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Unsolicited Review

The endocrine aspects of endometriosis

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Abstract

Endometriosis is a chronic gynecologic disease of reproductive-age women, causing menstrual pain and infertility. Endocrine and inflammatory mechanisms drive its development, with estrogen/progesterone imbalance contributing to extrauterine implantation and persistence of ectopic endometrial cells. Chronic pain also induces stress-related disorders, worsening the quality of life. Infertility results from inflammatory, ovarian, and endometrial changes, and adverse pregnancy outcomes are reported. Diagnosis of endometriosis is clinical and imaging based. Furthermore, gastrointestinal, urinary, or autoimmune comorbidities complicate endometriosis management. Hormonal treatments, including progestins, estro-progestins, gonadotropin-releasing hormone analogs (GnRH-a), or oral antagonists, suppress menstruation and relieve pain. The relevant endocrine aspects and the systemic comorbidities make endometriosis a syndrome that requires a multidisciplinary diagnostic and therapeutic approach.

Keywords: endometriosis, estrogens, progesterone, inflammation, pregnancy, hormonal treatment, autoimmunity

Significance

Endometriosis is increasingly recognized as a systemic endocrine disorder, rather than a localized gynecological disease. This review highlights the central role of estrogen–progesterone imbalance in driving chronic pain and infertility while also exploring how hormonal dysregulation contributes to altered metabolic profiles in affected women. The interaction between sex hormones and immune dysfunction is examined in the context of autoimmune comorbidities frequently associated with endometriosis. By integrating current evidence on hormonal pathophysiology with therapeutic strategies—including progestins, combined hormonal contraceptives, and gonadotropin-releasing hormone analogs (GnRH-a) or antagonists—this review provides a comprehensive endocrine-focused perspective on endometriosis. These insights support the need for hormone-centered, multidisciplinary management approaches and advance our understanding of the systemic nature of this complex disease.

Introduction

Endometriosis is a benign gynecologic disease characterized by the presence of endometrial tissue outside the uterine cavity. It primarily affects women of reproductive age and is commonly associated with dysmenorrhea and infertility.[1] The incidence is 2%-10% among fertile age women and 30%-40% among those with infertility, although advancements in diagnostic techniques have led to an increased detection rate.[2] Sex steroid hormonal changes are considered the primary pathogenetic factors,[3] which contribute to implantation, proliferation, and invasion of pelvic peritoneum by ectopic endometrial cells. Genetic and epigenetic mechanisms are also described.[4] The localization of the endometriotic lesions is widespread in the pelvic cavity, often affecting various organs and functions, even though some extra pelvic endometriosis implants have been described (Figure 1). The most common symptoms are pain and infertility, and the clinical presentation combined with imaging allows noninvasive diagnosis, without a surgical biopsy and histological confirmation.[1] The presence of comorbidities and nonspecific symptoms complicates the diagnostic pathway

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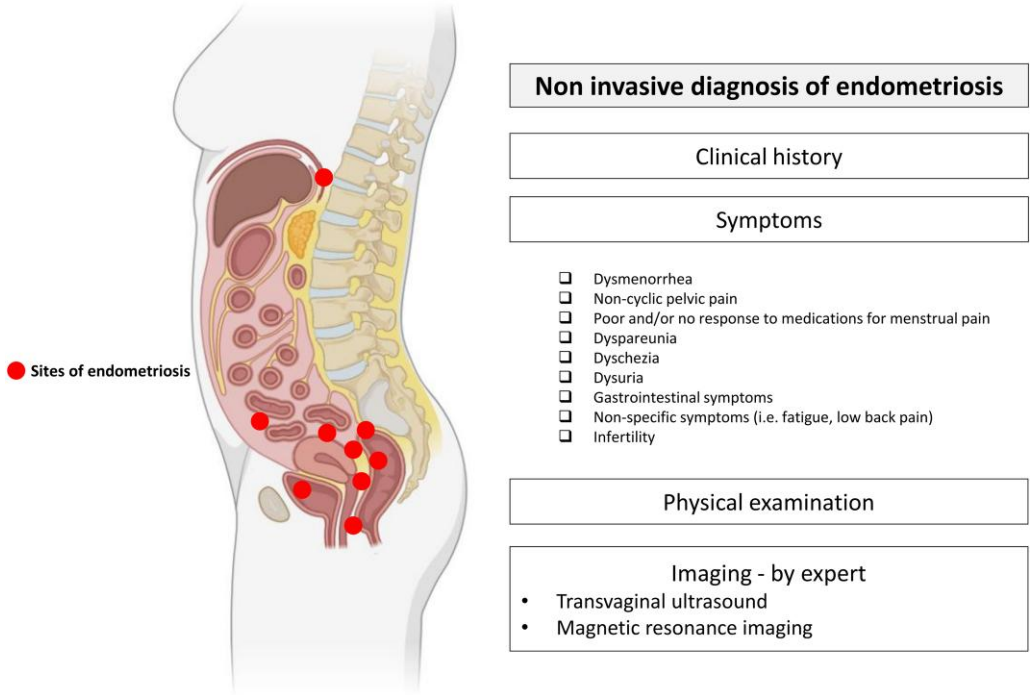

Figure 1. Endometriosis locations and the noninvasive diagnostic tools. Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity, with the most common sites being within the pelvis, particularly on the ovaries, peritoneum, uterosacral ligaments, and Pouch of Douglas. Endometriotic lesions can also appear in less typical sites, including the bowel and bladder, and, more rarely, in extrapelvic regions such as the diaphragm. The noninvasive diagnosis of endometriosis relies on a comprehensive approach that combines clinical history, symptom assessment, and imaging techniques, including transvaginal ultrasound and magnetic resonance, performed by experts.

and therapeutic management,[5] further reinforcing the need for a multidisciplinary approach and supporting the classification of endometriosis as a chronic systemic disorder.[6]

Role of ovarian sex hormones

Serum estrogen and progesterone levels in women with endometriosis are not significantly different from those found in healthy women. Increased estrogen receptor (ER) activity, local estrogen production in endometriotic lesions, and reduced progesterone receptor (PR) activity (progesterone resistance) are key factors driving the development of endometriotic lesions. These endocrine changes influence the peritoneal scavenger pathway (apoptosis, autophagia, immune function) allowing the survival, proliferation, and invasion of endometriotic cells into the peritoneum. Ectopic cells undergo the typical menstrual cycle changes; however, neoangiogenesis, neurogenesis,[7] and fibrogenesis[8] are also observed, with chronic inflammation and the entrapment of nerve fibers, contributing to pain symptoms (Figure 2).

