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Endometriosis – hormones and treatment

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Abstract

Endometriosis is a prevalent condition, affecting 10-15% of women of reproductive age and approximately 70% of those with chronic pelvic pain. An estimated 176 million women worldwide are affected by this disease. The condition occurs predominantly between menarche and menopause, with peak incidence between the ages of 25 and 45. Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity, leading to the formation of lesions most commonly in the ovaries but also in the fallopian tubes, gastrointestinal tract, and occasionally in distant locations like the pleura and central nervous system. Symptoms include chronic pelvic pain, heavy and painful menstrual periods, dyspareunia, painful urination, and defecation. Diagnosis involves a combination of medical history, physical examination, imaging techniques, and the gold standard, diagnostic laparoscopy. There is an average delay of 6.7 years between symptom onset and diagnosis, often due to variable and confusing symptoms resembling other conditions. The pathogenesis of endometriosis involves genetic, hormonal, and environmental factors, with significant roles played by estrogens and progesterone. Treatment strategies focus on managing symptoms through pain relief, hormonal therapy, and surgical interventions, although no permanent cure exists. Hormonal imbalances, particularly the interaction of progesterone and estrogens, play a crucial role in disease progression. Current research explores various treatment options, including hormonal therapy, nonsteroidal anti-inflammatory drugs, antioxidants, and surgical methods to improve the quality of life for patients.

Running title: Endometriosis review

Keywords: endometriosis, hormones, treatment

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Introduction

Endometriosis affects 10-15% of women of reproductive age and about 70% of patients with chronic pelvic pain. [1,2]. It is estimated that this disease affects approximately 176 million women worldwide [3]. The vast majority of endometriosis cases occur in patients between menarche and menopause, with the peak incidence occurring between the ages of 25 and 45 [4]. Endometriosis is a condition in which active endometrial foci (glandular cells and stroma) or endometrial-like tissue are found outside the uterine cavity [5]. Malignant transformation of endometriosis is considered extremely rare, with an estimated incidence of less than 1% [6]. Endometrial tissue is most commonly found in the ovaries, causing the formation of chocolate cysts, but it can also be found in the fallopian tubes, uterosacral ligaments, gastrointestinal tract, and less commonly in the pleura, pericardium, or central nervous system [5]. Lesions can be located within previous surgical incisions and even in distant parts of the body, such as the cerebellum [7]. Rare subtypes of extrapelvic endometriosis include cutaneous endometriosis, which is characterized by the presence of non-neoplastic endometrial tissue on the skin [8]. Endometrial lesions develop near blood vessels, which supports their survival, and they become highly innervated, contributing to the chronic pelvic pain experienced by many patients [9]. In the case of endometriosis, approximately 30% of women are asymptomatic, while around 50% experience chronic pain associated with the disease. The remaining 20% experience sporadic pain related to endometriosis [10]. Heavy periods accompanied by intense pain, dyspareunia, painful urination or defecation can indicate endometriosis. Patients also complain of symptoms such as diarrhea and bloating, abdominal discomfort, and occasionally recurrent pain in the lower limbs or bleeding from the rectum and urinary tract [11]. Clinical diagnosis should be a process combining medical history, physical examination including palpation for tenderness, presence of nodules or adhesions, and imaging diagnostics such as abdominal, transvaginal, or transrectal ultrasound, contrast X-ray of the large intestine, and urography [12]. The gold standard remains diagnostic laparoscopy, which involves surgically obtaining tissue samples for histopathological examination [11]. The average delay of 6.7 years between symptom onset and surgical diagnosis of endometriosis, with longer waits in publicly funded healthcare systems (8.3 years compared to 5.5 years), highlights significant challenges in early diagnosis within primary healthcare settings [13]. These delays may result from variable and often confusing symptoms that can resemble other common conditions such as irritable bowel syndrome [14]. There are several theories regarding the causes of endometriosis that attempt to logically explain the relationship between symptom severity and disease progression. However, none of these models are sufficient to fully explain the clinical diversity of the disease manifestations [15,16]. It is undisputed that genetic factors and the impact of environmental factors play a role in the development of endometriosis. However, researchers primarily attribute a significant role to hormones—steroid hormones, in particular. Besides the misplacement of cells in incorrect locations, the main essence of the disease lies in their reaction to these hormones. As a consequence of their action, the foci undergo alternating growth and shedding according to the menstrual cycle. This leads to uncontrolled bleeding and inflammatory conditions [17]. Endometriosis can affect fertility by altering the peritoneal environment and causing anatomical distortions in the pelvis, which can lead to difficulties in conceiving for about 30% of patients [18]. Endometriosis is also associated with many other conditions, including gastrointestinal diseases, malignant tumors, cardiovascular diseases, depression, and autoimmune disorders [19]. In light of the above, endometriosis can be considered a significant health issue that many women face, both during their reproductive years and postmenopause. This article aims to review the available literature on the pathogenesis, hormonal balance, and potential treatments for endometriosis.

