged in soft tissues instead of reaching the endometrium. This mislocalization can ultimately lead to the development of endometriosis. **[21]**

Another important topic undeniably linked to the development of endometriosis—and long recognized as a common phenomenon in patients with the disease—is **altered immune response**. It is believed that impaired immune surveillance may reduce the elimination of retrograde menstrual debris, allowing dysfunctional endometrial cells to survive within the uterine cavity. Additionally, it has been suggested that the **observed abnormal immune response** may promote the survival and growth of ectopic endometrial cells.
Women with endometriosis exhibit **increased concentrations of macrophages in the peritoneal fluid**, which normally play a role in recognizing foreign or damaged cells within

the peritoneal cavity. Once identified, these cells are processed by macrophages and presented to T lymphocytes. However, in patients with endometriosis, peritoneal macrophages exhibit impaired function and are induced to release growth factors and cytokines, which may promote the survival of ectopic endometrial cells. Similarly, altered cytokine production by helper T cells may modify the composition of the peritoneal fluid, thus creating a favorable environment for the ectopic proliferation of endometrial tissue. It is well known that the regulation and activation of macrophages and lymphocytes depends on a delicate balance of cytokine expression, which is disrupted in endometriosis. **[22] [23]**

A significant approach to studying the **biological pathways involved in the development of endometriosis** is through the examination of genetic variants contributing to the disease. Endometriosis is considered hereditary due to findings showing a significantly higher incidence among first-degree relatives of women affected by the disease. The role of genetic factors in the development of endometriosis is supported by numerous studies. Research on monozygotic twins revealed that endometriosis was present simultaneously in 14 out of 16 twin pairs, and further twin studies confirmed a greater likelihood of the condition occurring among close relatives. **[24] [25]** Pedigree studies have identified genomic regions likely to contain variants associated with familial endometriosis—broad regions that include multiple potentially relevant genes. However, these regions require further investigation to clarify the specific susceptibility variants involved. One study conducted in England and Australia, which examined chromosomal linkage in sister pairs with endometriosis, showed a significant association with **chromosomal region 10q26 [26]**, while more recent research identified **region 7p15.2** as significantly linked to the disease **[26]**. Unfortunately, the exact genes responsible for the hereditary nature of endometriosis have not yet been identified.

Although current epidemiological data on endometriosis is fairly limited, some studies suggest that **lifestyle and dietary factors** may influence the development of the disease. A diet rich in fruits and vegetables, combined with a reduction in meat products, is believed to be protective against endometriosis. It is also worth noting the roles of parity and nutritional status in the pathogenesis of the disease. Specifically, women with few or no children, and those with a low body mass index (BMI), appear to be at higher risk of developing endometriosis. **[27] [28]**

Other lifestyle factors that may disrupt normal physiological functions and thus increase the risk of endometriosis include: **lack of physical activity**, **tobacco smoking**, and **alcohol**

consumption. Physical activity is thought to lower the risk of endometriosis, as it reduces menstrual bleeding and helps normalize estrogen balance. Tobacco smoking, in turn, increases the expression of pro-inflammatory mediators, disrupts the synthesis of prostaglandin E2 and natural steroids **[29]**, and this disturbance in steroidogenesis may contribute to increased estrogen synthesis and reduced progesterone production. **[30]**
As for alcohol consumption, it is important to note that this substance affects pituitary luteinizing hormone, and activates the enzyme aromatase, which leads to increased estrogen production and enhanced conversion of testosterone to estrogen. **[29] [30]**

How to diagnose endometriosis and what are the treatment methods?

Currently, the most accurate diagnostic method for endometriosis—often referred to as the "gold standard"—is laparoscopy, which allows for a detailed inspection of the abdominal cavity as well as histological analysis of suspicious lesions. Thanks to laparoscopy, microscopic changes can be detected in women both with visible endometriosis and without it. However, despite its effectiveness, laparoscopy is not an ideal method. It is expensive and invasive, which poses risks for patients undergoing the procedure. Like any surgical intervention, it can increase the risk of bleeding and infection. Therefore, other methods with various advantages are also currently used, such as imaging techniques and, increasingly in recent years, biomarkers. **[31]**