Estrogens play a fundamental role in the survival and progression of endometriotic lesions, acting as key biological drivers of chronic inflammation. Evidence indicates that endometriotic tissue expresses the complete set of steroidogenic genes, including aromatase, enabling the de novo local synthesis of estradiol (E2).[9,10] Endometriotic cells express a full cascade of steroidogenic proteins and enzymes (steroidogenic acute regulatory protein [STAR]), enabling the conversion of cholesterol into substantial quantities of E2. The nuclear receptor steroidogenic factor-1 plays a pivotal role in this process by recruiting steroidogenic gene promoters, thereby enhancing E2 synthesis.[11] Overexpression of cyclooxygenase-2 (COX-2) drives persistent local production of both prostaglandins and estrogens, through a self-sustaining feedback loop.[12]

Furthermore, the upregulation of ERβ and downregulation of ERα are described in endometriosis.[13] Epigenetic modifications, such as the hypermethylation of ERα promoter regions, lead to decreased expression, while the ERβ promoter becomes hypomethylated, resulting in an increased expression.[3,9,14] ERβ activation promotes pathways that enhance endometriotic lesion survival and stimulate the production of inflammatory mediators, which in turn activate nociceptors, contributing to the characteristic pain associated with endometriosis,[9] lesion persistence, and progression.[13] The pathological levels of local E2 biosynthesis have also been associated with decreased apoptosis in endometriotic stromal and epithelial cells, compared to eutopic endometrial ones.[15] Furthermore, estrogens influence immune function within endometriotic lesions. Peritoneal fluid macrophages from women with endometriosis exhibit increased ERβ expression, and in a mouse model, E2 treatment has been shown to enhance macrophage recruitment to lesions and upregulate macrophage migration factor expression.[13] This estrogen-driven immune modulation contributes to the inflammatory response and lesion maintenance in endometriosis.[3]

The inadequate transcription of PR genes despite the presence of bioavailable progesterone explains the progesterone resistance,[16] resulting in the growth of endometriotic lesions.[9] The dysregulation of PRA and PRB isoforms, coactivators, and downstream effectors[17] and the epigenetic promoter hypermethylation and microRNA-mediated regulation have been implicated in progesterone resistance.[17]

Building on the evidence of estrogen and progesterone signaling dysregulation in endometriosis, emerging research suggests that environmental factors, particularly endocrine-disrupting

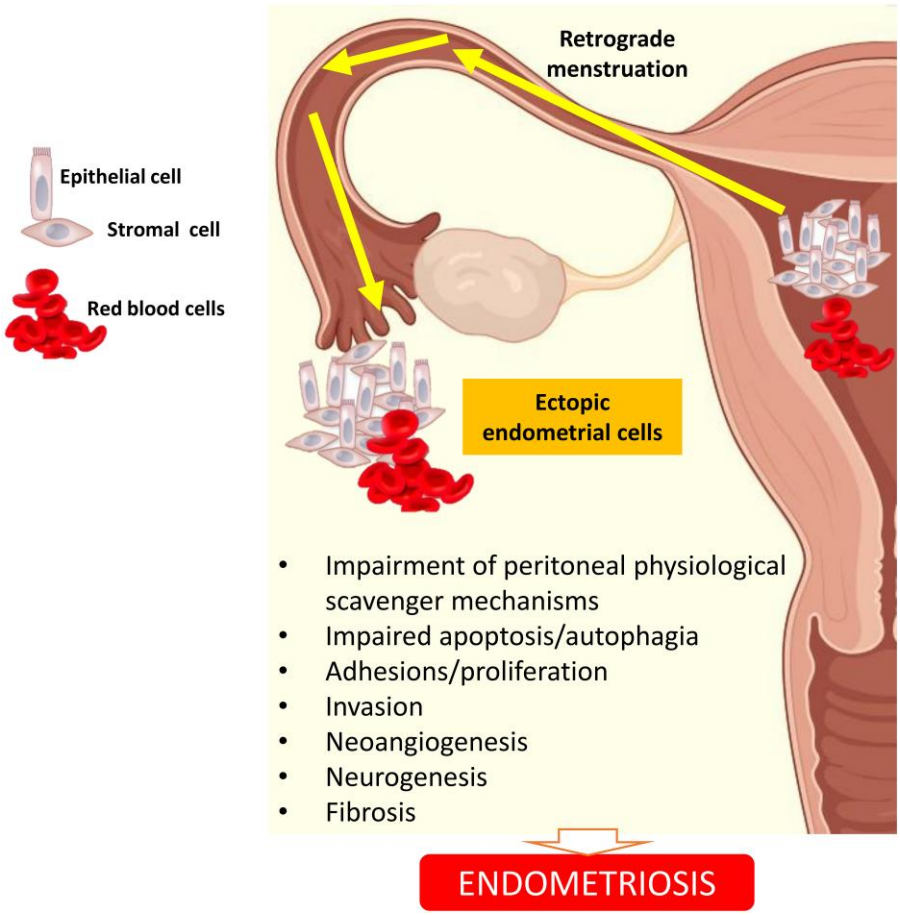

Figure 2. Pathogenetic mechanisms of endometriosis. The pathogenesis of endometriosis is multifactorial and involves a complex interplay between cellular, immunological, and molecular mechanisms. One key factor is the impairment of peritoneal physiological scavenger mechanisms, which limits the clearance of ectopic endometrial cells, allowing them to implant and persist. Additionally, defects in apoptosis and autophagy contribute to the survival of these cells outside the uterine cavity, while enhanced cellular proliferation and adhesion promote lesion establishment and growth. Invasion into surrounding tissues is facilitated by increased expression of matrix metalloproteinases and other proteolytic enzymes. Neoangiogenesis supports lesion survival by supplying nutrients and oxygen, whereas neurogenesis contributes to the development of chronic pelvic pain through increased nerve fiber density within lesions. Over time, chronic inflammation and tissue remodeling lead to fibrosis, further exacerbating symptoms and contributing to disease progression.

chemicals (EDCs), may further contribute to the pathogenesis and persistence of the disease. Compounds such as polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), phthalates, and bisphenol A (BPA) have been shown to interfere with hormonal signaling, modulate immune responses, and alter gene expression via epigenetic mechanisms. A recent meta-analysis of 30 epidemiological studies confirmed a significant association between exposure to specific EDCs and an increased risk of endometriosis, with odds ratios ranging from 1.27 to 1.58.[18] Experimental studies further suggest that EDCs may promote ectopic endometrial growth by enhancing ER expression and proinflammatory signaling[19] or by altering gene regulation through epigenetic modifications.[20] These findings support the hypothesis that EDC exposure acts as an environmental cofactor in susceptible individuals, promoting lesion survival and immune dysregulation and potentially contributing to resistance to hormonal therapy. Including the impact of EDCs adds a critical dimension to understanding the complex endocrine and environmental interplay underlying endometriosis.

