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REVIEW

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Role of hormonal therapies in endometriosis: balancing efficacy and safety

Simone Ferrero[a,b], Michele Paudice[a,c], Umberto Perrone[d,e], Francesco Paolo Rosato[a], Giuseppe Gullo[f], Valerio Gaetano Vellone[c,g] and Fabio Barra[a,e]

[a]Unit of Obstetrics and Gynecology, Azienda Ospedaliera Metropolitana, Genoa, Italy; [b]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy; [c]Department of Integrated Diagnostic and Surgical Sciences (DISC), University of Genoa, Genoa, Italy; [d]Unit of Obstetrics and Gynecology Viareggio, P.O. Versilia - AUSL Toscana Nord Ovest, Camaiore, Italy; [e]Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; [f]Department of Obstetrics and Gynaecology, AOOR Villa Sofia-Cervello, University of Palermo, Palermo, Italy; [g]Pathology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

ABSTRACT

Introduction: Endometriosis is a chronic, estrogen-dependent inflammatory disorder requiring long-term management strategies that balance efficacy with systemic safety. Although hormonal therapies remain the cornerstone of treatment, the optimal degree of estrogen suppression needed to achieve durable symptom control while minimizing adverse effects remains controversial.

Areas covered: This narrative review, based on a targeted PubMed/MEDLINE literature search and review of major guideline documents published up to January 2026, critically evaluates the efficacy, mechanisms of action, and safety profiles of combined oral contraceptives, progestins, GnRH agonists, and oral GnRH antagonists within an estrogen-threshold modulation framework.

Expert opinion: Combined oral contraceptives and progestins remain preferred first-line therapies because they provide effective pain control with acceptable tolerability and preservation of bone health. GnRH agonists and oral GnRH antagonists offer more profound endocrine suppression and are particularly useful in women with moderate-to-severe pain or inadequate response to first-line treatment, although their use is limited by hypoestrogenic adverse effects. Increasing evidence suggests that maximal estrogen suppression is not universally necessary to achieve clinical benefit and may expose patients to unnecessary long-term toxicity. Future management will likely move toward individualized estrogen-threshold modulation integrated with multimodal pain management and biomarker-driven approaches.

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Endometriosis; estrogen suppression; progestins; GnRH antagonists; hormonal therapy; chronic pain

1. Introduction

Endometriosis is a chronic, estrogen-dependent, inflammatory condition characterized by the presence of endometrial-like tissue outside the uterine cavity, primarily affecting women of reproductive age. It is estimated to affect approximately 10% of women globally and up to 50% of those with infertility or chronic pelvic pain [1,2]. Despite its high prevalence and substantial impact on quality of life, fertility, sexual function, and work productivity, endometriosis is underdiagnosed and undertreated, with diagnostic delays often exceeding seven years [3].

Although surgery plays a role in selected patients, recurrence rates after conservative surgery are high, with cumulative recurrence rates ranging from 20% to 50% within 5 years [4]. Therefore, endometriosis should be considered a chronic condition requiring long-term management [5]. Hormonal therapy is the cornerstone of medical management for endometriosis, especially for women not currently seeking pregnancy.

The primary therapeutic goals of hormonal therapies are to relieve pain symptoms, theoretically slow disease progression, and reduce the risk of recurrence after surgery. A wide array of hormonal agents is currently available, including combined oral contraceptives (COCs), progestins, gonadotropin-releasing hormone (GnRH) agonists, and antagonists. Each class differs in its mechanism of action, clinical efficacy, safety profile, and suitability for long-term use. The growing number of therapeutic options has increased the potential to personalize treatment, but it also poses new challenges. Efficacy must be weighed against side effects such as breakthrough bleeding, hypoestrogenism-related symptoms, metabolic changes, and potential long-term risks such as bone mineral density (BMD) loss [6]. Moreover, patient preferences, treatment adherence, costs, and access to newer agents also influence therapeutic choices in clinical practice. Recent advances, including the introduction of oral GnRH antagonists, highlight the need to revisit the positioning of hormonal therapies within the treatment landscape. In this context, a comprehensive and critical evaluation of available options is essential to guide evidence-based, individualized treatment planning.

This review aims to provide an up-to-date, comprehensive overview of hormonal therapies currently available for endometriosis, with a focus on the balance between efficacy and safety. A narrative approach was adopted, integrating evidence from randomized controlled trials, systematic reviews, meta-analyses, and observational studies. Emphasis is placed on balancing therapeutic benefits against short- and long-term adverse effects, and on identifying unmet needs and

CONTACT Simone Ferrero simoneferrero@me.com Azienda Ospedaliera Metropolitana, Largo R Benzi 10, 16132, Genoa, Italy

Article highlights

- Endometriosis is a chronic estrogen-dependent inflammatory disease requiring long-term therapeutic strategies that balance symptom control with systemic safety.
- Hormonal therapies (including combined oral contraceptives, progestins, GnRH agonists, and oral GnRH antagonists) are the cornerstone of medical management for women not seeking pregnancy.
- Clinical evidence suggests a graded relationship between the depth of estradiol suppression and pain reduction, but deeper suppression is associated with increased hypoestrogenic adverse effects such as vasomotor symptoms and bone mineral density loss.
- Progestins and combined oral contraceptives provide moderate endocrine suppression suitable for long-term management. In contrast, GnRH agonists and antagonists achieve more profound suppression and are typically reserved for second-line therapy given their hypoestrogenic adverse effects.
- The development of oral GnRH antagonists has enabled dose-dependent modulation of estrogen levels, supporting the concept of an estrogen-threshold approach rather than universal profound suppression.
- Future management of endometriosis is likely to move toward precision endocrine modulation, tailoring the minimal effective level of estrogen suppression to disease phenotype, symptom severity, and patient-specific risk factors.

future directions in hormonal management. The selection of references was guided by relevance, methodological rigor, and clinical significance, with literature sourced from PubMed, Embase, Scopus, and the Cochrane Library databases up to February 2026.

2. Pathophysiological rationale for hormonal therapies

Endometriosis is an estrogen-dependent disease, and this hormonal dependency forms the cornerstone of its medical management. Estradiol (E_2), primarily synthesized in the ovaries but also produced locally in endometriotic lesions via aberrant aromatase expression, promotes proliferation, inflammation, and angiogenesis, thereby sustaining the ectopic endometrial tissue [7–9]. Local estrogen production is further exacerbated by overexpression of the steroidogenic acute regulatory protein and reduced expression of 17β-hydroxysteroid dehydrogenase type 2, thereby limiting E_2 inactivation [10]. This hormonal milieu leads to a feed-forward loop that perpetuates lesion growth and resistance to apoptosis [11].

In addition to estrogen dependency, endometriosis is characterized by a functional resistance to progesterone. The eutopic and ectopic endometrium in women with endometriosis exhibits reduced expression of progesterone receptor-B (PR-B), with a predominance of the PR-A isoform, which is a weak transcriptional activator [12,13]. This altered PR isoform ratio impairs progesterone responsiveness and contributes to a deficient secretory transformation of the endometrium, disrupted decidualization, and poor response to progestin-based therapies [14]. Moreover, epigenetic modifications, such as promoter methylation of PR-B, may further explain the attenuated progesterone signaling observed in endometriotic tissues [15].

Hormonal signaling in endometriosis is intricately linked to the inflammatory microenvironment of the lesions. Estrogen enhances the production of prostaglandin E_2 (PGE_2), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and other proinflammatory cytokines through estrogen receptor (ER)-mediated pathways, particularly ER-β, which is upregulated in endometriotic implants [16–18]. ER-β promotes lesion survival not only by stimulating inflammation and angiogenesis but also by suppressing ER-α and PR expression, further aggravating hormonal resistance. In contrast to normal endometrium, where ER-α predominates, endometriotic lesions exhibit an inverted ER-β/ER-α ratio, favoring pathogenic estrogenic responses.

