LUMEN ET VIRTUS
ISSN: 2177-2789

ENDOMETRIOSIS: A SYSTEMATIC REVIEW ON THE PATHOPHYSIOLOGY, COMPLICATIONS AND THERAPEUTIC APPROACHES FOR A COMPLEX CHRONIC DISEASE

https://doi.org/10.56238/levv15n42-051

Submitted on: 20/10/2024 **Publication date:** 20/11/2024

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ABSTRACT

Objective: The general objective of this study is to analyze the scientific production on Endometriosis, identifying the main complications and treatments of this pathology. Methodology: This is a systematic review focused on understanding the essential aspects of Endometriosis. The survey was guided by the question, "What are the main complications and treatments for endometriosis?" To find answers, searches were performed in the PubMed database using five descriptors combined with the Boolean term "AND": (Infertility) AND (Endometriosis) AND (Endometrial diseases) and (Female infertility) AND (Endometrial diseases). This resulted in a total of 23 articles, of which 23 were selected for detailed analysis. Results: The main complications identified include chronic pelvic pain, infertility, and a variety of problems related to inflammation and the presence of endometriotic tissue outside the uterus. Hormonal treatments, such as progestins and GnRH agonists, are the most commonly used, although new therapies are being investigated, such as aromatase inhibitors and selective hormone receptor modulators. In addition, surgical approaches are often necessary for cases that are severe or resistant to medical treatments. The review also highlights the importance of early diagnosis and

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multidisciplinary management to improve patient outcomes. Conclusion: It is concluded that endometriosis is a complex condition that requires a multifaceted approach to its management. The characterization of complications and the development of effective treatment strategies are essential to improve the quality of life of patients. The combination of hormonal and surgical treatments and new therapies in development offers hope for more effective control of the disease.

Keywords: Endometriosis. Complications. Treatment.

INTRODUCTION

Endometriosis refers to the ectopic implantation and growth of endometrial tissues often found in the ovary, ligaments, peritoneal surface, intestine, and bladder. This disease, clinically manifesting as chronic pelvic pain and infertility, affects up to 6% to 10% of women of reproductive age. Patients with endometriosis are currently treated with active disease hormone suppression, symptomatic treatment, and surgical ablation of visible lesions. These therapeutic procedures cannot overcome the high recurrent propensity of this disease, and in many cases the disease becomes a persistent disease negatively impacting fertility and quality of life. The long-term application of natural compounds, e.g., phytoestrogens from food sources, has been investigated for their potential preventive and therapeutic benefits. (CAI et al., 2021).

Several theories about the pathophysiological process of endometriosis are raised and studied by researchers. The retrograde menstruation hypothesis emphasizes the ectopic growth of regurgitated endometrial tissues during menstrual cycles. It has been proposed that endometrial stem cells may play a key role in this process. Coelomic metaplasia and localized inflammatory responses may explain the appearance of peritoneal lesions. At the cellular and molecular levels, evidence of excessive estrogen stimulation, inflammation, increased angiogenesis, and active proliferation are commonly seen in cases of endometriosis. Among these changes, excessive estrogenic activity is well recognized to be widely involved in all pathological aspects of endometriosis (CAI et al., 2021).

Endometriosis may best be considered a "syndrome", either because it is closely related to a wide range of symptoms, including severe dysmenorrhea, chronic pelvic pain, heavy menstruation, bowel and bladder symptoms, fatigue, and depression, or because very little is known about endometriosis due to its high heterogeneity of symptoms and increasingly apparent complexity of pathogenesis (GUO; ZHANG, 2024). Current treatments for endometriosis aim to relieve pain associated with endometriosis and/or treat infertility associated with the disease and include surgical and medical treatment. Ovarian suppression limits lesion activity and growth, leading to reduced pain symptoms. Common methods of ovarian suppression include oral contraceptives and gonadotropin-releasing hormone (GnRH) agonists with additional HRT (GRUBER; MECHSNER, 2021). While ovarian suppression may relieve pain symptoms, the treatment is also contraceptive and therefore inappropriate for women who intend to become pregnant (HOGG; HORNE; ERIN, 2020).