Emerging evidence from genetic, biochemical, and molecular studies suggests that lower systemic androgen levels, particularly bioavailable testosterone, may play a causal role in the development and symptom severity of endometriosis. Recent Mendelian randomization analyses have demonstrated causal effect of genetically predicted lower testosterone on endometriosis.[21,22] A short anogenital distance is a proxy for low prenatal testosterone and has been correlated with a higher risk of developing endometriosis in adult life.[23] Lower prenatal and postnatal testosterone cause earlier menarche and shorter menstrual cycles, both well-established risk factors for endometriosis, because they increase the cumulative menstrual exposure over a woman's lifetime.[24,25] Furthermore, clinical research indicates that reduced circulating testosterone correlates with increased days per month of pelvic pain and pain sensitivity, due to the inverse association with inflammation, and/or through links with β-endorphin levels within the central nervous system.[24,26] Thus, this hormonal environment, characterized by low androgens and unopposed estrogen action, creates a setting conducive to the development and persistence of endometriotic lesions. At the tissue level, endometriotic lesions express androgen receptors and steroid-converting enzymes, such as 5α-reductase, enabling local conversion of testosterone to dihydrotestosterone

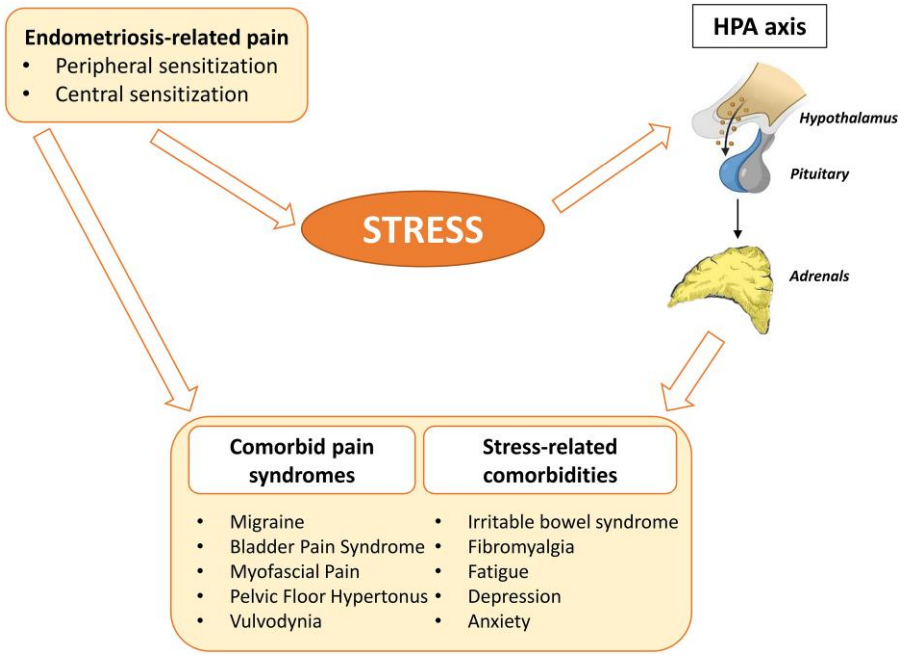

Figure 3. Endometriosis, pain, and stress mechanisms: Comorbid pain syndromes and stress-related comorbidities. Endometriosis is a chronic pain disorder with complex interactions between peripheral and central pain mechanisms. Women with endometriosis frequently experience comorbid pain syndromes, which share features of central sensitization and altered pain processing. Chronic pelvic pain may lead to long-term changes in the nervous system, amplifying pain perception, that in turn contributes to the development of stress-related comorbidities. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and elevated cortisol levels further exacerbate inflammation and pain sensitivity, creating a vicious cycle of pain and stress.

and active androgen signaling.[27] Moreover, androgens are known to modulate immune function, and their relative deficiency may exacerbate estrogen-driven immune activation and neuroinflammation within endometriotic lesions.[28] While the precise mechanisms remain to be fully elucidated, these observations suggest a potential modulatory role for testosterone in lesion persistence and pain processing, warranting further investigation.

Symptoms: pain

Dysmenorrhea is the most common symptom of endometriosis patients, and depending on the locations of lesions, dyspareunia, dysuria, dyschezia, and nonmenstrual pelvic pain can be associated, causing a diminished quality of life and decreased daily functioning, work productivity, and sexual satisfaction.[29] The mechanisms contributing to endometriosis-induced pain are neurogenic inflammation, neuroangiogenesis, and fibrosis. From a neurobiological perspective, pain disorders, such as endometriosis, result from a peripheral sensitization and cross-organ sensitization as shown by the presence of comorbid pain syndromes, namely vulvodynia, irritable bowel syndrome (IBS), painful bladder syndrome/interstitial cystitis, and myofascial pain/pelvic floor hypertonus[30] (Figure 3). Neuroplasticity of peripheral sensory nerves is a central process in the development of chronic visceral pain. The peripheral hypersensitivity of nociceptive fibers at lesion sites may play a role in allodynia and hyperalgesia seen in endometriosis patients[31] with marked changes in cortical and spinal sensory pathways leading to central sensitization, as a consequence of reiterative peripheral signaling.[32,33] Endometriosis-related pain is associated with stress, through the activation of the hypothalamus–pituitary–adrenal axis,[34] and stress-related disorders: Sexual dysfunction, fibromyalgia, chronic fatigue, migraine, and mental health disorders[35,36] (Figure 3). Robust epidemiological research shows elevated risks of depression, anxiety, bipolar disorder, eating disorders, personality disorders, and even substance use disorders among individuals with endometriosis—and intriguingly, psychiatric conditions may also precede and increase endometriosis risk, suggesting a bidirectional relationship.[37] Genetic studies bolster this connection: Large-scale analyses reveal significant phenotypic and genetic correlations between endometriosis and depression, anxiety, and eating disorders, likely due to pleiotropy and shared heritable mechanisms.[38,39] Clinically, poor body image contributes to psychological distress in endometriosis, mediated by factors such as low self-esteem and self-criticism.[40] This is particularly relevant given that pelvic pain, hormonal treatments, and abdominal bloating ("endo belly") can drastically alter body perception and bodily self-awareness.[41] Furthermore, disordered eating behaviors may emerge as maladaptive coping strategies in response to chronic pain, low body appreciation, or a perceived loss of control over the body.[42] In individuals with endometriosis, body image disturbance often coexists with impaired sexual functioning, shame, and avoidance behaviors, further compounding emotional distress and intimacy challenges.[43]

Sexual dysfunction is a prevalent and multifaceted issue among individuals with endometriosis, affecting up to 50%-70% of patients at some point during their disease course.[44] Deep dyspareunia is the most commonly reported issue; however, sexual dysfunction in endometriosis extends beyond pain and encompasses diminished sexual desire, reduced arousal, orgasm difficulties, and impaired satisfaction and intimacy. Furthermore, hormonal treatments, which are widely used to manage endometriosis-associated symptoms, may themselves influence sexual function,[45] through their suppression of circulating estrogen and androgens, both of which play critical roles in the neuroendocrine regulation of sexual desire and arousal.