Altogether, the coexistence of enhanced local estrogen biosynthesis, progesterone resistance, and receptor dysregulation establishes a hormone-inflammation circuit that underlies both the pathogenesis and persistence of endometriotic lesions. Targeting these hormonal axes thus represents a rational and biologically grounded therapeutic approach, which explains the widespread use of estrogen-suppressive and progestin-based hormonal therapies in clinical practice.

3. Combined oral contraceptives

COCs are the most widely prescribed first-line pharmacological treatment for endometriosis-associated pain. Their therapeutic effect derives from suppression of ovulation, stabilization of circulating E_2 concentrations, reduction in menstrual flow, and attenuation of prostaglandin-mediated inflammatory pathways. Continuous or extended regimens eliminate withdrawal bleeding and appear more effective than cyclic administration in reducing dysmenorrhea, likely because suppression of hormone fluctuation limits activation of inflammatory cascades within ectopic implants [19].

Endocrinologically, COCs do not induce profound hypoestrogenism but rather suppress endogenous ovarian E_2 production through inhibition of ovulation while maintaining systemic estrogen exposure via exogenous ethinylestradiol. As a result, circulating E2 concentrations generally remain within a suppressed but not absent range, typically corresponding to low-to-mid follicular phase levels (rather than the menopausal concentrations observed with GnRH agonists or high-dose GnRH antagonists; see below) [20]. Although endogenous hormone levels may fluctuate during the pill cycle, particularly during the hormone-free interval, COCs markedly attenuate cyclic ovarian hormonal peaks and reduce estrogen-driven proliferative and inflammatory signaling in many patients. This degree of endocrine modulation appears sufficient to provide symptom control while largely preserving systemic estrogen-dependent functions such as bone metabolism and cardiovascular homeostasis [21].

Clinical evidence supports their efficacy in reducing dysmenorrhea and nonmenstrual pelvic pain due to endometriosis compared with placebo (Table 1) [30]. Continuous regimens appear superior to cyclic schedules for pain suppression [31]. In adolescents and young women with suspected early-stage disease, COCs are a pragmatic empirical therapy that combines symptom control with contraceptive benefit and relative

Table 1. Major randomized controlled trials evaluating combined oral contraceptives in the management of endometriosis.

Authors, year	Ref	Population	Intervention	Comparator	Main outcomes	Key findings
Muzii et al. 2000	[22]	Women after laparoscopic excision of ovarian endometriomas; not seeking pregnancy	Cyclic low-dose monophasic COC	No postoperative hormonal therapy	Endometrioma recurrence; pain persistence/ recurrence	No significant long-term difference in recurrence rates, but time-to-recurrence was longer and 12-month cumulative recurrence was lower with COC.
Vercellini et al. 2002	[23]	Women with recurrent moderate-severe pelvic pain after conservative surgery	Continuous COC ethinylestradiol 20 µg + desogestrel 150 µg	Continuous cyproterone acetate 12.5 mg/day	Satisfaction; pain scores; health-related quality of life; side effects	Both arms showed substantial pain reduction and improved QoL; no major between-group differences; satisfaction 67% COC vs 73% cyproterone acetate.
Harada et al. 2008	[24]	Women with dysmenorrhea and radiologic evidence of endometriosis	Low-dose monophasic COC (ethinylestradiol + norethisterone)	Placebo	Dysmenorrhea severity, endometrioma volume	Dysmenorrhea was significantly milder with COC vs placebo across cycles; endometrioma volume (≥3 cm) decreased in COC arm; no serious COC-related adverse effect reported.
Seracchioli et al. 2010	[25]	Post-laparoscopic excision of endometrioma	Cyclic or continuous COC (24 months)	No therapy	Endometrioma recurrence	Both COC regimens reduced recurrence vs no therapy; no difference between cyclic and continuous
Seracchioli et al. 2010	[26]	Post-laparoscopic excision of ovarian endometrioma	Cyclic or continuous low-dose monophasic COC (24 months)	No therapy	Pain recurrence	COC reduced dysmenorrhea recurrence; continuous regimen superior at 6 months
Guzick et al. 2011	[27]	Women with endometriosis-associated pelvic pain	Continuous monophasic COC (norethindrone 1 mg + ethinylestradiol 35 µg daily)	Depot leuprolide 11.25 mg intramuscularly every 12 weeks + add-back norethindrone acetate (5 mg daily)	Pain scores, mood, sexual satisfaction	Both groups improved significantly; no significant differences in magnitude of pain reduction between continuous COC and leuprolide regimen.
El Taha et al. 2021	[28]	Women with endometriosis-associated chronic pelvic pain/ dysmenorrhea > 6 months	Monophasic COC ethinylestradiol 30 µg + drospirenone 3 mg	Dienogest 2 mg/day	VAS change (non-cyclic pelvic pain + dysmenorrhea), Biberoglu and Behrman scores, health-related quality of life, tolerability	Both improved pain and health-related quality of life; between-group pain difference not significant; dienogest had fewer side effects / better tolerability than COC in this trial.
Cooper et al. 2024	[29]	Women undergoing conservative surgery for endometriosis	COC 30 µg ethinylestradiol and 150 µg LNG, (taken cyclically each month, continuously or in a tricycle regimen)	Long-acting progestogen (DMPA or LNG-IUS)	Endometriosis Health Profile-30 pain domain at 3 years; treatment failure	No difference in pain at 3 years; both arms improved 40% vs preop; fewer further procedures/ second-line treatments in the long-acting progestogen arm

long-term skeletal safety compared with profoundly hypoestrogenic therapies [32,33].

COCs also play an important role in secondary prevention following conservative surgery (Table 1). Observational studies indicate that prolonged postoperative use significantly reduces recurrence rates of ovarian endometriomas compared with no hormonal therapy [34,35]. The protective effect likely reflects suppression of ovulation and reduction of cyclical hormonal fluctuations that promote the recurrence of ovarian endometriomas. However, response may be attenuated in deep endometriosis, where fibrosis, neuroangiogenesis, and progesterone resistance contribute to a partially hormone-independent pain component [36]. In such phenotypes, stronger endocrine suppression or progestin-dominant regimens may be required.

Most adverse effects of COCs are mild and often transient during the initial months of therapy. These include nausea, breast tenderness, headache, breakthrough bleeding, and mood changes. Irregular bleeding is more frequent with continuous regimens and ultra-low-dose estrogen formulations, potentially affecting adherence [37].

More clinically significant risks relate to thromboembolic and cardiovascular events. Estrogen-containing contraceptives increase hepatic synthesis of procoagulant factors and reduce anticoagulant activity, resulting in a hypercoagulable state. Large cohort studies demonstrate a two- to four-fold increased relative risk of venous thromboembolism (VTE) among COC users compared with non-users [38]. The absolute risk in healthy reproductive-age women remains low, generally estimated at 5–12 events per 10,000 woman-years, but increases substantially in the presence of additional risk factors such as obesity, smoking, thrombophilia, or prolonged immobilization. Arterial thrombotic events, including ischemic stroke and myocardial infarction, are rare in young women but become clinically relevant in those over 35 years of age who smoke or have hypertension, diabetes, or migraine with aura [39]. The estrogen dose influences risk, with higher ethinylestradiol doses associated with greater thrombotic potential. Progestin type also modulates risk, with levonorgestrel-containing formulations generally demonstrating a more favorable thrombotic profile compared with desogestrel or drospirenone [38].

Emerging evidence suggests that COCs containing natural estrogens, such as E_2 valerate or estetrol, may provide a more favorable hemostatic profile compared with ethinylestradiol-containing formulations. In fact, pharmacodynamic studies have demonstrated smaller effects on thrombin generation, activated protein C resistance, and coagulation markers, potentially reflecting reduced hepatic estrogenic stimulation [40,41]. Observational studies and meta-analytic data also suggest a lower relative risk of VTE with natural estrogen-based formulations compared with ethinylestradiol-containing COCs [42,43]. Preliminary studies further suggest that estetrol/drospirenone formulations may provide clinically meaningful improvements in endometriosis-associated pain while maintaining a favorable tolerability profile [44]. However, current evidence remains limited and heterogeneous, particularly regarding long-term clinical outcomes and direct comparisons with traditional ethinylestradiol-based regimens in women with endometriosis. Therefore, natural estrogen-containing COCs should currently be regarded as promising alternatives rather than established superior options.