In addition, GnRH agonists are associated with side effects such as memory loss, insomnia, and hot flashes in a recent study of endometriosis patients with long-term

use. Treatments may also include nonsteroidal anti-inflammatory drugs such as ibuprofen, however, long-term pain management for women with endometriosis usually encompasses a combination of treatments. In addition to medical therapy, laparoscopic surgery to remove lesions may provide symptom relief in some patients, however, up to 50% of women experience a relapse of symptoms within 2 years of surgery (HOGG; HORNE; ERIN, 2020).

This systematic review article aims to compile and evaluate the existing scientific evidence on the pathophysiology, complications and main therapeutic methods of Endometriosis. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this work intends to serve as a resource for health professionals, researchers, and academics, helping to optimize preventive and diagnostic approaches to Endometriosis.

METHODOLOGY

This is a systematic review that seeks to understand the main complications and treatments of endometriosis, as well as to demonstrate the means used in diagnosis and therapeutic approaches, aiming to ensure early diagnosis and effective treatment of this disease. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the main complications and treatments for endometriosis?"

The searches were carried out through searches in the PubMed database. Five descriptors were used in combination with the Boolean term "AND": (Infertility) AND (Endometriosis) AND (Endometrial diseases) and (Female infertility) AND (Endometrial diseases). From this search, 23 articles were found, which were subsequently submitted to the selection criteria.

The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition to review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 23 articles were found. After applying the inclusion and exclusion criteria, 10 articles were selected to compose the discussion collection.

RESULTS

Table 1 - Created by the author

Author	Main Collaborations in the Systematic Review
Vannuccini et al., 2022	Description of the pathophysiology of endometriosis, including the theory of retrograde menstruation and the mechanisms of cell proliferation and peritoneal invasion. Discussion of estrogen dependence and progesterone resistance. Analysis of the effects of chronic inflammation and fibrogenesis on pain associated with endometriosis. Contributions on the complexity of symptoms, including chronic pelvic pain, dyspareunia, and dysuria.
Yang et al., 2024	Exploration of the molecular mechanisms of estrogen signaling in endometriotic lesions. Discussion of c-MYC, Greb-1, and FGF-9 signaling pathways associated with estrogen-mediated endometrial stromal cell (ESC) growth. Analysis of progesterone resistance and the cellular mechanisms involved.
Camboni; Marbaix, 2021	Detailing the macroscopic and pathological appearance of endometriotic lesions. Description of the different forms of pelvic and extrapelvic endometriosis. Discussion of pathological findings throughout the course of the disease, including changes in lesion pigmentation and fibrotic scar formation. Contributions on the influence of the gut microbiota and the relationship with autoimmune diseases.
Guo; Zhang, 2024	Investigation of the relationship between the gut microbiota and endometriosis. Discussion on the influence of the microbiota on T lymphocyte differentiation and inflammatory response. Analysis of the link between endometriosis and autoimmune diseases, including B and T cell activation and immune dysfunction.
Gonnella et al., 2024	Study on the association between obesity and endometriosis severity. Discussion of the mechanisms by which obesity may influence disease progression. Analysis of clinical observations suggesting that obese women have more severe forms of endometriosis.
Chen et al., 2023	Exploration of the theory of coelomic metaplasia and Müllerian remnants as mechanisms of endometriotic lesion formation. Discussion of hormonal treatments, including the efficacy of progestins, agonists, and GnRH antagonists. Analysis of the side effects of hormonal treatments and progesterone resistance. Investigation of obstetric complications associated with endometriosis.
Brichant et al., 2021	Evaluation of the efficacy and safety of the GnRH antagonist elagolix in women with endometriosis. Discussion of the side effects associated with the use of elagolix, including hot flashes and bone loss. Analysis of the use of cetrorelix as a treatment and its results in reducing the severity of endometriosis. Consideration of adverse effects of treatments, such as abnormal uterine bleeding and headaches.
Singh; Sethi, 2022	Contributions on pelvic adhesions in patients with deep endometriosis. Discussion of how pelvic adhesions interfere with the release and transport of eggs, affecting fertility. Analysis of the mechanisms by which chronic inflammation in endometriosis creates a local environment unfavorable to conception.