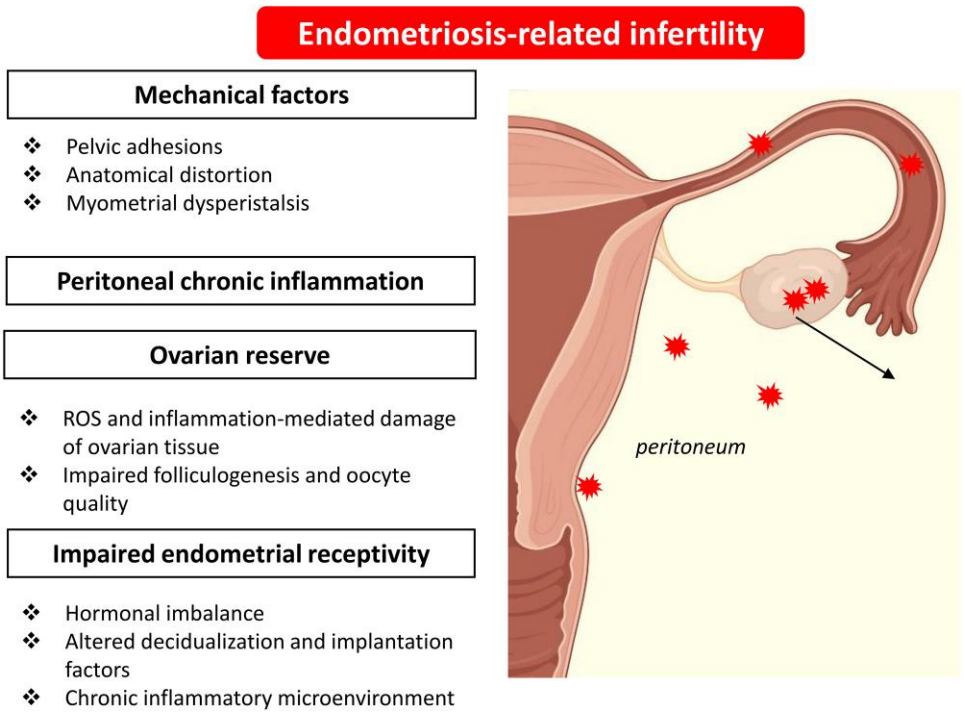

Figure 4. Mechanisms of infertility in endometriosis. Anatomical distortion due to pelvic adhesions interferes with ovum release, tubal pick-up, and sperm transport. Inflammatory processes within the peritoneal environment alter cytokine and prostaglandin levels, creating a hostile milieu that impairs fertilization and embryo implantation. Oxidative stress and immune dysfunction negatively affect oocyte quality, sperm function, and endometrial receptivity. The ovarian reserve may be compromised, either due to the disease itself or as a consequence of surgical interventions. Thus, timely fertility preservation strategies such as oocyte cryopreservation should be considered.

Symptoms: infertility

Endometriosis is a leading cause of infertility, affecting approximately 30%-50% of women with the condition. Notably, about 10% of patients undergoing assisted reproductive technology (ART) treatments are affected by endometriosis, underscoring its clinical relevance in fertility care. The link between endometriosis and infertility is multifactorial, involving both anatomical and functional disruptions.[46,47] Anatomical distortion due to pelvic adhesions can interfere with fertilization; inflammation within the peritoneal environment creates a hostile milieu; additionally, oxidative stress and immune dysfunction may negatively affect oocyte quality, ovarian reserve, and endometrial receptivity (Figure 4). In cases of severe endometriosis, especially those involving bilateral endometrioma or recurrent endometriomas, fertility preservation strategies such as oocyte cryopreservation should be considered. This is particularly important for patients at risk of diminished ovarian reserve due to the disease itself or as a result of surgical intervention. Overall, individualized fertility counseling is essential in the management of endometriosis. Patient's age, disease severity, ovarian reserve, and reproductive goals should be considered, in order to guide therapeutic decisions and optimize reproductive outcomes.[48]

Mechanisms of endometriosis-related infertility

Inflammation

Erythrocytes carried into the peritoneal cavity by menstrual reflux and/or bleeding lesions release into the peritoneal environment pro-oxidant and proinflammatory factors, such as hemoglobin and its highly toxic by-products heme and iron. The abnormal macrophage activation initiates the process of inflammation and induces oxidative stress affecting the reproductive mechanisms.[49]

Ovarian reserve and oocyte quality

In patients with ovarian endometriosis (OMA), a local inflammation in the ovarian cortex results in massive fibrosis of the periendometrioma and loss of cortex-specific stroma, associated with a vicious circle of dysregulated folliculogenesis.[50] Exosomes from in vitro culture of the endometrioma wall are cell-derived vesicles containing microRNAs (miRNAs) that regulate post-transcriptional gene expression, and some genes may impact the ovarian reserve.[51]

Anti-Mullerian (AMH) hormone maintains follicle dormancy. Serum AMH levels are decreased in women with endometriomas even prior to surgical intervention, suggesting that ovarian reserve may be compromised by the disease itself, independently of surgical impact.[52,53] The surgical removal of OMA exerts significant damage on the ovary, further reducing ovarian reserve, including AMH levels.[54-56] Endometriosis also negatively affects oocyte quality, in terms of several relevant clinical and biological outcomes, altered morphology, lower cytoplasmic mitochondrial content, and increased apoptosis.[57,58]

Impaired endometrial receptivity

A defective implantation in endometriotic women could be due to a reduced endometrial receptivity or decidualization capacity, which is dependent upon hormonally regulated molecular processes. Functional dysregulation of steroid hormone signaling in endometriosis plays an important role in

impairing endometrial receptivity.[59,60] Dysregulations of selected genes that are implicated in the implantation process and decreased HOXA10 and HOXA11 expression are involved in impaired endometrial receptivity in endometriosis.[46] Additionally, aberrant expression of integrins Beta 3 and reduction of other transcriptional factors (IGFBP1, GATA2, FOXO1, ARID1A, NOTCH1, and WNT4) and inactivated FOXO1 are compromised in the eutopic endometrium of women with endometriosis.[61]