Regarding oncologic safety, long-term COC use is associated with a reduced risk of ovarian and endometrial cancer, an effect that persists for years after discontinuation. Conversely, a slight increase in breast cancer incidence has been reported during current or recent use. However, absolute excess risk in young women remains small and appears to diminish after cessation [45]. In patients with endometriosis, who may already have a modestly increased ovarian cancer risk, the protective ovarian effect may represent an additional benefit [46].

COCs generally preserve BMD. However, very low-dose estrogen formulations used over prolonged periods in adolescents have raised concerns regarding optimal peak bone mass acquisition, although data remain inconclusive [33,47]. Additionally, COCs are associated with a modestly increased risk of mood disturbances, including depressive symptoms, in women with endometriosis compared to COC users without endometriosis. Large cohort analyses demonstrate that women with endometriosis using COCs have a higher incidence of depression. However, the absolute risk increase is small, and most women tolerate COCs without significant psychiatric effects [48]. Mood lability and depression are frequent reasons for discontinuation of COCs in this population, and the likelihood of discontinuation is higher among those with a prior diagnosis of depression; this effect does not differ by progestin type or between combined and progestin-only formulations [49]. The relationship between COC use and mood symptoms is debated, with some women experiencing mood worsening and others reporting mood improvement or no effect [50–52]. Individual susceptibility, including prior psychiatric history and sensitivity to hormonal changes, should guide therapeutic decisions.

Contraindications to COCs are primarily related to thrombotic and cardiovascular risk. Absolute contraindications (representing unacceptable health risk) include current or history of VTE with risk factors for recurrence, known thrombogenic mutations, major surgery with prolonged immobilization, current or history of ischemic heart disease or stroke, severe uncontrolled hypertension (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg), migraine with aura, severe or decompensated cirrhosis, hepatocellular adenoma or malignant liver tumor, current breast cancer, systemic lupus erythematosus with positive or unknown antiphospholipid antibodies [53].

Relative contraindications (where risks usually outweigh benefits) include adequately controlled or moderate hypertension (systolic 140–159 mmHg or diastolic 90–99 mmHg), VTE without risk factors for recurrence, smoking in women aged ≥ 35 years, obesity (BMI ≥ 30 kg/m^2), symptomatic gallbladder disease, inflammatory bowel disease with increased VTE risk, and diabetes with complications or duration > 20 years [53]. Routine screening for thrombophilias before initiating COCs is not recommended, as the rarity of fatal VTE makes population screening inefficient. Otherwise, individualized risk assessment is essential, and progestin-only therapy or non-estrogenic alternatives should be considered [54]. In patients with endometriosis requiring long-term therapy, these contraindications are particularly relevant because treatment often extends over many years. Careful baseline and longitudinal assessment of cardiovascular and thrombotic risk factors is therefore essential, particularly in women with obesity, smoking, hypertension, migraine with aura, or other conditions associated with increased vascular risk [20,53].

4. Progestins

Progestins are a cornerstone of long-term medical management in endometriosis [55,56]. Unlike COCs, progestin-only regimens exert their therapeutic effect in endometriosis not only by suppressing ovulation but also through direct endometrial and immunomodulatory actions, which are particularly relevant in the context of progesterone resistance and chronic inflammation [13,56,57]. Progestins induce decidualization and atrophy of ectopic endometrial tissue, downregulate estrogen receptor expression, reduce aromatase activity, inhibit matrix metalloproteinases, suppress inflammatory mediators such as interleukin-1β and tumor necrosis factor alpha, and attenuate nuclear factor kappa B activation [58,59]. These molecular mechanisms are central to their efficacy in endometriosis, especially where progesterone resistance and chronic inflammation perpetuate disease activity. Some progestins, including medroxyprogesterone acetate and norethindrone acetate, exhibit partial glucocorticoid receptor activity, contributing to their anti-inflammatory effects [55]. Progestins also modulate estrogen thresholds by downregulating local E_2 biosynthesis and estrogen receptor expression, thereby reducing proliferative signaling in ectopic lesions [59]. Dienogest maintains E_2 levels within the low-to-mid follicular range, thereby reducing proliferative signaling while preserving bone safety [60]. This pharmacodynamic profile is particularly advantageous for long-term management of endometriosis, as it balances efficacy with minimization of hypoestrogenic adverse effects. These actions collectively differentiate progestin-only regimens from COCs, making them particularly suitable for patients with contraindications to estrogen exposure. In addition, some authors have hypothesized that progestin-only therapies, particularly dienogest, may offer theoretical

advantages in specific inflammatory or progesterone-dysregulated disease phenotypes by avoiding exogenous estrogen exposure and exerting direct antiproliferative and anti-inflammatory effects on endometriotic lesions [61,62]. However, progesterone resistance remains a major biological challenge in endometriosis and may contribute to reduced responsiveness to hormonal therapies overall.

Progestin-only regimens provide significant and sustained pain relief in endometriosis, with efficacy comparable to or exceeding other hormonal therapies. Dienogest significantly reduces dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia compared with placebo, with sustained efficacy during long-term treatment [28,56,63]. Meta-analyses show that dienogest reduces overall pelvic pain compared to placebo and is superior to placebo for dyspareunia and nonmenstrual pelvic pain [63,64]. Additionally, dienogest has demonstrated similar efficacy to GnRH agonists for endometriosis-associated pain, including deep endometriosis, with a better safety profile and fewer adverse effects [56,64].

Norethisterone acetate (2.5 mg/day) is as effective as COCs in improving endometriosis-associated pain and deep endometriosis, with satisfaction rates of 60–70% [55]. The LNG-IUS provides effective long-term control of dysmenorrhea and chronic pelvic pain in women with endometriosis and adenomyosis, particularly in adolescents and young women requiring prolonged therapy [55,65,66]. Its favorable safety profile, preservation of BMD, and lack of increased thromboembolic risk make it an attractive option for long-term management [67]. Postoperative use of LNG-IUS has been associated with reduced pain recurrence and lower risk of symptom relapse following conservative surgery [68,69]. However, because LNG-IUS primarily exerts local endometrial effects and does not consistently suppress ovulation or fully inhibit ovarian estrogen production, its efficacy in preventing postoperative recurrence of ovarian endometriomas appears less consistent across studies [70–72]. This distinction may reflect the partially ovulation-dependent pathogenesis of ovarian endometriomas [71]. Therefore, LNG-IUS may be particularly suitable for long-term symptom control and postoperative maintenance strategies, whereas stronger systemic endocrine suppression may still be required in selected patients at high risk of endometrioma recurrence.

Progestins are particularly valuable in the secondary prevention following conservative surgery for endometriosis, as continuous postoperative administration significantly decreases the risk of recurrence of endometriomas and pain compared with expectant management [69]. Regardless of lesion type and medication used, patients who discontinue therapy experience a higher incidence of recurrence, indicating that the protective effect of these medications vanishes rapidly after discontinuation [73]. Regular and prolonged medication until the patient wishes to conceive is therefore highly recommended to prevent postoperative recurrence [73].

In the maintenance setting, progestins may provide more robust suppression of lesion activity than COCs, particularly in patients with progesterone-sensitive phenotypes. A network meta-analysis of 16 RCTs demonstrated that the LNG-IUS is the most effective intervention in reducing both recurrence and pain after conservative surgery, followed by dienogest [74]. Cohort evidence from a network meta-analysis of 22 studies ranked LNG-IUS highest for preventing endometrioma recurrence, followed by dienogest and GnRH agonist plus LNG-IUS, with all showing significantly lower recurrence risk than expectant management [70]. Dienogest has demonstrated efficacy in reducing endometrioma recurrence and may overcome progesterone resistance by upregulating progesterone receptor B expression [62,75]. Higher progestin doses may partially compensate for reduced progesterone responsiveness in some patients by providing stronger decidualizing, antiproliferative, and anti-inflammatory effects on endometriotic tissue, as well as deeper suppression of local estrogen biosynthesis [62,76]. However, clinical evidence supporting a clear dose-response relationship remains limited, and dose escalation is frequently constrained by adverse effects and reduced tolerability.