Vercellini et al., 2023	Discussion of how endometriosis can negatively affect the course of pregnancy, including fibrosis of the pelvic vessels and stiffness of the arterial wall. Research on the relationship between endometriosis and obstetric complications, such as miscarriage and preeclampsia. Analysis of genetic and epigenetic changes that may link endometriosis to adverse pregnancy outcomes.
Ghasemi et al., 2022	Study of the pain mechanisms associated with endometriosis, including nociceptive and neuropathic processes. Discussion of neurogenic factors, such as BDNF and NGF, and their overexpression in endometriotic lesions. Analysis of central and behavioral changes observed in patients with endometriosis, including central sensitization and psychological impact.

DISCUSSION

Endometriosis is a chronic disease characterized by the presence of endometrium-like tissue outside the uterine cavity, affecting women of reproductive age with pelvic pain and infertility. Prevalence ranges from 2 to 10% of women of reproductive age, 30–50% among infertile women, and 5–21% among women with severe pelvic pain. The pathophysiology of endometriosis is still a matter of investigation, but the endocrine and inflammatory antecedents are well characterized, recognizing an estrogen dependence and a resistance to progesterone. The main mechanisms involved in the ectopic localization of endometrial cells include retrograde menstruation, vascular and lymphatic dissemination, and/or metaplasia/stem cells. The most accepted theory is that of retrograde menstruation, according to which fragments of the menstrual endometrium migrate through the fallopian tubes to the peritoneal cavity, where they implant, proliferate and invade the pelvic peritoneum. The return flow of endometrial cells to the pelvis is physiological, resulting in apoptosis/autophagy and cell-mediated immunity, the elimination system of these cells, while in endometriotic patients hormonal influences and genetic/epigenetic factors determine a compromise of these mechanisms, promoting cell survival, proliferation, and peritoneal invasion (VANNUCCINI et al., 2022).

Increased estrogen receptor activity, estrogen production in endometriotic lesions, and progesterone resistance are the determinants of impaired apoptosis, reduced immune function, and increased inflammation. Thus, endometriotic cells attach, penetrate and invade the peritoneum, determining the growth of lesions that undergo cyclic bleeding with repeated tissue injury and repair, neoangiogenesis and neurogenesis. Fibroblast-myofibroblast transdifferentiation contributes to collagen production and fibrogenesis, with nerve fiber trapping that, associated with chronic inflammation, explains pain symptoms (VANNUCCINI et al., 2022).

Endometriosis is an estrogen-dependent inflammatory disease characterized by excessive estrogen signaling in endometriotic lesions. This is attributed to elevated estrogen production, inadequate estrogen metabolization, and altered expression of estrogen receptors. The upregulation of ER and the downregulation of ER in the ectopic endometrium suggest that ER functions as a primary estrogen receptor in the endometrium. Estrogen activation of ER stimulates the expression of PGE2 and Ras-like estrogen-regulated growth inhibitor (RERG), thereby promoting the proliferation of enESCs. In addition, other signaling pathways, including c-MYC, Greb-1, and FGF-9, have been associated with estrogen-mediated growth of ESC (YANG et al., 2024).

Coelomic metaplasia, another well-recognized theory for the formation of endometriotic lesions, is based on the transformation of the peritoneal mesothelium. In addition, the Müllerian remnant hypothesis proposed that endometriosis can be differentiated from embryological remnants. The mechanism by which endometriotic lesions originate "in situ" by metaplasia or from Müllerian remnants further explains endometriosis in adolescents soon after menarche and in fetuses with absence of menstruation (CHEN et al., 2023).