Endometriosis and pregnancy

Pregnancy is often associated with a temporary improvement in endometriosis-related symptoms, largely due to the hormonal and immunological changes that occur during gestation. Elevated levels of progesterone lead to decidualization of ectopic endometrial tissue, which can suppress lesion activity and reduce inflammatory responses.[62] However, not all patients experience relief, and in some cases, decidualized lesions or endometriomas may enlarge, rupture, or cause complications such as ovarian torsion. Furthermore, women with endometriosis have been reported to have an increased risk of pregnancy complications: Preterm birth, preeclampsia, and intrauterine growth retardation are the most frequent complications, but also postpartum hemorrhage has been described.[63,64] In addition, rare but severe and unpredictable complications during pregnancy have been reported with puerperal changes in ectopic lesions.[64,65]

Pregnancy-related changes in endometriotic lesions

One of the most notable changes during pregnancy is the decidual transformation of ectopic endometriotic tissue. The decidualization of endometriosis in pregnancy is attributed to increased progesterone levels, and it is clinically observed especially in OMAs. Although there is limited data regarding the growth dynamics of endometriosis lesions in pregnancy, in most cases, lesions remain unchanged or reduce in size.[66,67] Similarly, MRI studies have reported a significant decrease in the size of deep infiltrating endometriosis (DIE) lesions after pregnancy.[68]

The hormonal environment during pregnancy plays a critical role in the changes observed in endometriotic lesions.[69] Several mechanisms contribute to pregnancy-induced modifications in these lesions: (1) the absence of cyclic menstruation and retrograde bleeding during pregnancy reduces the stimulation and proliferation of peritoneal and ectopic implants; (2) high levels of placental steroid hormones exert a direct effect on endometriotic lesions, promoting decidualization and decreasing the intra- and perilesional inflammatory status; and (3) decidualization of ectopic endometrial lesions involves the transformation of stromal fibroblasts into epithelioid-like decidual cells along with a substantial influx of immune cells. This process is associated with a long-lasting alteration of lesion activity, which may persist beyond pregnancy.[70]

Postpartum persistence of endometriotic changes

Although pregnancy-induced decidualization often results in the reduction of ectopic lesions, the long-term persistence of these changes remains uncertain. The resumption of menstrual cycles and ovulation postdelivery may contribute to the reappearance of symptoms and lesion regrowth in some women. In contrast, other findings indicate that pregnancy may have a prolonged suppressive effect on endometriosis. The immune-mediated changes associated with decidualization, including the influx of immune cells into ectopic lesions, may contribute to a sustained alteration in lesion activity, potentially delaying recurrence.[62]

Endometriosis and metabolism

Emerging evidences suggests that endometriosis affects metabolism in multiple tissues, including liver and adipose tissues, because of the systemic inflammation, increased oxidative stress, and altered energy homeostasis. Studies have identified changes in lipid metabolism, glucose homeostasis, and mitochondrial function in women with endometriosis, both locally within the lesions and systemically.[71,72] Systemic low-grade inflammation and oxidative stress in endometriosis may disrupt metabolic pathways, potentially increasing the risk for metabolic comorbidities such as dyslipidemia and insulin resistance. The significant impact of endometriosis on metabolic processes suggests that the disease extends beyond the reproductive system. Patients with endometriosis often exhibit a lower body mass index (BMI), potentially due to altered hepatic gene expression affecting lipid metabolism.[73] Metabolomic analyses have revealed reductions in key metabolites such as carnitine, creatine phosphate, nicotinamide adenine dinucleotide hydride, flavin adenine dinucleotide, tryptophan, and malic acid in endometriotic tissues, suggesting compromised cellular energy metabolism.[74]

Cardiovascular changes

Recent studies suggest a potential association between endometriosis and an increased risk of cardiovascular diseases (CVDs).[75-77] In the prospective Nurses' Health Study (NHS) II, which enrolled 116 430 women, whose 5296 reported a laparoscopically diagnosis of endometriosis, an increased risk of combined coronary heart disease (CHD) (risk ratio 1.62, 95% CI 1.39-1.89) was found. An increased risk of stroke (multivariable-adjusted hazard ratio 1.34, 95% CI 1.10-1.62) was also confirmed, of which nearly 40% was attributed to the impact of prior hysterectomy/oophorectomy.[78] Chronic systemic inflammation, oxidative stress, and immune dysregulation—hallmarks of endometriosis—are known contributors to endothelial dysfunction and atherogenesis. The emerging evidence suggests that the systemic chronic inflammation and an elevated atherogenic lipid profile in endometriosis may contribute to an increased risk of coronary heart disease (CHD),[79] myocardial infarction, composite CVD, ischemic stroke, and all-cause mortality.[80,81] In addition to the established mechanisms underlying cardiovascular risk in endometriosis, adrenal dysfunction may also play a pathogenetic role. Chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, frequently associated with the persistent stress response observed in patients with endometriosis, can lead to dysregulated cortisol secretion, which may perpetuate inflammatory processes and impair stress adaptation.[35,82] Moreover, a preliminary study reported that women with endometriosis exhibit a significantly elevated aldosterone-to-renin ratio, despite normal aldosterone levels, along with increased systolic blood pressure—findings suggestive of heightened aldosterone activity.[83] These hormonal imbalances may further contribute to the cardiovascular abnormalities seen in endometriosis, including endothelial dysfunction, vascular inflammation, fibrosis, hypertension, and metabolic alterations.

Altogether, these findings support the existence of a potential endocrine–immune interface, linking chronic stress, adrenal hormone dysregulation, and cardiovascular comorbidity in endometriosis.[84] This underscores the importance of addressing not only the gynecologic and inflammatory aspects of the disease but also HPA axis dysfunction and stress management as part of a comprehensive, multidisciplinary care approach.

Endometriosis and autoimmune comorbidities

Endometriosis is increasingly recognized as a systemic condition with endocrine–immune interactions that contribute to its pathogenesis and progression.[6,85] The estrogenic environment activates macrophages to secrete proinflammatory cytokines with concomitant reduced PR activity.[86] Endocrine and immune modifications may explain the epidemiological evidence linking endometriosis to a number of autoimmune disorders. Indeed, notable autoimmune comorbidities, affecting multiple organ systems beyond the reproductive tract, affect patients with endometriosis.[87] In particular, an increased association with organ-specific autoimmune diseases: Coeliac disease, inflammatory bowel diseases (IBD), thyroid disorders, and systemic autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis[88-91] (Figure 5). This observation underscores the extensive impact of endometriosis across multiple body systems. However, the relationship between endometriosis and autoimmune diseases remains incompletely understood. It is unclear whether systemic immune dysregulation predisposes individuals to both conditions or if endometriosis itself triggers local and systemic immune alterations that lead to autoimmune diseases.[92-95] One proposed hypothesis suggests that hormonal imbalances inherent to endometriosis may facilitate the development of autoimmune disorders.[96] Estrogens modulate key immune pathways for autoimmune disorders, including the type 1 interferon response, CD4+ T helper cell differentiation, and autoreactive B cell survival.[97] Consequently, hormonal disturbances intrinsic to the disease as well as hormonal therapies used to manage endometriosis may act as drivers of autoimmune diseases.