Adverse effects of progestins are generally related to their endocrine and metabolic activity. They are typically well tolerated, with no significant difference in study withdrawal due to adverse effects compared to placebo [56,77]. Irregular uterine bleeding is the most common side effect, occurring in >10% of patients, particularly during the first months of therapy [62,77]. Breakthrough bleeding may be more pronounced with progestin-only regimens than with COCs due to the absence of estrogen stabilization of the endometrium; however, bleeding frequency and intensity decrease progressively during continued treatment [62,78]. Other frequent adverse effects include weight gain (≤10%), breast tenderness, acne (>10% with subdermal implant), decreased libido, and mood changes (≤10%) [6,55,62,77,79]. Mood disturbances deserve careful consideration, although evidence regarding causality remains mixed [62].

Unlike estrogen-containing therapies, progestins are not associated with an increased risk of VTE and are considered safer in women with thrombotic risk factors [20,80,81]. There is no statistically significant increased risk of VTE among women using progestin-only pills, implants, or LNG-IUS compared with nonusers [82]. Depot medroxyprogesterone acetate (DMPA) may be associated with a slightly elevated risk of VTE. However, this likely translates into a small increase in the absolute number of thrombotic events [81,82]. Patients at increased risk of thrombosis can be provided progestin-only, non-estrogen-containing therapies because these do not increase VTE risk [20].

DMPA is associated with a dose-dependent reduction in BMD due to profound suppression of E_2, with losses of 5.7–7.5% after 2 years of use [83]. However, current longitudinal and cross-sectional evidence suggests that BMD recovery occurs after discontinuation, with losses appearing substantially or fully reversible after 2–5 years of follow-up, though recovery at the hip and femoral neck generally takes longer than at the spine [83,84]. Complete recovery may not occur in all adolescents who use DMPA for 2 years or more [83]. The American College of Obstetricians and Gynecologists recommends that concerns about BMD should not prevent continuing DMPA use beyond 2 years, and shared decision-making is advised [83]. Dienogest and norethindrone acetate, by maintaining E_2 within a low but not menopausal range, appear to have a more favorable skeletal profile. In a randomized trial comparing dienogest to leuprolide acetate, changes in mean lumbar BMD were +0.25% with dienogest versus −4.04% with leuprolide ($p = 0.0003$), and markers of

bone resorption increased with leuprolide but not with dienogest [85]. However, long-term studies show that 3 years of dienogest use is associated with significant decreases in BMD at both the lumbar spine (−4.4%) and femoral neck (−3.6%), with bone loss predominantly occurring during the first year of treatment [86,87]. In another study, osteopenia was observed in 27.5% of patients undergoing long-term dienogest (DNG) therapy for more than 15 months [88]. In adolescents, 52 weeks of dienogest was associated with a 1.2% decrease in lumbar BMD, with partial recovery 6 months after discontinuation [89]. A 24-week placebo-controlled trial in Chinese women showed no effect of dienogest on BMD levels [90].

Absolute contraindications to systemic progestin therapy are limited. Unlike COCs, progestins do not have contraindications related to thromboembolism, migraine with aura, or cardiovascular risk factors [39,77]. Contraindications include severe hepatic dysfunction and known hormone-dependent malignancy. DMPA should be used with caution in adolescents and women at high risk for osteoporosis due to its effects on BMD [77,83]. Relative contraindications include severe depression with prior progestin intolerance.

Clinically, progestins occupy a central position in the therapeutic hierarchy of endometriosis and are recommended as first-line treatment alongside COCs [77]. They are particularly appropriate for long-term administration, for patients with contraindications to estrogen, and for those with moderate-to-severe pain requiring more robust suppression [62]. In deep disease and postoperative maintenance, they often represent the preferred strategy [91]. Progestins combine a moderate reduction in systemic estrogen with direct anti-proliferative and anti-inflammatory effects at the tissue level, making them especially well-suited for chronic disease control.

Up to one-third of patients do not respond adequately to first-line hormonal therapies due to progesterone resistance, adverse effects, or limited tolerability [62]. Importantly, treatment non-response in endometriosis cannot be explained solely by progesterone resistance, as persistent pain may also reflect central sensitization, peripheral nerve remodeling, neuroinflammation, and nociplastic pain mechanisms that progressively become partially independent of active hormonal stimulation [62,77]. Endometriotic lesions promote neuroangiogenesis and sustained inflammatory signaling through complex interactions among immune cells, sensory nerve fibers, and estrogen-dependent pathways, potentially contributing to chronic pain persistence despite adequate endocrine suppression. In addition, fibrosis, deep infiltrating disease, pelvic floor dysfunction, and cross-organ sensitization may further reduce responsiveness to hormonal therapies. Consequently, lack of response to progestins should not automatically be interpreted as pharmacological failure alone, but rather as a manifestation of the multifactorial nature of endometriosis-associated pain, often requiring individualized and multimodal management strategies.

5. GnRH agonists

GnRH agonists have been, for several decades, a potent second-line medical strategy for the treatment of moderate-to-severe endometriosis [77,92]. Their use demonstrated that profound suppression of ovarian steroidogenesis could induce a substantial reduction in endometriosis-related pain and in lesion activity. Unlike progestins or COCs, which modulate estrogen within a partially suppressed range, GnRH agonists induce near-complete pituitary desensitization following an initial flare effect, resulting in marked suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion and consequent reduction of E_2 to menopausal levels (typically below 15–20 pg/ml). Profound hypoestrogenism interrupts multiple estrogen-dependent pathways central to endometriosis progression. E_2-driven proliferation, angiogenesis, inflammatory cytokine production, and neuroangiogenic signaling are substantially reduced when circulating estrogen falls below a critical biological threshold. Treatment with GnRH agonists initially stimulates the release of gonadotropins (the so-called flare effect), but after approximately 2 weeks, release is suppressed through receptor downregulation and desensitization.

Clinical trials have consistently demonstrated significant reductions in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia during treatment with agents such as leuprolide acetate, goserelin, and nafarelin [92]. A 2023 Cochrane review found low-certainty evidence that GnRH agonists reduced pelvic pain, dysmenorrhea, dyspareunia, and pelvic tenderness compared with placebo [92]. Approximately 85% of women with endometriosis-associated pain treated with GnRH agonists experience pain relief [62].

However, the efficacy of GnRH agonists comes at the cost of systemic hypoestrogenism. E_2 concentrations frequently fall below 15–20 pg/ml, inducing vasomotor symptoms (hot flushes affecting > 10% of patients), vaginal dryness, sleep disturbances, mood changes, and reduced sexual function [92–94]. More importantly, prolonged suppression leads to accelerated loss of bone mineral density. A 2022 prospective study found that 6 months of goserelin-induced amenorrhea resulted in significant bone loss at both the lumbar spine and the femoral neck (both $p < 0.001$), with only partial recovery 6 months after restoration of menses [95]. A 2003 Cochrane review on the effects of GnRH agonist monotherapy on BMD confirmed significant BMD loss [96]. Current guidelines recommend that GnRH agonist use should not exceed 6 months without add-back therapy due to concerns about BMD loss, which may be irreversible with prolonged use [97].