Endometriosis can be located inside the pelvis or in extra-pelvic sites, often affecting multiple sites. Three different forms of pelvic endometriosis have been identified, namely superficial peritoneal, ovarian, and deep infiltration endometriosis (DIE). DIE is defined as endometriosis that infiltrates the peritoneum by > 5 mm and is usually located in the most declined part of the pelvis (including Douglas' pouch, sigmoid, rectum, uterosacral and wide ligaments, vagina, ureter, and bladder). In extra-pelvic locations. Endometriotic foci have been reported in different sites: abdominal cavity (abdominal wall, groin, and perineum), abdominal organs (kidneys, liver, pancreas, intestine, and bile ducts), thorax, nerve and extrapelvic muscle, skin, lymph node, nose, eyes, and brain (CAMBONI; MARBAIX, 2021).

The macroscopic pathological findings of endometriosis depend on the duration of the disease, depth of penetration of the lesions, location, and timing of the menstrual cycle. Endometriotic implants range from punctual foci and small stellate spots (usually less than 2 cm) to cystic, nodular or polypoid masses. The lesions have different appearances during the course of the disease due to the accumulation of hemosiderin. They are initially depigmented or red, then evolve into mature lesions of blue or dark pigmentation, and finally become white fibrotic scars. The appearance of endometriosis can change under hormonal stimulation and the lesions become more swollen and congested due to bleeding during the menstrual cycle. Hemorrhages and the resulting accumulation of iron are

responsible for generating an inflammatory condition that leads to fibrosis, scars and adhesions, causing distortion of the normal pelvic anatomy (CAMBONI; MARBAIX, 2021).

The most common site of involvement is the ovary, where endometriosis presents as blood-filled ovarian endometriotic cysts (endometriomas), commonly known as chocolate cysts. In more than half of the cases, endometriomas are bilateral and usually not 8 of 16 do not exceed 15 cm in diameter. Endometriomas have fibrotic walls, a smooth lining, and dense, dark-brown cystic content, often adherent to adjacent organs (CAMBONI; MARBAIX, 2021).

Gut dysbiosis and bacterial metabolites can lead to disruption of the intestinal barrier, translocation of bacteria and endotoxins, dysregulation of the immune system, resulting in oxidative stress and inflammatory responses, thereby increasing the prevalence of various autoimmune diseases. Many researchers have worked to link autoimmune diseases to endometriosis because endometriosis shares characteristics with some autoimmune diseases, including polyclonal B-cell activation, T-cell and B-cell dysfunction, decreased apoptosis, tissue damage, and multiorgan involvement, and endometriosis is often associated with autoimmune diseases (GUO; ZHANG, 2024).

The gut microbiota can influence the differentiation of T lymphocytes into different types of helper T lymphocytes (Th1, Th2, and Th17) or regulatory T lymphocytes (Treg cells), such as segmented filamentous bacteria (SFB) that directly stimulate the differentiation of Th17, Clostridium spp. that participate in inducing the production of Treg, and Bacteroides involved in the regulation of Th1/Th2 balance. Many studies have shown that Th17 cells and their cytokine profiles are significantly increased in the peritoneal fluid of women with endometriosis, and excess IL-17 Th17 cells are related to disease severity (GUO; ZHANG, 2024).

In the surgical diagnosis of endometriosis, it was found that a higher proportion of obese women (defined as a body mass index [BMI] > 30 kg/m2) had advanced and more severe disease, with a reduced number of these women having an early and minimal stage of the disease. Such a postulate could easily be tested in experimental models for endometriosis, but to date, few studies have been conducted (GONNELLA et al., 2024).

Endometriosis is a highly underdiagnosed and undertreated disease, with a long time interval of 8 to 12 years between the onset of symptoms and the definitive diagnosis. Because most symptoms are non-specific, there are currently no noninvasive diagnostic techniques that can accurately identify a problem that can definitively diagnose a condition. However, a thorough medical history, a gynecological examination with a speculum, a bimanual pelvic examination, imaging techniques, ultrasound, three-dimensional and four-