Description of stormal cells in endometriosis

The stromal cells of disease foci exhibit dysfunctions in gene function unrelated to changes in DNA sequence, involving key transcription factors. They display insufficient expression of progesterone receptor and overly effective production of GATA-6 factor, steroidogenic factor-1, and estrogen receptor-beta. These cells can transform cholesterol into estradiol and progesterone, and produce proteins and enzymes such as aromatase. [20].

Hormones

Progesterone

One of the steroid hormones included in the group of progestagens, playing a significant role in the discussed issue, is progesterone. Its target includes the uterus, where under the influence of this steroid, cyclic physiological changes occur. Through the hypothalamic-pituitary axis, gonadotropin-releasing hormone influences the secretion of luteinizing hormone. This, in turn, stimulates ovulation and contributes to the transformation of the ovarian follicle remnants into the corpus luteum, which produces progesterone in large quantities [21]. Physiologically, the compound formed is a significant element involved in the implantation of the blastocyst by influencing the secretion of enzymes that dissolve the zona pellucida and changes

in the uterine lining. Through its action, it weakens the response of Th1, Tc, and NK cells and stimulates the production of anti-inflammatory factors such as IL-4 and IL-10. In feedback loops, it reduces gonadotropin-releasing hormone secretion, thereby inhibiting axis activity, while also stimulating its own production in corpus luteum cells. Progesterone causes a decrease in the number of receptors binding to oxytocin and prostaglandins and can mimic GABA, thereby reducing uterine contractions [22]. In the event that fertilization does not occur and the corpus luteum, responsible for a high percentage of progesterone production, degenerates, a process of shedding ensues, which involves bleeding. This, in turn, leads to inflammatory processes in the affected areas. [23]. Progesterone is a lipophilic molecule, a female steroid with 21 carbon atoms. Despite its name suggesting female origins, it occurs in both sexes [24]. Due to its chemical nature, progesterone can penetrate cell membranes and act intracellularly by binding to nuclear PR (progesterone receptor) receptors, which are transcription factors belonging to the NR3C subgroup of nuclear receptors [25]. Disruptions in PR function are crucial in the development of endometriosis. In the endometrium, these receptors enable progesterone to act on stromal and epithelial cells, on smooth muscle cells in the myometrium, and on glandular epithelial cells and stromal fibroblasts in the cervix [26]. Progesterone can also influence human cells through non-genomic effects [27]. PR receptors are also found in ovarian cells and the hypothalamus. They can be detected as functional isoforms with distinct molecular masses: PR-A, located in the cell nucleus, and PR-B, observable in both the nucleus and cytoplasm. The resulting complex initiates a cascade of events leading to specific effects through classical mechanisms, such as acting as a transcription factor. In terms of endometrial growth, PR-A plays a crucial role by interacting with estrogens [28]. PR receptors are most abundant in the mid-cycle, with their numbers lowest in the late secretory phase. In endometriosis, this cyclical pattern is disrupted. Sources indicate that conditions associated with inflammation, driven by cytokines, contribute to the methylation of the PRG promoter, which is involved in transcription and the formation of PR-B, while the promoter for PRA remains unmethylated. This phenomenon leads to an imbalance favoring PRA over PRB [29]. Foci of endometriosis exhibit, compared to the endometrium, not only reduced levels of PR but also increased production of progesterone. Therefore, despite extensive considerations, the role of progesterone in this phenomenon is not entirely clear [30]. There is a theory that despite their presence, PR may be biologically inactive, which explains the lack of sensitivity to this hormone [31]. This phenomenon leads to the disruption of progesterone's normal interaction with stromal cells, inhibiting the secretion of paracrine factors responsible for stimulating adjacent epithelial cells to produce type 2 17β-hydroxysteroid dehydrogenase (17β-HSD-2). The interruption of this normal process results in reduced metabolism of estradiol (E2) to estrone (E1) by this enzyme, leading to the accumulation of E2, which is responsible for inflammation in ectopic endometriotic lesions [32,33]. There are reports that progesterone influences the expression of PTEN (phosphatase and tensin homolog deleted on chromosome 10), leading to increased autophagy through inhibition of the PI3K/AKT pathway. In patients with endometriosis, this process is disrupted, likely due to faulty responses to this crucial hormone. In these patients, PTEN expression is improperly reduced, resulting in the persistence of abnormal stromal cells [34].