The concept of add-back therapy emerged in response to these limitations. Based on the estrogen threshold hypothesis, which posits that an E_2 concentration of 30–40 pg/ml causes endometriosis regression without hypoestrogenic side effects (i.e. vasomotor symptoms and bone loss), low-dose estrogen-progestin or progestin-only regimens are administered concomitantly to maintain serum E_2 within a therapeutic window [98]. Clinical studies have demonstrated that appropriately dosed add-back therapy mitigates vasomotor symptoms and bone loss without compromising pain control. Add-back therapy using high-dose progestin alone (norethindrone acetate, 5 mg orally per day) or low-dose combined estrogen and progestin can mitigate adverse effects and allow for extended treatment courses.

Despite their effectiveness, GnRH agonists are second-line therapy due to their high cost and adverse effects of decreased BMD and vasomotor symptoms, which limit their long-term use. Their use is generally reserved for patients with moderate-to-severe pain refractory to first-line hormonal options, for short-term preoperative disease suppression, or in specific clinical scenarios where rapid and profound estrogen reduction is desired.

Alternative administration strategies aimed at reducing treatment burden and costs have also been explored. Small, randomized studies suggest that extending the dosing interval of triptorelin 3.75 mg depot from every 4 weeks to every 6 weeks may maintain comparable hormonal suppression and clinical efficacy while reducing the number of injections and overall treatment costs [99,100]. In addition, a 3-month depot formulation of triptorelin has demonstrated noninferior efficacy compared with monthly administration in randomized trials [101]. However, these approaches remain insufficiently validated for routine use and are not specifically endorsed by current guidelines.

6. GnRH antagonists

The development of oral GnRH antagonists is a major evolution in the pharmacological management of endometriosis (Table 2). Unlike GnRH agonists, which initially stimulate and subsequently desensitize pituitary gonadotrophins, antagonists competitively and immediately block GnRH receptors at the pituitary level, producing rapid, dose-dependent suppression of LH and FSH without an initial flare effect. Gonadotropin concentrations decrease within 6 hours, and E_2 concentrations are reduced within 24 hours of administration. This pharmacodynamic profile allows for more precise modulation of ovarian E_2 production and has redefined the practical application of the estrogen threshold model [79].

Elagolix was the first oral GnRH antagonist approved for endometriosis-associated pain. In two pivotal phase III trials (Elaris EM-I and EM-II), elagolix significantly reduced dysmenorrhea and nonmenstrual pelvic pain compared with placebo, with higher response rates observed at the 200 mg twice-daily dose than at the 150 mg once-daily dose [103]. In Elaris EM-I, the percentage of women who had a clinical response with respect to dysmenorrhea was 46.4% in the lower-dose elagolix group and 75.8% in the higher-dose elagolix group, as compared with 19.6% in the placebo group; in Elaris EM-II, the corresponding percentages were 43.4% and 72.4%, as compared with 22.7% ($p < 0.001$ for all comparisons). For nonmenstrual pelvic pain, response rates were 50.4% and 54.5% for the lower and higher doses in EM-I versus 36.5% for placebo, and 49.8% and 57.8% in EM-II versus 36.5% for placebo ($p \leq 0.003$ for all comparisons). These efficacy differences correlated with greater E_2 suppression at higher doses. The mean E_2 concentration is approximately 42 pg/ml with the 150 mg once-daily regimen, while the higher dosage of 200 mg twice daily induces a hypoestrogenic state with a mean E_2 of approximately 12 pg/ml. However, increased efficacy at higher doses was accompanied by more frequent hypoestrogenic adverse effects. Hot flushes occurred in 24% of patients on the low dose and 46% on the high dose. In long-term extension studies over 12 months, BMD decreased progressively, particularly with the higher-dose regimen [104]. These findings reinforced the principle that while deeper estrogen suppression enhances symptom control, it also increases systemic risk. The low dose is approved for 24 months of use, while the high dose is approved for only 6 months due to concerns about bone mineral density. More recently, elagolix with add-back therapy (200 mg twice daily with 1 mg E_2/0.5 mg norethindrone acetate once daily) has been studied, showing that add-back therapy from baseline resulted in BMD changes of less than 1% at 6 and 12 months, compared to 2.4% loss in lumbar spine with monotherapy at 6 months [106].

Table 2. Studies on oral GnRH antagonists in endometriosis.

Authors, year	Ref	Phase/ design	Regimen	Comparator	Duration	Key efficacy findings	Key safety findings
Ács et al. 2015	[102]	Phase 2 RCT	Elagolix 150 mg QD	Placebo	8–24 weeks	↓ Dysmenorrhea, NMPP, dyspareunia vs placebo	Mild hypoestrogenic AEs, small BMD loss
Taylor et al. 2017 (EM-I/II)	[103]	Phase 3 RCT	Elagolix 150 mg QD / 200 mg BID	Placebo	6 months	Dysmenorrhea responders 46–76%, NMPP 50–58%	Dose-dependent vasomotor AEs, BMD ↓
Surrey et al. 2018	[104]	Phase 3 Extension	Elagolix 150 / 200 mg	–	12 months	Sustained pain improvement: dysmenorrhea 52–78%	BMD decline ≤ 3%
Agarwal et al. 2021	[105]	Post-hoc EM-I/II	Elagolix 150/200 mg	Placebo	6 months	Pain relief independent of amenorrhea	Expected hypoestrogenic AEs
Miller et al. 2024	[106]	Phase 3 RCT	Elagolix + add-back	Placebo	12 months	Significant pain reduction; improved tolerability	Add-back preserves BMD
Osuga et al. 2021	[107]	Phase 2 RCT	Relugolix 10/20/40 mg	Placebo / Leuprorelin	24 weeks	40 mg comparable to leuprorelin	Dose-dependent BMD ↓
Osuga et al. 2021	[108]	Phase 2 RCT	Relugolix 40 mg	Leuprorelin	24 weeks	Non-inferior pain reduction	Faster menses recovery
Harada et al. 2022	[109]	Phase 3 RCT	Relugolix 40 mg	Leuprorelin	24 weeks	Non-inferior pelvic pain reduction	Similar safety
Giudice et al. 2022	[110]	Phase 3 RCT	Relugolix CT	Placebo	24 weeks	↑ Responders for dysmenorrhea & NMPP	<1% BMD loss then stable
Becker et al. 2024	[111]	Extension	Relugolix CT	–	104 weeks	Sustained long-term pain relief	Stable BMD
Donnez et al. 2020	[112]	Phase 2b RCT	Linzagolix 75–300 mg	Placebo	12–24 weeks	Dose-dependent ↓ pain	BMD ↓ with higher doses
Donnez et al. 2024	[113]	Phase 3 RCT	Linzagolix 75 mg / 200 mg + ABT	Placebo	6 months	Significant ↑ responders; improvement in dyschezia	<1% BMD loss; few vasomotor AEs

ABT add-back therapy; AEs: adverse effects; BID twice daily; BMD: bone mineral density; NMPP: nonmenstrual pelvic pain; QD once daily.

Linzagolix further expanded this model by allowing both partial and full estrogen suppression depending on dose. In the phase III EDELWEISS 3 trial, the 200 mg dose with add-back therapy (1.0 mg E_2; 0.5 mg norethindrone acetate) met the primary efficacy objective, showing clinically meaningful and statistically significant reductions in dysmenorrhea (72.9% responders versus 23.5% for placebo, $p < 0.001$) and nonmenstrual pelvic pain (47.3% versus 30.9%, $p = 0.007$) at 3 months [113]. The 75 mg dose alone demonstrated a clinically meaningful and statistically significant reduction in dysmenorrhea (44.0% versus 23.5%, $p < 0.001$) but did not reach statistical significance for nonmenstrual pelvic pain. In both groups, hypoestrogenic effects were mild, with low rates of hot flushes and bone density loss of less than 1%. In the phase 2 dose-ranging trial, doses of 75–200 mg resulted in significantly greater proportions of responders for overall pelvic pain at 12 weeks (61.5%, 56.4%, and 56.3% for 75, 100, and 200 mg, respectively, versus 34.5% for placebo) [112]. Mean BMD loss at the spine at 24 weeks was less than 1% at doses of 50 and 75 mg and increased in a dose-dependent fashion up to 2.6% for 200 mg. This flexible dosing strategy exemplifies active estrogen threshold titration, enabling clinicians to tailor the intensity of suppression to disease severity and patient tolerance.