Hormonal treatments for endometriosis

Hormonal drugs are the primary treatment for endometriosis, aiming to suppress menstruation through artificial menopause or pseudopregnancy.[34] Endometriosis requires a lifelong management strategy, with the goal of optimizing the use of medical therapy and avoiding repeated surgical procedures.[1] While they do not cure the disease, they effectively reduce pain and can delay or abolish the need for surgery.[98] Progestins are first-line treatments, with GnRH analogs or oral GnRH antagonists used as second-line options. Combined hormonal contraceptives (CHCs) are also commonly prescribed off-label[99] (Figure 6). These hormonal treatments exert their effects by targeting key pathogenic mechanisms of endometriosis, primarily through suppression of the hypothalamic–pituitary–ovarian (HPO) axis. This suppression induces a state of amenorrhea or pseudodecidualization, thereby inhibiting the cyclical hormonal stimulation required for the growth and maintenance of endometriotic lesions.[34,100-102]

Selective progesterone receptor modulators (SPRMs) and selective estrogen receptor modulators (SERMs) have been investigated as potential treatments for endometriosis due to their ability to modulate hormonal signaling at the tissue level.

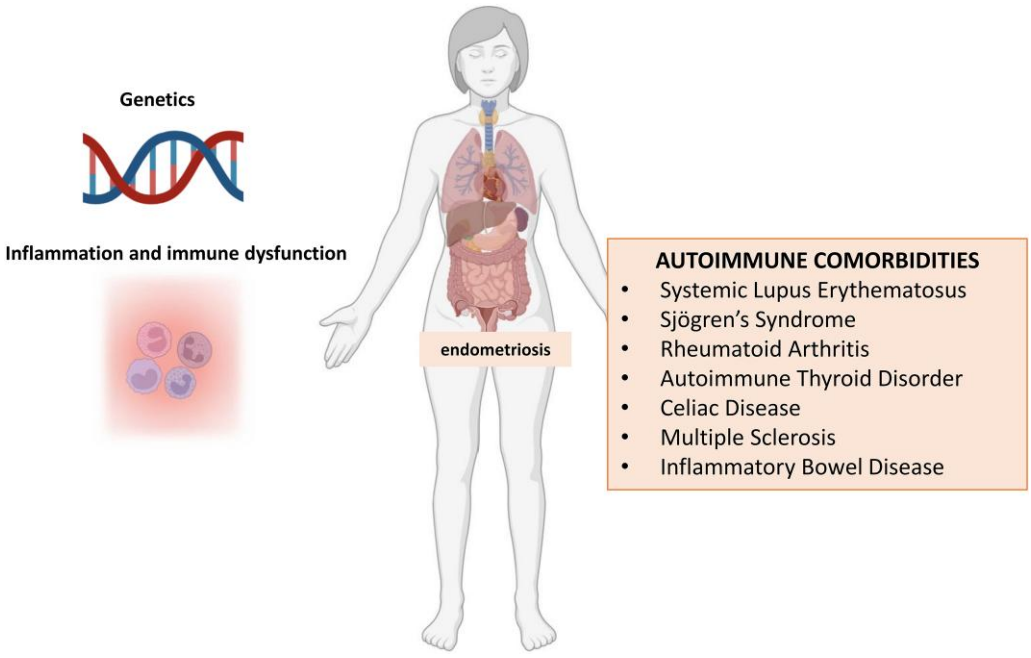

Figure 5. Endometriosis and autoimmune comorbidities. The association between endometriosis and immune-mediated comorbidities arise from shared pathophysiological mechanisms involving chronic inflammation, immune system dysregulation, and genetic susceptibility. In endometriosis, persistent activation of inflammatory pathways and the presence of proinflammatory cytokines contribute to an environment similar to that seen in autoimmune conditions. Aberrant immune responses, such as impaired natural killer (NK) cell activity, altered T-cell profiles, and the production of autoantibodies, may allow ectopic endometrial tissue to evade immune clearance, mirroring processes found in autoimmunity. Furthermore, genome-wide association studies (GWAS) have identified overlapping genetic loci that predispose individuals to both endometriosis and certain autoimmune disorders, supporting a common genetic background.

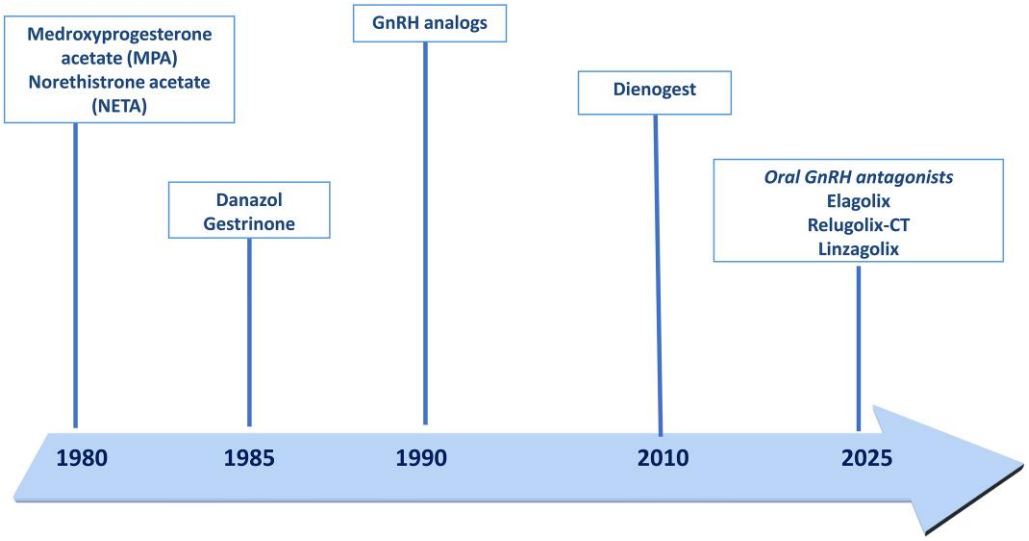

Figure 6. Hormonal drugs approved for endometriosis.