Estrogens

Estrogens are another group of steroid hormones that play a crucial role in the development of endometriosis. This group includes hormones such as 17β-estradiol (E2) and estrone. They perform several important functions, including influencing the development of female secondary sexual characteristics, maintaining bone density, regulating cholesterol levels, and also controlling the menstrual cycle by affecting the endometrium. This aspect is significant in terms of both endometriosis development and endometrial cancer [35]. Estrogen's influence on the uterine mucosa includes stimulating the proliferation of endometrial cells and maintaining its proper structure to prepare for embryo implantation. Additionally, estrogens stimulate the development of blood vessels in the endometrium, which is crucial for supplying nutrients to the developing mucosa [36]. The extent of endometrial growth stimulation largely depends on the duration of interaction between bioavailable 17β-estradiol (E2) and its receptor. It has been determined that the minimal dose of E2 required to induce sensitivity in the endometrium ranges from 1.5 to 3 ng. However, findings suggest that the level of estradiol must exceed a certain threshold to initiate early growth events associated with it in the uterus [37]. Estrogens can induce the aforementioned cellular processes through mechanisms such as direct or indirect regulation of gene expression via nuclear estrogen receptors or by interacting with estrogen receptors present on the cell membrane, which are coupled with G-proteins [38]. The mentioned nuclear estrogen receptor exists in two isoforms, ERα and ERβ, which estrogen acts upon, thereby influencing the endometrium. [39]. Evidence obtained from studies on mouse models and isolated cells from patients with endometriosis indicates the involvement of ERβ (estrogen receptor beta) in nearly all gynecological pathologies, including menstrual bleeding disorders, endometriosis, and endome-

trial cancer [38]. It has also been observed that the expression of this receptor is significantly higher in women with endometriosis, which results in the inhibition of ERα expression [40]. Estrogen receptor beta (ERβ) plays a unique role in endometriosis tissue, where it interacts with cytoplasmic apoptotic mechanisms and the inflammasome complex, thereby increasing IL-1β expression. This action aims to prevent cell death induced by TNF-α and enhance the adhesive and proliferative activities of endometriosis tissues [41]. ERβ also contributes to epithelial-to-mesenchymal transition (EMT), which occurs during embryogenesis and in various pathological conditions such as cancer [42]. In the mentioned process, epithelial cells lose their polarized cytoskeletal organization and intercellular connections, acquiring high mobility characteristic of mesenchymal cells. This transformation is considered a preliminary condition for the development of primary endometrial changes [43]. ERβ also stimulates the expression of genes involved in unfolded protein response and inhibits the IL-6/JAK/STAT3 signaling pathway, as well as suppresses the TNFα/NF-kB signaling pathway in eutopic endometrium. This contributes to the dysfunction of endometrium associated with endometriosis [44]. Other studies also demonstrate that ERβ directly modulates the expression of mitochondrial DNA (mtDNA) genes, which ensures the resistance of endometrial cells to apoptosis induced by oxidative stress through the induction of ROS-scavenging enzyme, superoxide dismutase, and anti-apoptotic Bcl-2 protein [45].

Menstrual cycle – dependence between estrogen and progesterone levels, essential for maintaining proper endometrial proliferation

Before assessing specific relationships between estrogen and progesterone in women suffering from endometriosis, it is important to first recall how these relationships manifest in healthy women during the menstrual cycle and how they influence changes in the endometrium. The ovarian cycle consists of the follicular phase, ovulation, and the luteal phase. In the uterine cycle, we distinguish menstruation (corresponding to the early follicular phase), the proliferative phase (corresponding to the mid to late follicular phase), and the secretory phase (corresponding to the luteal phase) [46]. In the follicular phase, estrogen is the dominant ste-