Relugolix combination therapy introduced an additional refinement by integrating fixed low-dose E_2 (1 mg) and norethisterone acetate (0.5 mg) add-back from treatment initiation. In the SPIRIT 1 and SPIRIT 2 trials, relugolix combination therapy significantly reduced dysmenorrhea and nonmenstrual pelvic pain while maintaining BMD close to baseline over 24 weeks [110]. In SPIRIT 1, 75% of patients in the relugolix combination therapy group met the dysmenorrhea responder criteria compared with 27% in the placebo group (treatment difference 47.6%, 95% CI 39.3–56.0; $p < 0.0001$); in SPIRIT 2, 75% versus 30% (treatment difference 44.9%, 95% CI 36.2–53.5; $p < 0.0001$). For nonmenstrual pelvic pain, 58% in SPIRIT 1 and 66% in SPIRIT 2 were responders in the relugolix combination therapy group compared with 40% and 43% in placebo groups, respectively ($p < 0.0001$ for both). The least squares mean percentage change in lumbar spine BMD in the relugolix combination therapy versus placebo groups was −0.70% versus 0.21% in SPIRIT 1 and −0.78% versus 0.02% in SPIRIT 2. In the 2-year open-label extension study, after an initial BMD loss of less than 1% at week 24, BMD plateaued at week 36 and remained sustained for 104 weeks of treatment [111]. By combining antagonist-induced suppression with immediate hormonal add-back, this regimen maintains E_2 within a controlled therapeutic window, preventing profound hypoestrogenism while preserving efficacy. This approach operationalizes the estrogen threshold hypothesis in a standardized formulation.

GnRH antagonists disrupt systemic estrogen production, thereby reducing estrogen receptor activation, inflammatory amplification, and neuroangiogenic signaling in endometriotic lesions. Although intracrine estrogen synthesis within lesions may persist, reduction of circulating E_2 below a proliferative threshold appears sufficient to attenuate clinical symptoms in most patients. The absence of an initial flare effect represents a pharmacodynamic advantage over GnRH agonists, although flare-related symptoms with agonists can be mitigated in clinical practice through appropriate treatment scheduling and temporary add-back or progestin administration during treatment initiation [93]. Adverse effects are primarily related to estrogen deprivation and are dose dependent. Hot flushes, night sweats, decreased libido, mood changes, and vaginal dryness occur more frequently with deeper suppression [103]. BMD loss is the principal long-term safety concern and necessitates duration limits or add-back therapy for higher-dose regimens [104,106,110,111]. A network meta-analysis found that relugolix 40 mg and elagolix 400 mg had significantly increased incidence of adverse events, with odds ratios of 6.88 (95% CI, 2.18–24.58) and 1.85 (95% CI, 1.05–3.30), respectively [114]. Lipid profile alterations have also been reported, although clinical significance appears modest in short-term studies. Unlike estrogen-containing therapies, GnRH antagonists do not increase thromboembolic risk, making them suitable for patients with contraindications to combined hormonal contraceptives.

Contraindications include severe hepatic impairment (for certain formulations) and preexisting osteoporosis when profound suppression is anticipated without adequate add-back. Careful monitoring is recommended in patients with baseline low bone mineral density, significant mood disorders, or cardiovascular risk factors potentially exacerbated by hypoestrogenism. It should be noted that elagolix and relugolix combination therapy does not reliably suppress ovulation, and patients should be counseled to use contraception.

GnRH antagonists are the most refined pharmacological tool for estrogen-threshold modulation. They are considered second-line therapy for endometriosis-associated pain, reserved for patients with moderate-to-severe pain refractory to first-line hormonal options (combined oral contraceptives and progestins). They allow clinicians to move along a continuum of estrogen suppression intensity, from moderate reduction comparable to progestin-induced levels to profound hypoestrogenism, depending on dose and formulation. This flexibility makes them particularly valuable in women with moderate-to-severe pain refractory to first-line therapies, in those with deep disease, and in patients requiring rapid symptom control without surgical intervention.

The emergence of oral antagonists signals a transition from uniform profound suppression toward individualized estrogen-threshold modulation. By enabling dose-adjustable control of E_2, they embody the evolution of endometriosis pharmacotherapy from empiric suppression to targeted hormonal titration, balancing efficacy with long-term safety. The median time to resumption of menses is rapid (31 days for relugolix combination therapy), offering advantages for women planning future fertility. Thus, while GnRH antagonists remain a powerful tool in selected patients, their role has progressively shifted from long-term suppressive therapy to targeted, time-limited interventions within a personalized endocrine strategy, with newer formulations incorporating add-back therapy that allows extended use for up to 2 years.

7. Estrogen threshold modulation

For decades, the pharmacological management of endometriosis has been guided by the assumption that profound suppression of ovarian estrogen production was necessary to

induce lesion regression and pain relief. This concept, derived from early experiences with GnRH agonists, equated therapeutic efficacy with profound hypoestrogenism, often resulting in E_2 concentrations within the menopausal range (20 pg/ml). While effective in reducing pain, this strategy was associated with significant adverse effects, including vasomotor symptoms, BMD loss, and unfavorable metabolic changes. The development of oral GnRH antagonists has challenged this paradigm by demonstrating that partial, dose-dependent suppression of E_2 may be sufficient to control symptoms while preserving safety.

The concept of an 'estrogen threshold' posits a serum E_2 window that is low enough to inhibit endometriotic lesion activity yet high enough to maintain bone and metabolic health. The conceptual framework of estrogen-threshold modulation across different hormonal therapies is summarized in Figure 1. The term 'estrogen suppression' refers to reduction of circulating endogenous estradiol concentrations, whereas 'estrogen-threshold modulation' or 'endocrine modulation' refers to the therapeutic strategy of achieving sufficient estrogen reduction to control symptoms while avoiding profound hypoestrogenism and its systemic consequences.

Clinical trials with elagolix have shown that moderate E2 suppression (mean approximately 42 pg/ml with 150 mg daily dosing) is associated with meaningful reductions in dysmenorrhea and nonmenstrual pelvic pain, whereas more profound suppression (mean approximately 12 pg/ml with 200 mg twice daily) yields incremental efficacy at the cost of increased hypoestrogenic symptoms and accelerated bone loss [103]. Similar dose-dependent effects have been observed with relugolix combination therapy, reinforcing the notion that profound hypoestrogenism is not required to achieve clinical benefit [110].

However, it should be acknowledged that the estrogen-threshold framework is currently supported primarily by studies evaluating pain relief, quality of life, and treatment tolerability, particularly in trials of GnRH antagonists. Robust evidence defining disease-specific estrogen thresholds for lesion regression, postoperative recurrence prevention, or long-term organ preservation remains limited. Nevertheless, emerging imaging-based data suggest that hormonal suppression may influence the natural history of endometriosis beyond symptom control. Meta-analyses and longitudinal ultrasound studies have demonstrated reduced progression rates and partial regression of some lesions,