Imaging methods such as transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) are appropriate for diagnosing two phenotypes of endometriosis: deep infiltrating endometriosis, which may occur in the rectosigmoid ligaments, uterosacral ligaments, and rectovaginal septum; and endometriomas, which are cysts formed when endometrial tissue implants in the ovaries—here, TVUS is the first-choice method. Additionally, lesions in the sigmoid colon, ileum, and urinary system can be detected using complementary imaging techniques such as transrectal ultrasound, multidetector computed tomography (MDCT), or MRI. Another interesting test is scintigraphy, which can be used to examine kidney function in cases of suspected ureteral endometriosis. Although ultrasound and MRI show high sensitivity (91%) and specificity (98%) in detecting and ruling out endometrial lesions—especially deep ones—they are not recommended for identifying peritoneal lesions, mainly because such lesions are often smaller than the detection threshold of the imaging equipment. **[32]**
Undoubtedly, one of the major goals for researchers and science is to find a minimally

invasive method for diagnosing endometriosis. Blood, endometrial tissue, and urine biomarkers appear to be a promising solution. Although they may be used as diagnostic markers, they do not provide information about the location of endometrial lesions. A widely used biomarker is CA-125; however, although it is usually elevated in women with endometriosis, it can also be elevated in other medical conditions and thus has no value as a single diagnostic test for the disease described in this article. **[31]**

The choice of endometriosis therapy depends on the severity of symptoms, extent and location of the disease, reproductive plans, and the patient's age. Still, no fully effective treatment method has been found. Currently available therapies are divided into two types: pharmacological treatments, which aim primarily to inhibit the growth of endometrial implants, and surgical treatments, aimed at removing or destroying lesions. **[33]**

Hormonal therapy works by suppressing fluctuations in gonadotropin and ovarian hormones, resulting in the inhibition of ovulation and menstruation and a reduction in the inflammatory process. **[34]** Since endometriosis is an estrogen-dependent disease, current treatments focus on reducing circulating estrogen levels. First-line medications include combined oral contraceptives and progestins. They act by inhibiting ovulation and decidualization and reduce lesion size. Moreover, they offer several additional benefits that may be significant for patients with endometriosis: they are available in various dosing forms, alleviate pain symptoms in most patients (which are a major problem affecting daily life), are well tolerated, and are affordable. Despite these benefits, about ¼ of patients do not respond to treatment and may experience side effects such as breakthrough bleeding, breast tenderness, nausea, headaches, and mood swings. **[35][36]**

The second-line treatment for endometriosis is hypoestrogenic therapy using gonadotropin-releasing hormone (GnRH) agonists. This therapy is effective in women who do not respond to combined oral contraceptives or progestins. GnRH agonists work by inducing negative feedback in the pituitary gland, suppressing gonadotropin secretion, and consequently decreasing the synthesis of steroid hormones by the ovaries. A limitation of hypoestrogenic therapy is that these drugs cannot be taken orally due to destruction by digestive enzymes; therefore, parenteral administration—subcutaneous, intramuscular, or vaginal—is recommended. Side effects of GnRH agonists include vasomotor symptoms, mood instability, and genital tissue hypotrophy. **[35]**

Another strategy for treating endometriosis is hyperandrogenic therapy, using medications such as danazol or gestrinone. These drugs induce a pseudomenopausal state by inhibiting GnRH release, indirectly increasing androgen levels and decreasing estrogen levels by suppressing ovarian function, which contributes to the regression of endometrial implants. However, this class of drugs is not recommended for long-term use due to androgenic side effects caused by increased free testosterone, such as seborrhea, hirsutism, weight gain, and lipid disorders. **[37]**

A new class of drugs that can be used in the treatment of endometriosis is aromatase inhibitors (AIs), which are highly specific and act by inhibiting the P450 aromatase enzyme—the final enzyme in the estrogen biosynthesis pathway—ultimately halting local estrogen production. The use of these drugs not only reduces lesion size but also alleviates pelvic pain. However, in premenopausal women, AIs should be combined with other drug classes such as progestins, combined oral contraceptives, or GnRH agonists. The best outcomes with minimal side effects have been observed with combined oral contraceptives or progestins. **[38]**

Side effects of aromatase inhibitors include bone calcium loss (increasing the risk of osteoporosis), vaginal dryness, insomnia, vasomotor symptoms, nausea, and headaches. The most potent drugs in this class—anastrozole and letrozole—are administered orally and can reduce serum 17β-estradiol levels by nearly 99% within just one day of use. **[39]**