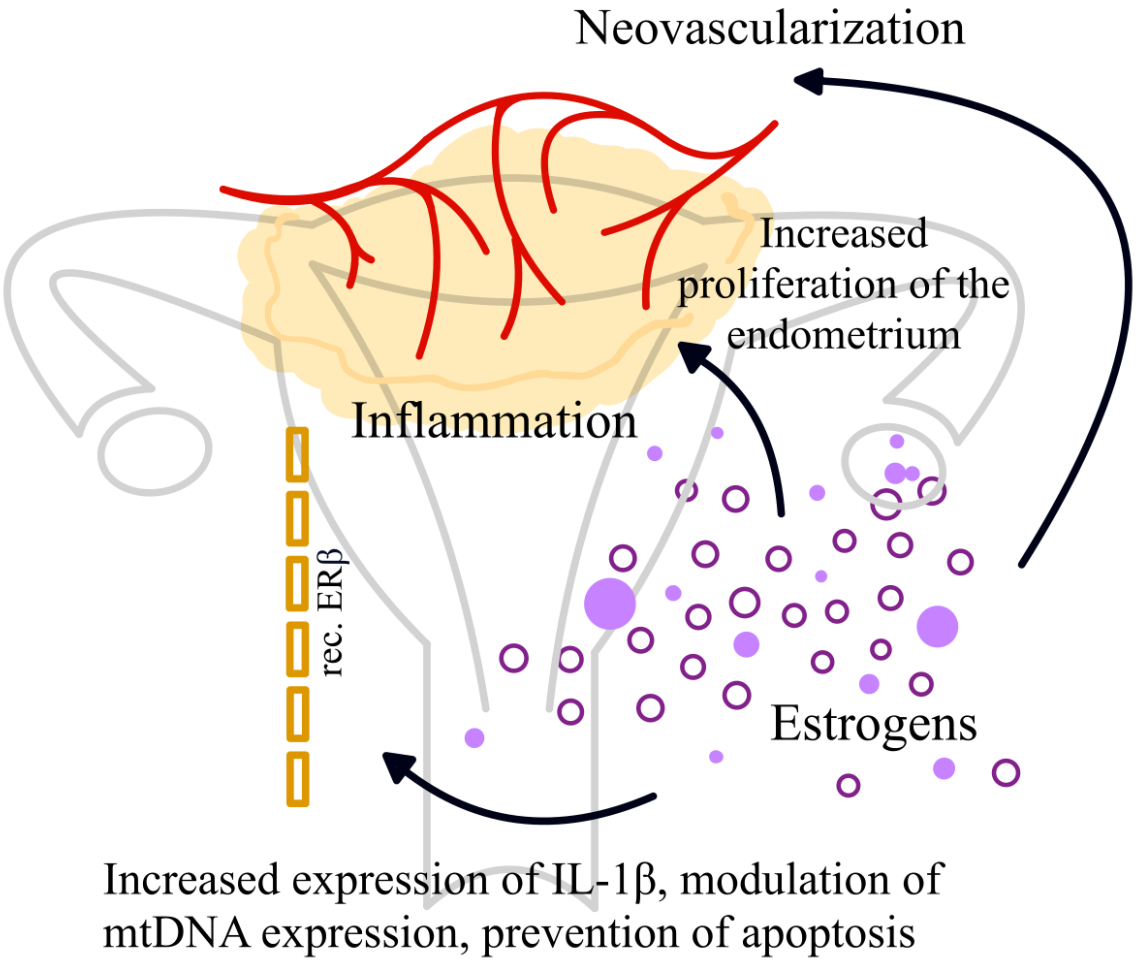

FIGURE 1 Development of inflammation in endometriosis

roid hormone. Ovulation is triggered by an increase in LH and FSH levels. In the luteal phase, progesterone predominates, although estrogen remains present [47]. However, in situations where the balance between these two hormones is disrupted, due to an increased ratio of estrogens to progesterone, it can lead to excessive and uncontrolled stimulation of endometrial cell growth [48]. It is widely known that progesterone and estrogen mainly act through related receptors, triggering cascades of signaling pathways, which in endometriosis can lead to hormonal signaling disruptions, resulting consequently in progesterone resistance and estrogen dominance. This hormonal imbalance leads to increased inflammation and can exacerbate pelvic pain associated with the disease [49].

In **figure 1**, a diagram of the development of inflammation in endometriosis is presented.