dimensional transperineal ultrasound, magnetic resonance imaging (MRI), and biochemical tests are beneficial in early diagnosis of the disease. Common symptoms include dysmenorrhea and non-menstrual pelvic pain, which can progress to chronic pelvic pain, with a relevant impact on daily life. Other endometriosis-related pains are dyspareunia, dyschezia, and dysuria, usually associated with DIE lesions. According to the anatomical involvement of the bowel, patients may alternate constipation and diarrhea, dyschezia or blood in the stool (in particular perimenstrually) or when the urinary tract is affected, recurrent dysuria, cyclic macrohematuria or interstitial cystitis are observed. Chest and shoulder pain should be considered suspicious of diaphragmatic endometriosis, while endometriosis in the ileocecal or periappendicular region has been significantly associated with abdominal pain, nausea, vomiting, and diarrhea (GHASEMI et al., 2022) (VANNUCCINI et al., 2022).

Regarding the pathophysiology of endometriosis-related pain, nociceptive (including inflammatory), neuropathic mechanisms, and a combination of these mechanisms are involved, under the influence of hormonal aberrations, stress, inflammation, and the interaction between the peripheral and central nervous systems. Neurogenic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are reported to be overexpressed in the peritoneal fluid and endometriotic lesions of affected women. Neurotrophic factors also respond to estrogens, prostaglandins, and cytokines and stimulate the growth and sensitization of sensory nerve fiber terminals, particularly in DID, presenting high nerve fiber density (VANNUCCINI et al., 2022).

The development of a vicious cycle characterized by nociceptor sensitization and local neoneurogenesis, triggered by inflammatory and immunological mediators, is observed in endometriosis. The endometriotic lesions themselves send noxious signals to spinal cord neurons from the dorsal root and activate spinal microglia to maintain pain stimuli, resulting in a central sensitization. In fact, a number of central changes are observed: changes in the behavioral and central response to harmful stimulation, changes in brain structure, altered activity of both the HPA and the autonomic nervous system, and psychological distress, with greater volume in regions involved in pain modulation and regulation of endocrine function. In fact, the chronic pain and stress experienced by patients with endometriosis can cause multiple psychiatric illnesses and somatoform disorder is the most common. Traits of anxiety and depression and an increased tendency to pain catastrophizing are commonly present in patients with endometriosis and may amplify pain perception. Another frequently present but often overlooked symptom in women with

endometriosis is chronic fatigue, although the exact mechanism is not yet fully understood (VANNUCCINI et al., 2022).

Infertility is the other main symptom of endometriosis, although a diagnosis of endometriosis does not always imply infertility. Endometriosis is identified in approximately 30% of women in infertile couples. The disease adversely affects fertility by different mechanisms that act at the level of the pelvic cavity, ovary and uterus. The pelvic cavity is a hostile environment because chronic inflammatory changes in peritoneal fluid and distortion of the normal anatomy of the fallopian tubes hinder tube-ovarian contact and affect sperm-oocyte interaction; the ovary produces low-quality oocytes, impaired folliculogenesis, and luteal function, with reduced ovarian reserve by AOM and/or surgery. In addition, in endometriosis, the uterus itself has an altered endometrial receptivity mainly due to changes in local growth factors (integrin, LIF, activin, CRH), hormonal aberrations (ER and PR) and myometrial dysperistalsis, due to the association with adenomyosis (VANNUCCINI et al., 2022).

Pelvic adhesions, documented in the majority of patients with deep infiltrative endometriosis (DIE) lesions (VANNUCCINI et al., 2022), can disrupt pelvic anatomy, interfere with oocyte release, or prevent oocyte uptake or transport through the fallopian tubes (SINGH; SETHI, 2022). In addition, chronic pelvic inflammation can result in a local environment unfavorable to conception. Cytokines, growth factors, prostaglandins, and reactive oxygen species, found in high levels in the peritoneal fluids and lesions of patients with endometriosis, can interfere with ovulation, oocyte uptake, sperm function, gamete fertilization, and embryo migration. Peritoneal macrophages, which increase in number and present a phenotype dysfunction in women with endometriosis, are central to these phenomena. Its increased ability to produce pro-inflammatory mediators perpetuates pelvic inflammation and promotes the recruitment of other immune cells. Because endometriosis can negatively affect the course of pregnancy it is more difficult to hypothesize. In advanced forms of endometriosis, a fibrotic entrapment of the pelvic vessels can determine an increase in arterial wall stiffness with a secondary decrease in vascular compliance, thus hindering the physiological hemodynamic adaptation that occurs during pregnancy (VERCELLINI et al., 2023).