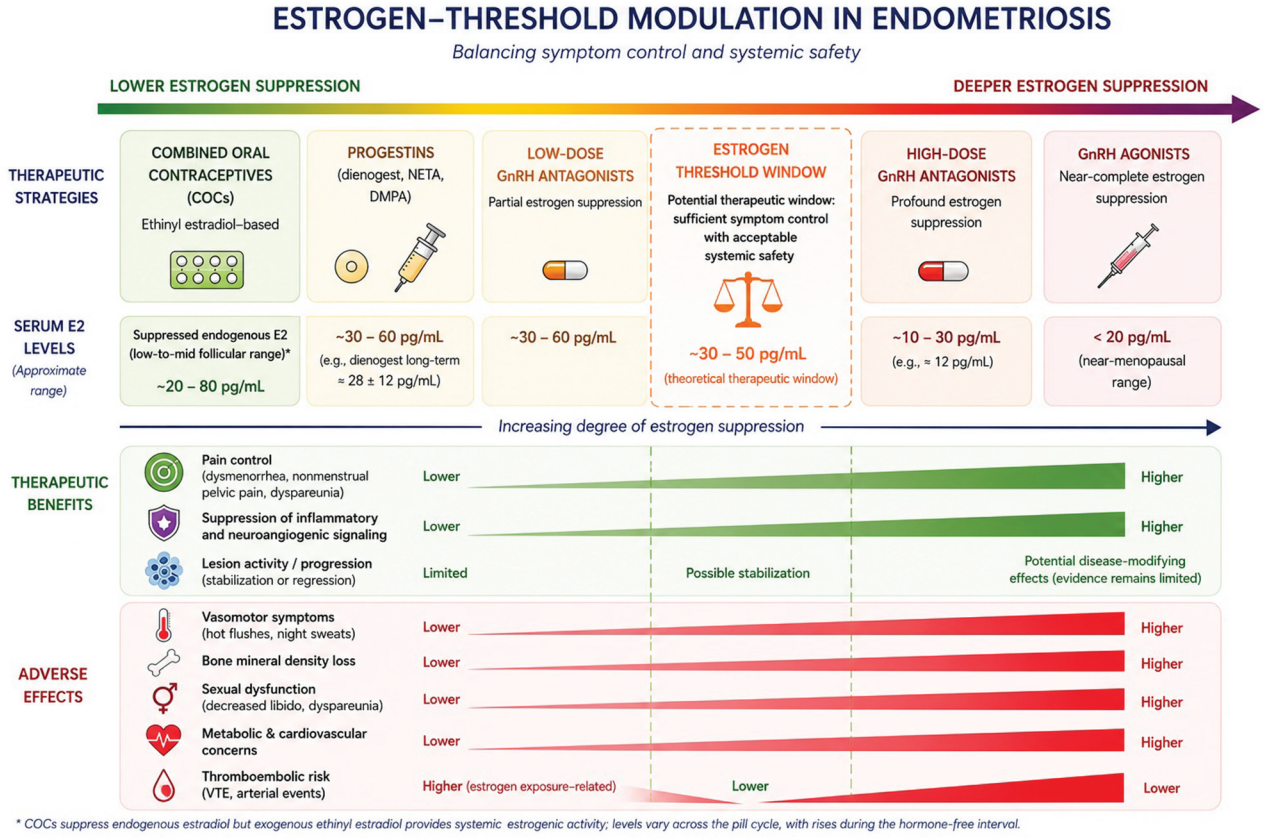

Figure 1. Conceptual framework of estrogen-threshold modulation in endometriosis. Hormonal therapies can be positioned along a continuum of estrogen suppression, ranging from moderate modulation with combined oral contraceptives and progestins to profound hypoestrogenism with GnRH agonists and high-dose GnRH antagonists. Increasing suppression is generally associated with greater pain control and suppression of inflammatory signaling, but also with higher risk of hypoestrogenic adverse effects. The proposed 'estrogen-threshold window' represents a theoretical balance between symptom control and systemic safety. Current evidence supporting this framework is strongest for pain-related outcomes, whereas evidence regarding lesion progression, recurrence prevention, and organ preservation remains limited.

particularly ovarian endometriomas rather than deep infiltrating lesions, during continuous hormonal therapy, although responses appear compartment-dependent [115,116]. Postoperative hormonal suppression has also been associated with lower recurrence rates after conservative surgery [69]. To date, no studies have directly compared different degrees of estrogen suppression against imaging-based lesion outcomes or long-term organ preservation. Thus, while the estrogen-threshold hypothesis is biologically plausible and clinically validated for pain control, its applicability to disease modification remains incompletely defined. Future studies should integrate imaging-based progression, fibrosis evolution, postoperative recurrence, organ function preservation, and biomarker-guided phenotyping in order to establish clinically meaningful estrogen thresholds beyond symptom control alone.

Endometriotic lesions depend on estrogen signaling for proliferation, angiogenesis, and inflammatory amplification, yet they also exhibit intracrine estrogen production through aromatase overexpression and altered expression of steroidogenic enzymes. Endometriotic stromal cells aberrantly express aromatase, which converts androgens to estrogens, and lack 17β-hydroxysteroid dehydrogenase type 2, which normally inactivates E_2 [117]. This creates a positive feedback loop in which E_2 stimulates prostaglandin E_2 production, which in turn stimulates aromatase activity [7]. Reducing circulating E_2 may disrupt systemic stimulation while residual intracrine activity persists at sub-proliferative levels. Thus, lesion stabilization rather than complete atrophy may be sufficient for pain control in many patients. Moreover, neuroangiogenic and inflammatory pathways are highly sensitive to fluctuations in estrogen; modest reductions may attenuate these signals.

Importantly, the estrogen threshold is unlikely to be uniform across all patients. Phenotypic heterogeneity (such as superficial peritoneal disease, ovarian endometrioma, or deep endometriosis) may influence hormonal responsiveness. Deep lesions characterized by dense fibrosis and nerve infiltration may require lower E_2 levels to achieve symptomatic control, whereas early-stage disease might respond to milder suppression. Additionally, interindividual variability in progesterone receptor expression and inflammatory activation may modulate sensitivity to estrogen deprivation. Endometriotic lesions demonstrate progesterone resistance characterized by reduced expression of progesterone receptor B (PR-B) relative to PR-A, mediated by epigenetic modifications [76,118]. This progesterone resistance may influence the degree of estrogen suppression required for symptom control.

The threshold model reframes the role of add-back therapy. Rather than being viewed solely as a mitigation strategy for adverse effects, add-back regimens can be conceptualized as tools to fine-tune systemic E_2 exposure. In relugolix combination therapy, low-dose E_2 (1 mg) and norethisterone acetate (0.5 mg) are administered concomitantly with the GnRH antagonist (40 mg) to maintain serum E_2 within a controlled range, thereby preserving bone health while sustaining symptom control [110]. This strategy exemplifies active estrogen-threshold modulation rather than profound estrogen suppression.

Meta-analyses have demonstrated that add-back therapy with GnRH agonists reduces BMD loss without compromising pain relief. Similarly, elagolix with add-back therapy (200 mg twice daily plus E_2 1 mg/norethindrone acetate 0.5 mg) demonstrated sustained efficacy through 12 months, with minimal bone loss (1% change from baseline), compared with more substantial loss with monotherapy [106].

The assumption that profound estrogen suppression is required for effective control of endometriosis-associated pain has shaped therapeutic strategies for decades. GnRH agonists, by inducing profound hypoestrogenism, provided early proof that near-menopausal estrogen suppression could significantly reduce dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia. However, this model equated efficacy with biochemical menopause, often overlooking the systemic consequences of sustained estrogen deprivation. Profound suppression achieved with GnRH agonists typically lowers E_2 to menopausal levels (20 pg/ml), which reliably reduces lesion activity but also induces vasomotor symptoms, vaginal atrophy, sleep disturbance, reduced sexual function, mood instability, and, most importantly, accelerated BMD loss [93]. Even with add-back therapy, bone loss may not be completely abolished, and long-term use remains limited. These adverse effects illustrate the biological cost of profound suppression and challenge its sustainability in a chronic disease that often requires years of management.

When considering COCs, the paradigm shifts further. Unlike GnRH agonists or high-dose GnRH antagonists, COCs provide partial endocrine suppression while maintaining systemic estrogen exposure through exogenous estrogen administration. This profile is generally sufficient to control pain in many women with mild-to-moderate disease while preserving bone health and avoiding profound hypoestrogenism. However, the trade-off is a different spectrum of adverse effects related to estrogen exposure, particularly thromboembolic and cardiovascular risk in susceptible patients [20].