Treatment

Treatment of endometriosis depends on the severity of symptoms, age, and reproductive goals of each patient. It is worth emphasizing that endometriosis is a multifactorial disease, with hormones being just one element influencing its development. Therefore, therapy for endometriosis often includes various strategies, which may involve the use of pain relievers such as ibuprofen, paracetamol, or naproxen to help alleviate pain symptoms caused by endometriosis [50]. According to the recommendations of the Polish Society of Gynecologists and Obstetricians, the therapy for endometriosis should be based on a long-term plan aimed at maximizing pharmacological treatment and minimizing the number of surgical procedures. For the treatment of chronic pain, the first-line pharmacological therapy should include combined oral contraceptives (COCs), preferably those containing dienogest [51]. In women experiencing pelvic pain and who do not plan immediate pregnancy, pharmacological agents are the preferred choice [52]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of medications used in the treatment of endometriosis because they are quite safe, readily available, and help women manage painful menstrual periods [53]. Hormonal therapy also finds its application because it can help limit the growth of endometrial tissue. It may include oral contraceptives, progestins, and gonadotropin-releasing hormone analogs (GnRH analogs) [54]. Hormonal therapy, however, is associated with varying responses due to the existence of genetic and epigenetic concepts [55]. It includes various groups of drugs. One of them is danazol, a derivative of 17α-ethynyltestosterone, which exhibits androgenic activity. It strongly inhibits GnRH, affecting the pituitary gland by reducing LH and FSH secretion. Unfortunately, this drug has many side effects such as weight gain, acne, breast volume reduction, and hirsutism. [56-58]. Another group of drugs used are GnRH analogues, which are derivatives of GnRH. They induce a hypogonadotropic effect, resulting in reduced estrogen levels. Many studies have shown that these analogues are as effective as danazol in inhibiting symptoms and reducing the growth of endometriosis. However, their use also comes with side effects such as weight gain, edema, hirsutism, muscle pain, osteoporosis, vaginal dryness, and headaches [57,59-61]. Progestins are derivatives of progesterone that mimic its activity. They are responsible for inhibiting the implantation and development of dysfunctional endometrium, inhibiting angiogenesis, and exhibiting anti-inflammatory effects. The precise analgesic mechanism of progestins is not fully understood, as the exact mechanisms of pain in endometriosis are also poorly understood [62,63]. There are many other drugs such as oral contraceptives and aromatase inhibitors that show similar therapeutic effects but differ in terms of side effects [57]. Current research also analyzes the potential role of antioxidants in the treatment of endometriosis. Taking supplements of vitamins C and E has been found to effectively reduce the severity of painful menstruation and improve dyspareunia and pelvic pain among patients [64]. However, when curcumin was used in treatment, despite its potential anti-inflammatory and antioxidant properties, it did not prove to be an effective therapeutic agent [65]. Surgical methods, on the other hand, are used to remove endometrial lesions and proliferating foci of endometriosis. This procedure can be performed using laparoscopy, where a laparoscope is inserted through a small incision in the abdominal cavity [66]. It should be noted, however, that currently there is no permanent cure for endometriosis, but appropriate therapy can alleviate symptoms and improve the patient's quality of life.

Conclusions

Endometriosis is a complex and multifactorial disease affecting millions of women worldwide, predominantly during their reproductive years. Despite its high prevalence, there remains a significant delay in diagnosis due to the nonspecific and varied symptoms that often resemble other conditions. The disease's pathogenesis is intricately linked to genetic, hormonal, and environmental factors, with estrogens and progesterone playing pivotal roles. Hormonal imbalances and disruptions in hormonal receptor function contribute to the disease's progression and the associated chronic pain and infertility. Treatment strategies are multifaceted, aiming to manage symptoms and improve patients' quality of life. Pharmacological treatments, including NSAIDs and hormonal therapies such as combined oral contraceptives, progestins, and GnRH analogs, are commonly used. However, these treatments often come with significant side effects and variable

efficacy due to genetic and epigenetic factors. Surgical interventions, although effective in removing lesions, do not offer a permanent cure and carry their own risks. Recent research highlights the potential role of antioxidants and other novel therapeutic agents, but their effectiveness remains inconclusive. Despite advances in understanding and managing endometriosis, the disease remains a significant health issue, necessitating continued research into more effective and less invasive treatments. Comprehensive, long-term management plans tailored to individual patients' needs and reproductive goals are essential for improving outcomes and quality of life for those affected by endometriosis.

Ethical approval
This study is not related to either human or animal use.

Acknowledgments
Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

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