Another group of drugs used in the treatment of endometriosis is nonsteroidal anti-inflammatory drugs (NSAIDs), which are generally used in combination with all the other medications mentioned. It's important to note that NSAIDs do not affect ovulation but only help minimize symptoms and reduce the pain experienced by patients. Additionally, they are widely used for treating both chronic inflammation and primary dysmenorrhea. Patients using these medications should consider possible side effects such as gastric ulcers, cardiovascular events, and acute renal failure. **[31]**

In addition to the aforementioned classic medications used in the treatment of endometriosis, recent years have seen the emergence of new therapeutic methods which, alongside their beneficial effects, sometimes carry a lower risk of adverse effects.

The first of these drugs is **elagolix**—an orally administered GnRH antagonist which, unlike GnRH agonists, can partially suppress estradiol levels. This prevents the development of a

hypoestrogenic state and thereby reduces the side effects typically associated with estrogen suppression. Elagolix has proven effective in alleviating symptoms such as dysmenorrhea and pelvic pain, while also improving patients' quality of daily life. **[40]**

Another drug that may soon be used in endometriosis treatment is **resveratrol**. Why might it be effective? As is well known, one of the characteristics of endometriosis is elevated oxidative stress, which damages cells and affects the production of cytokines, angiogenic factors, iNOS, and COX. Resveratrol may induce the production of antioxidant enzymes, increasing the antioxidant capacity of tissues by up to 50%. In addition to that, it inhibits the expression of IL-6, IL-8, TNF-α, and COX-2, showing anti-inflammatory and anti-angiogenic effects by suppressing VEGF expression. Furthermore, resveratrol inhibits the production of reactive oxygen species by monocytes, macrophages, and lymphocytes, and reduces cell proliferation driven by NF-κB. Through inhibition of NF-κB, it also limits the epithelial–mesenchymal transition (EMT), which is essential for the formation of endometriotic lesions, via the PI3K/AKT/NF-κB pathway and regulation of genes involved in this process. **[41][42][43]**

Some plant-derived compounds may also exhibit anti-inflammatory and antioxidant properties, which seem to be crucial in the treatment of endometriosis. One such substance is **curcumin**, which can significantly reduce COX-2 expression, TNF-α and IL-6 production, and inhibit the epithelial–mesenchymal transition necessary for endometriosis development. **[44]** Moreover, curcumin can reduce cell proliferation, the size of endometrial lesions, and may lower the activity of matrix metalloproteinase-9 (MMP-9) as well as decrease VEGF expression, thereby demonstrating anti-angiogenic effects. **[45]**

In situations where symptoms persist or when the side effects of current medications outweigh the benefits, **surgical treatment** should be considered. Surgery is also recommended for patients with anatomical abnormalities of the pelvic organs, postoperative adhesions, bowel obstruction, or urinary tract obstruction. The standard procedure involves cauterization of endometriotic foci and reconstruction of pelvic anatomy. Excision of ectopic lesions often results in significant relief of pelvic pain and may also enhance fertility. The most radical surgical treatment is **hysterectomy**, with or without **oophorectomy**, depending on the patient's age. Hysterectomy combined with bilateral salpingo-oophorectomy and removal of all visible endometriotic lesions has a high success rate, with remission achieved in approximately 90% of cases. **[32]**

Conclusions

Endometriosis is a chronic inflammatory disorder predominantly affecting women of reproductive age. It remains a significant clinical challenge and an enigma in contemporary medicine, as, despite various hypotheses concerning its etiology, no singular, definitive cause has been established. Similarly, there is currently no therapeutic approach capable of fully resolving the condition or eliminating its associated symptoms. Diagnostic delays are common due to the nonspecific and often subtle clinical presentation, which may contribute to the progression of advanced pathological changes by the time of diagnosis.

Women affected by endometriosis require comprehensive, interdisciplinary medical management. In addition to persistent physical symptoms—particularly those exacerbated during menstruation—patients frequently encounter fertility issues. These reproductive challenges may further predispose individuals to mood disorders, including depression and anxiety, which often stem from both diminished self-worth and the psychological burden of chronic pain.

Disclosure

Authors do not report any disclosures.

Author's contributions

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