Emerging research has demonstrated the relationship between endometriosis and obstetric complications, including miscarriage, preterm birth, premature rupture of membranes, antepartum hemorrhage, placental abruption, placenta previa, preeclampsia, gestational hypertensive and metabolic disorders (diabetes or cholestasis), and adverse neonatal outcomes (small for gestational age, low birth weight, neonatal intensive care

admission, and neonatal death). Endometriosis and obstetric diseases share some molecular features and pathophysiological mechanisms of the defective junctional zone, disturbed uterine peristalsis, and aberrant inflammation. Several differentially expressed genes involved in endometriosis are common in adverse pregnancy outcomes, such as preeclampsia, small for gestational age, or preterm birth. Changes of imprinted gene groups (CDKN1C, DLX5, GATA3) in the link between endometriosis and abnormal decidualization are considered critical regulators of embryogenesis and placentation. Adverse maternal environments can lead to placental genetic and epigenetic aberrations, which alter the ability of the placenta to modulate fetal exposure and maternal cortisol response, causing infant neurobehavioral deficits. In addition to suboptimal placentation, overexpression of COX-2 and prostaglandin secretion in chronic inflammation can lead to early cervical ripening and uterine hypercontractility in women with endometriosis, thereby causing adverse fetal outcomes (CHEN et al., 2023).

Hormone therapies are the most commonly used to treat women with endometriosis. The goal is to block menstruation by causing a state of iatrogenic menopause or pseudopregnancy. Current medical hormone therapy does not definitively cure the disease, but it is able to control pain symptoms to prevent or delay surgery and control the disease in the long term. First-line hormonal therapies include progestins, while second-line therapies are represented by GnRH agonists (GnRH-a) and antagonists. Off-label use of combined oral contraceptives (COCs) is common. New hormonal drugs (aromatase inhibitors, selective estrogen receptor modulators (SERM), selective progesterone receptor modulators (SPRM)) are under investigation for the treatment of endometriosis (VANNUCCINI et al., 2022).

The most prescribed medications are ACOs and progestins. However, long-term users may complain of irregular bleeding, mastodynia and/or psychological disturbances, weight gain, mood swings, or, for some patients, inconvenient androgenic side effects (acne, hair loss, changes in lipid profile, and/or hirsutism). After binding to PR, progestins have anti-estrogenic, pro-apoptotic, anti-inflammatory, antivasculogenic, antiproliferative, and antineurogenic effects, all of which allow for pain relief and inhibition of disease progression. They reduce or suppress pain in about 90% of patients. They interrupt cell growth and induce decidualization and endometriotic atrophy. However, it should not be forgotten that endometriosis is well known to be a progesterone-resistant condition (BRICHANT et al., 2021).

Progestins, acting as natural progesterone, can induce anovulation and endometrial pseudodecidualization, resulting in atrophy of endometriotic implants by decreased

inflammation and angiogenesis. Progestin-only pills, including dienogest, norethisterone, and medroxyprogesterone, are currently the first-line treatment for symptomatic endometriosis and aim to prevent recurrence after surgery. In addition, progestins can be administered by other routes, such as intramuscularly, subcutaneously (etonogestrel implant), or intrauterine (levonorgestrel-releasing intrauterine device, LNG-IUD). Dienogest (2 mg daily), a derivative of 19-nortestosterone, may increase PRÿ expression in endometriotic lesions, potentially overcoming progesterone resistance. Several randomized controlled trials have proven its efficacy for endometriosis-associated pain in relation to different phenotypes. Dienogest can decrease the size of the ovarian endometrioma without decreasing the ovarian reserve and reduce pain symptoms related to infiltrating deep endometriosis (dysmenorrhea, dyspareunia, dyschezia and chronic pelvic pain), thereby improving the quality of life of patients. Norethisterone acetate (NETA, 2.5–15 mg daily), a derivative of 19-nortestosterone, has been confirmed to be effective over dienogest in reducing ovarian endometrioma size and endometriosis-related symptoms, while dienogest was superior in symptom relief and tolerability (CHEN et al., 2023).