Despite promising preclinical and early clinical data, the use of both SPRMs and SERMs in endometriosis remains experimental and confined to research settings, because of safety concerns and inconsistent effects on pain symptoms. Aromatase inhibitors (AIs), such as letrozole and anastrozole, suppress the local and systemic conversion of androgens to estrogens by inhibiting the enzyme aromatase, which is aberrantly expressed in endometriotic lesions. However, because of side effects (bone mineral density [BMD] loss and arthralgia), AIs are not routinely used in clinical practice.

Progestins

Progestins, including dienogest (DNG), norethindrone acetate (NETA), and medroxyprogesterone acetate (MPA), are considered first-line treatments for endometriosis due to their efficacy in reducing pain and lesions, lower cost, and fewer adverse effects compared to GnRH agonists.[103] These therapies can be administered via oral, intramuscular, subcutaneous, or intrauterine routes.

Dienogest, a 19-nortestosterone derivative, has shown significant effectiveness in reducing pain associated with endometriosis.[104] Studies indicate that DNG, with substantial improvements in dysmenorrhea, dyspareunia, and chronic pelvic pain, may also reduce the volume of OMAs.[105,106] Furthermore, DNG does not negatively impact BMD, unlike GnRH agonists, making it a favorable long-term treatment option.[107,108] Dienogest has also proven effective in controlling pain in rectovaginal endometriosis and preventing symptom recurrence postsurgery.[109,110]

Norethindrone acetate, another 19-nortestosterone derivative, is effective in relieving pain in women with endometriosis, but at high dose may cause androgenic side effects such as weight gain, acne, and seborrhea. Norethindrone acetate at a dose of 5 mg or 2.5 mg remains a viable treatment, particularly in cases of rectovaginal endometriosis.[111] Medroxyprogesterone acetate, a 17-OH progesterone derivative, is available in both oral and depot formulations. It is effective in reducing pain associated with endometriosis, but long-term use may result in concerns regarding BMD loss, especially with depot MPA formulations. Despite these concerns, MPA remains a useful option for managing endometriosis-related pain.

Other progestin options for treating endometriosis-related pain include the following:

- Desogestrel: It reduces dysmenorrhea, chronic pelvic pain, and deep dyspareunia, but breakthrough bleeding is a common side effect.[112]
- Drospirenone: It decreases pain and improves quality of life in women with endometriosis, but breakthrough bleeding should be acknowledged.[113]
- Etonogestrel implant: A progestin-based contraceptive that has shown efficacy in managing endometriosis-related pain.[114]
- Levonorgestrel-releasing intrauterine system (LNG-IUS): Several randomized controlled trials have assessed the efficacy in endometriosis treatment. Levonorgestrel induces endometrial glandular atrophy and decidual transformation of the stroma, reduces endometrial cell proliferation, and enhances apoptotic activity.[115] Levonorgestrel-releasing intrauterine system has proven effective in alleviating pelvic pain symptoms caused by peritoneal and rectovaginal endometriosis and in reducing dysmenorrhea recurrence after conservative surgery,[115,116] with few adverse events and a very low discontinuation rate. It does not cause hypoestrogenism and requires only a single medical procedure for insertion every 5-7 years, making it a favorable long-term therapeutic option for women with chronic pelvic pain associated with endometriosis who do not wish to conceive.

Progestin therapy for endometriosis is generally well tolerated, but side effects can occur, particularly with long-term use. Common adverse effects include irregular uterine bleeding, mood changes, breast tenderness, bloating, vaginal dryness, decreased sex drive, and weight gain.

Historically, danazol, an androgenic progestin, has been used orally for endometriosis-related pain at a dose of 600 mg/day. However, its systemic use has declined due to significant androgenic side effects, including weight gain, acne, hirsutism, and adverse lipid changes. To mitigate these effects while preserving therapeutic efficacy, danazol can be administered vaginally, even though it remains an off-label use.[117]

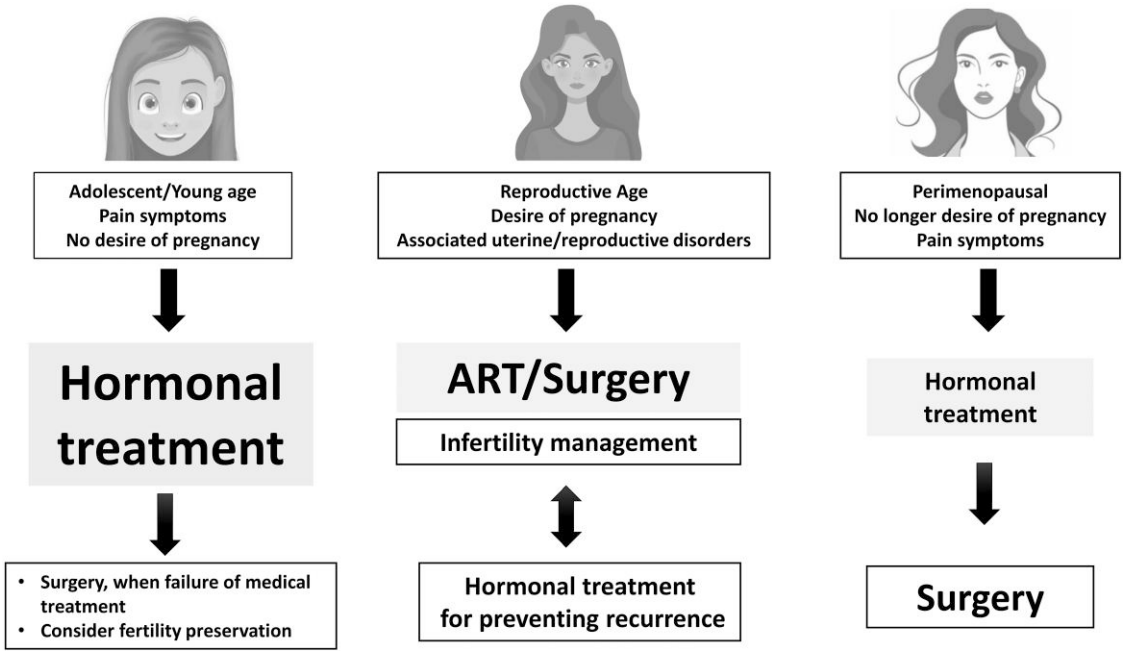

Figure 7. Treatment of endometriosis according to symptoms and age. The treatment of endometriosis should be individualized based on symptoms, age, and the patient's desire for pregnancy. In adolescents, management typically focuses on symptom relief, often using hormonal therapies such as combined oral contraceptives or progestins to reduce pain and suppress lesion growth while minimizing long-term side effects. In women of reproductive age, treatment depends heavily on fertility goals. For those desiring pregnancy, in case of infertility, assisted reproductive technologies or conservative surgery to remove endometriotic lesions may be prioritized to improve fertility outcomes. In women not seeking pregnancy, hormonal treatments are commonly used to manage pain and reduce recurrence. In the perimenopausal stage, treatment may still be required for persistent pain, and surgery may be an option for nonconservative treatment. In all cases, a multidisciplinary approach combining medical, surgical, and supportive care is essential for optimal quality of life.