Progestins occupy an intermediate position within this continuum. Agents such as dienogest and norethisterone acetate reduce gonadotropin secretion and maintain E_2 within a low-mid follicular range, often sufficient to suppress proliferative activity without inducing full hypoestrogenism. Long-term dienogest therapy has been associated with mean serum E_2 concentrations around 28 ± 12 pg/mL, consistent with the proposed 'estrogen-threshold' window that may allow symptom control while limiting profound hypoestrogenic effects [119].

The safety profile of progestins reflects the absence of exogenous estrogen, with minimal thromboembolic risk compared to COCs [20]. However, adverse effects include irregular bleeding, weight gain, acne, mood changes, and, in the case of depot medroxyprogesterone acetate, significant BMD loss due to more profound estrogen suppression. Thus, even within progestin therapy, the depth of suppression correlates with systemic consequences.

Collectively, these data indicate that profound estrogen suppression is not universally required to achieve clinical benefit. Instead, a graded relationship exists between E_2 reduction

and both efficacy and adverse effects. Profound hypoestrogenism reliably reduces symptoms but at the expense of skeletal and vasomotor health. Moderate suppression (achieved with progestins, lower-dose antagonists, or continuous COCs) may provide sufficient pain control in many patients while minimizing long-term systemic harm. The question is not whether profound suppression is effective; it clearly is, but whether it should remain the therapeutic goal for all patients. In a chronic inflammatory disease that often affects adolescents and young women requiring decades of management, sustainability becomes as important as efficacy. The emerging paradigm favors individualized estrogen-threshold modulation rather than universal induction of profound hypoestrogenism. Profound suppression retains a role in selected patients with severe, refractory disease, but it can no longer be considered the default endpoint of hormonal therapy.

8. Expert opinion

The therapeutic philosophy of endometriosis is at a turning point. For decades, clinical practice has been implicitly guided by the assumption that because endometriosis is estrogen-dependent, profound estrogen suppression must represent the optimal therapeutic endpoint. The success of GnRH agonists in reducing pain reinforced this paradigm, equating efficacy with biochemical menopause. Yet this approach, while effective in the short term, was never designed for a chronic inflammatory disease that frequently affects adolescents and young women, requiring decades of management.

The central limitation of profound suppression lies not in its efficacy, but in its sustainability. Profound hypoestrogenism reliably attenuates lesion activity, inflammatory amplification, and neuroangiogenic signaling. However, it does so at a systemic cost: BMD loss, vasomotor instability, sexual dysfunction, mood alterations, and potential long-term cardiometabolic consequences. Women with endometriosis already face elevated cardiovascular risk, with meta-analyses demonstrating increased hazard ratios for ischemic heart disease (HR 1.50, 95% CI 1.37–1.65) and cerebrovascular disease (HR 1.17, 95% CI 1.07–1.29) compared to women without the condition [120,121]. Prolonged estrogen deprivation may compound these baseline risks through adverse effects on lipid profiles, endothelial function, and metabolic parameters [122]. Even with add-back therapy, complete neutralization of these risks remains uncertain in prolonged use. In this context, profound suppression resembles an acute intervention strategy rather than a chronic disease model.

The advent of oral GnRH antagonists has provided decisive pharmacodynamic evidence that the relationship between E_2 suppression and symptom control is continuous rather than binary. Clinical response improves as estrogen levels fall, but adverse effects increase in parallel. Elagolix trials demonstrated that moderate suppression (mean E_2 approximately 42 pg/ml with 150 mg daily) achieved clinically meaningful pain reduction with fewer hypoestrogenic effects, whereas profound suppression (mean E_2 approximately 12 pg/ml with 200 mg twice daily) yielded incremental efficacy at the cost of increased vasomotor symptoms (46% versus 24%) and accelerated bone loss [103]. Relugolix combination therapy further supports this concept by achieving high response rates while preserving BMD [110].

Importantly, when all hormonal classes are viewed along a suppression spectrum, their roles become complementary rather than competitive. COCs provide moderate stabilization of E_2 with thromboembolic considerations related to estrogen exposure (VTE risk 7–10 per 10,000 women-years) [20]. Progestins exert direct anti-proliferative and anti-inflammatory actions while maintaining E_2 within a low but physiologically relevant range, with minimal thromboembolic risk. GnRH agonists achieve profound suppression with predictable systemic consequences, including bone loss and vasomotor symptoms. GnRH antagonists introduce precision, allowing clinicians to position each patient at a specific point along the suppression continuum through dose-dependent effects.

This spectrum-based model suggests that profound suppression should no longer be the default objective. Instead, it should be reserved for defined clinical scenarios: severe refractory pain, extensive deep disease, or short-term preoperative control. For many patients, particularly those early in their disease trajectory, moderate and sustainable endocrine modulation is likely sufficient and safer.

The future of endometriosis pharmacotherapy should be guided by three core principles. First, depth of suppression should be individualized based on disease phenotype and patient characteristics. Not all phenotypes require the same E_2 threshold. Deep endometriosis, characterized by dense fibrosis and nerve infiltration, appears more resistant to size regression with medical treatments and may demand more aggressive suppression. In contrast, superficial peritoneal disease or early-stage endometriosis may respond adequately to moderate modulation. Progesterone resistance, mediated by altered PR-B/PR-A ratios and epigenetic modifications, further modulates individual sensitivity to hormonal therapy [76]. Emerging evidence suggests that progesterone receptor status in endometriotic lesions predicts response to progestin-based therapy, with high PR expression associated with 100% positive predictive value for treatment response [123]. Such biomarker-guided approaches could enable precision stratification, avoiding ineffective trials of progestin therapy in resistant phenotypes. Second, long-term systemic health must be integrated into therapeutic decision-making from the outset. Bone integrity, cardiovascular profile, metabolic stability, and mental health are not secondary outcomes; they are essential determinants of treatment sustainability in a chronic condition affecting women over decades. The recognition that endometriosis itself confers increased cardiovascular risk underscores the importance of minimizing additional iatrogenic harm from prolonged hypoestrogenism. Third, research must move beyond pain scores alone. Biomarkers of progesterone resistance (including circulating microRNAs such as miR-125b-5p, miR-451a, and let-7b), inflammatory activity, or estrogen receptor signaling could eventually enable stratification of patients by endocrine sensitivity [124]. Integration of molecular profiling with clinical phenotype may define the next generation of precision endocrine therapy. Salivary microRNA panels are being explored as noninvasive tools to predict treatment response

and identify progesterone-resistant phenotypes before initiating therapy [124].

Endometriosis is not a malignancy requiring profound cytoreductive suppression. It is a chronic inflammatory disorder with endocrine dependence, immune dysregulation, and neurobiological complexity. The objective of pharmacotherapy should therefore be durable symptom control achieved with the minimal effective hormonal perturbation. Current guidelines emphasize that endometriosis requires sustained, suppressive treatment, with 25–34% of patients experiencing symptom recurrence within 12 months of discontinuing hormonal therapy. This chronicity necessitates treatment strategies that balance efficacy with long-term tolerability and safety.

Meta-analyses demonstrate that all hormonal treatments (from combined oral contraceptives to GnRH agonists) produce clinically significant pain reduction with little difference in effectiveness among options. This equipoise in efficacy across the suppression spectrum reinforces that profound suppression offers no categorical advantage over moderate approaches for most patients. Individual responses vary substantially, often necessitating trials of different medications within and across classes to achieve optimal symptom control while minimizing adverse effects.

Medication management should be individualized, considering age, predominant symptoms, pain severity, reproductive plans, disease extent, medication adverse effects, and cost. Hormonal treatments are often continued until pregnancy is desired or the patient reaches menopause, when symptoms typically improve with declining estrogen levels [3]. This prolonged treatment horizon makes sustainability paramount.

Profound estrogen suppression is not obsolete, but it is no longer synonymous with optimal care. The future lies in individualized estrogen-threshold modulation: identifying, for each woman, the lowest degree of suppression necessary to control disease while preserving long-term physiological resilience. This paradigm shift requires moving from uniform protocols to personalized strategies informed by disease phenotype, biomarker profiles, and individual risk-benefit considerations.

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Author contributions

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