Medroxyprogesterone acetate (MPA, 10–60 mg daily), a derivative of 17OH-progesterone available as an oral or depot formulation (administered every three months subcutaneously or intramuscularly), is as effective as gonadotropin-releasing hormone analogues (GnRH agonist) and limited to the treatment of refractory endometriosis due to the long-term hypoestrogenic state, consequently leading to bone loss. LNG IUD, a potent derivative of 19-nortesterone released directly into the uterine cavity, improves menstrual disorders and endometriosis-related pelvic pain symptoms. Commonly reported side effects of progesterone-based therapies are abnormal uterine bleeding, which progressively improves with continued treatment, headache, mood swings, and particularly with long-term use of depot MPA, as well as loss of bone marrow density (CHEN et al., 2023).

Endometriosis is an estrogen-dependent disease. GnRH agonists (leuprolide acetate, goserelin, etc.), by reducing the pulsatility of GnRH, repress the gonadotropic axis, preventing estrogen stimulation in the ectopic glands. This leads to postmenopausal estrogen levels leading to progressive bone loss and/or severe vasomotor symptoms that restrict its use to 6 months without replacement therapy. GnRH agonists also impact the development of endometriosis through the regulation of cell migration. GnRH antagonists (GnRHant) allow rapid inhibition of gonadotropin release. A small study evaluating the subcutaneous administration of cetrorelix 3 mg once weekly for 8 weeks showed a lower severity of disease during laparoscopy in 60% of patients (BRICHANT et al., 2021).

The main side effects were abnormal uterine bleeding (AUB) and headaches in 20% of patients. No effect was observed when assessing mood, hot flashes, libido, or vaginal dryness. Estradiol concentrations remained within the normal range to avoid bone loss (50 pg/mL). Elagolix, an oral GnRHant, allows inhibition of the gonadotrope within 24 h of administration. Its efficacy and safety were confirmed in a study of 155 women with endometriosis. Elagolix was evaluated in a double-blind, placebo-controlled study comparing two dosages for 6 months (150 mg and 200 mg daily). Long-term treatment with Elagolix allowed a significant reduction in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia. The main side effects were hot flashes, and it should be noted that bone loss and lipids increased after 12 months (BRICHANT et al., 2021).

CONCLUSION

Endometriosis is a chronic disease that affects women of reproductive age, characterized by the presence of endometrium-like tissue outside the uterus, causing symptoms such as pelvic pain and infertility. The prevalence is 2 to 10% of women in this age group, reaching 50% in cases of infertility and severe pain. Although the exact cause is not yet completely understood, theories suggest retrograde menstruation, where the endometrium migrates out of the uterus and implants itself in other areas, or coelomic metaplasia. The accumulation of endometriotic cells causes chronic inflammation, pain, and adhesion formation, also impacting nearby organs such as the ovaries and intestine. In many cases, the lesions can infiltrate organs deeper (DII), aggravating symptoms such as dyspareunia, dysuria, and bowel difficulties.

Endometriosis shares characteristics with autoimmune diseases, such as abnormal immune responses and increased inflammation. Studies suggest that changes in the gut microbiota and genetic and epigenetic factors may contribute to the development and severity of the disease. Diagnosis is usually delayed, due to the absence of reliable noninvasive methods and the fact that symptoms are nonspecific. Treatment is mainly focused on relieving symptoms, with hormonal therapies such as progestins and oral contraceptives, which help control pain and slow the progression of the disease, but do not cure it. In advanced cases, surgery may be necessary. In addition, endometriosis is associated with pregnancy complications, such as premature birth and miscarriages.

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