Combined hormonal contraceptives

Although the use of CHCs in endometriosis is off-label for the treatment of endometriosis, they are widely used in clinical practice due to their well-established extracontraceptive benefits, particularly for the management of pain and menstrual-related symptoms.[98,118] Combined hormonal contraceptives act primarily by suppressing ovulation through inhibition of the HPO axis, thereby reducing endogenous estrogen levels. Additional mechanisms include endometrial thinning and anti-inflammatory effects, all of which contribute to decreased pelvic pain. Given that endometriosis is a chronic estrogen-dependent disease, the use of CHCs should involve the lowest effective dose of estrogen. This approach reduces the risk of stimulating ectopic lesions while maintaining contraceptive efficacy and symptom control. Therefore, selecting CHC regimens with low-dose estrogen components and pairing them with progestins characterized by high uterotropic activity is critical to achieving optimal symptom control. These compounds exert a strong progestogenic effect on the endometrial tissue, counteracting the proliferative action of estrogen on both eutopic and ectopic endometrial tissues, thereby inducing endometrial decidualization and subsequent atrophy.

To optimize therapeutic outcomes, CHCs should be administered in a continuous or extended regimen, which eliminates or significantly reduces menstrual bleeding.

Modern CHC formulations may include natural estrogens, such as estradiol valerate, micronized 17β-estradiol, or estetrol (E4).[119] These compounds offer improved metabolic and hemostatic profiles compared to traditional ethinylestradiol-based regimens.[120] Notably, estetrol has shown promising effects in preclinical models of endometriosis, by modulated apoptosis, inflammation, and hormonal receptor activity.[121]

Thus, CHCs represent a well-established, accessible, and reversible therapeutic strategy for the management of endometriosis-associated pain. Their effectiveness is enhanced by continuous administration and careful selection of estrogen type and dose, particularly given the underlying hormone-responsive nature of the disease.

Gonadotropin-releasing hormone analogs

Gonadotropin-releasing hormone analogs (GnRH-a) such as goserelin, leuprolide, and triptorelin have been used since the 1990s in the treatment of endometriosis, where they are effective in alleviating pain.[98] However, the use of GnRH-a is limited by hypoestrogenic side effects, such as vasomotor symptoms, mood disturbances, vaginal dryness, decreased libido, and loss of BMD. These agents are approved for use as monotherapy for a maximum of 6 months due to these adverse effects. To extend treatment duration and improve tolerability, GnRH-a are often combined with add-back therapy—typically low-dose estrogen and/or progestin—which helps alleviate hypoestrogenic symptoms while maintaining efficacy and protecting bone health. However, GnRH-a are considered a second-line treatment for endometriosis, generally reserved for selected cases and for short-term use.[98]

Oral gonadotropin-releasing hormone antagonists

Three oral GnRH antagonists (elagolix, relugolix, and linzagolix) have yielded very robust results in randomized, placebo-controlled clinical trials (RCTs) for the treatment of endometriosis-associated pain. Unlike agonists, which initially cause a temporary surge in gonadotropins (flare effect), GnRH antagonists provide rapid, dose-dependent suppression of the

HPO axis without this initial hormonal flare. This allows for faster symptom relief and improved tolerability, along with rapid reversibility. Administered orally, they also offer greater convenience and patient adherence compared to injectable formulations. Furthermore, oral GnRH antagonists allow for flexible dosing, enabling partial estrogen suppression. However, in the absence of add-back therapy, hypoestrogenic side effects such as hot flushes and BMD loss remain significant concerns.[122]

The efficacy of elagolix was evaluated in 2 large, double-blind, phase III trials (Elaris EM-I and Elaris EM-II) and in the extension study.[123,124] In these both studies, the percentage of subjects who experienced a clinical improvement in dysmenorrhea at 12 weeks of treatment was 46.4% and 43.4% with 150 mg elagolix once daily and 75.8% and 72.4% with 200 mg elagolix twice daily. Overall, alleviation of both dysmenorrhea and nonmenstrual pelvic pain was sustained for 24 and 52 weeks. At week 52, elagolix causes a dose-dependent decrease in BMD (more than 3.5% at a dose of 200 mg). Thus, elagolix leads to marked improvements in dysmenorrhea and nonmenstrual pelvic pain, albeit at the cost of hot flushes and a pronounced decrease in BMD, if not combined with add-back therapy.[125]

The efficacy of relugolix combined with add-back therapy (ABT) was evaluated by a phase III clinical trials (SPIRIT-1 and 2) and extension study.[126,127] The dose of 40 mg with add-back therapy (1 mg of E2 and 0.5 mg NETA) met the dysmenorrhea responder criteria, rapidly from severe at baseline to mild by week 8 and was sustained through to week 24 and week 52. Bone mineral density changes in the lumbar spine from baseline to week 24 and 52 were less than 1%.

The efficacy of linzagolix was investigated at doses of 75 mg without ABT and 200 mg with add-back therapy.[128] In EDELWEISS 3 study, the proportion of responders for dysmenorrhea in the 200 mg linzagolix with add-back therapy group was 72.9% at 3 months. The proportion of responders for dysmenorrhea in the 75 mg linzagolix group was 44.0%. At 24 months (extension study), both doses demonstrated a high percentage of responders for dysmenorrhea and nonmenstrual pelvic pain, showing that the effects were sustained over a long-term period. At both doses, dysmenorrhea decreased rapidly from severe at baseline to mild by week 8 and was sustained through weeks 24 and 52. In both groups, hypoestrogenic effects were mild, with low rates of hot flushes and bone density loss of <1%. These characteristics suggest that lower doses of linzagolix could be suitable for chronic treatment of endometriosis-associated pain without the need for concomitant hormonal add-back therapy and may offer a viable option for women who do not wish to have add-back therapy or in whom it is contraindicated.

Conclusion

Endometriosis requires a lifelong management approach, with personalized treatment strategies tailored to the patient's age, symptom severity, and reproductive goals (Figure 7). Hormonal therapy is the first-line treatment, reducing pain, recurrence, and unnecessary surgeries. A multidisciplinary, patient-centered approach improves quality of life and addresses comorbidities.

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Authors' contributions

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Ethical approval

This study was conducted according to the Declaration of Helsinki. As this is a review of previously published literature and does not involve human participants, identifiable personal data, or animal subjects, ethical approval was not required in accordance with institutional and international guidelines.

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