Taylor & Francis
Taylor & Francis Group

Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: www.tandfonline.com/journals/ieds20

Safety of current strategies to manage moderate to severe pain in patients with endometriosis

Simone Ferrero, Fabio Barra, Giulia Vatteroni, Francesco Paolo Rosato, Giulio Evangelisti, Michele Paudice & Valerio Gaetano Vellone

To cite this article: Simone Ferrero, Fabio Barra, Giulia Vatteroni, Francesco Paolo Rosato, Giulio Evangelisti, Michele Paudice & Valerio Gaetano Vellone (11 Aug 2025): Safety of current strategies to manage moderate to severe pain in patients with endometriosis, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2025.2547017

To link to this article: https://doi.org/10.1080/14740338.2025.2547017

Safety of current strategies to manage moderate to severe pain in patients with endometriosis

Simone Ferrero [1,2], Fabio Barra [3,4], Giulia Vatteroni [1,2], Francesco Paolo Rosato [3], Giulio Evangelisti[5], Michele Paudice[6], Valerio Gaetano Vellone[7]

[1]Academic Unit of Obstetrics and Gynecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy

[2] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genova, Italy

[3] Unit of Obstetrics and Gynecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy

[4] Department of Health Sciences (DISSAL), University of Genoa, Genoa, Liguria, Italy

[5] Unit of Obstetrics and Gynecology, San Paolo Hospital - ASL2, Savona, Italy.

[6] Department of Integrated Diagnostic and Surgical Sciences (DISC), University of Genoa, Genoa, Italy

[7] Pathology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Corresponding author:

Simone Ferrero

E-mail: simoneferrero@icloud.com

Tel: 01139 010 511525

Mob: 01139 3477211682

Abstract

Introduction: Medical therapy is crucial in the long-term management of endometriosis, and its clinical efficacy must be balanced with a favourable safety profile.

Areas Covered: This review aims to provide a comprehensive overview of available drugs for the treatment of endometriosis, with an emphasis on their safety. A literature search was conducted using MEDLINE. EMBASE. and the Cochrane Library. Reference lists of relevant articles and recent book chapters were also examined.

Expert Opinion: First-line therapies include combined contraceptives and progestins, both effective in reducing pain. Combined contraceptives commonly cause breakthrough bleeding, nausea, headaches, breast tenderness, and libido changes. Progestins may lead to depression, decreased libido, weight gain, breast tenderness, and lipid alterations. Gonadotropin-releasing hormone agonists are second-line options but are limited by hypoestrogenic side effects, including vasomotor symptoms, urogenital atrophy, and bone mineral density (BMD) loss. Add-back therapy with norethindrone acetate or low-dose combined contraceptives mitigates these effects. GnRH antagonists provide immediate suppression without flare-up and may improve adherence; however, hot flushes and BMD loss remain concerns. While all hormonal therapies are suppressive rather than curative, optimizing safety and tolerability is essential for sustained use and symptom control.

Keywords: endometriosis, combined oral contraceptives, progestins, gonadotropin-releasing hormone agonist, gonadotropin-releasing hormone antagonist, nonsteroidal anti-inflammatory drugs

Article Highlights

- Medical therapy plays a crucial role in managing endometriosis-related pain; long-term treatment strategies should effectively balance clinical efficacy (control of pain symptoms and prevention of recurrence) with an acceptable safety profile.
- Progestins are a first-line treatment of endometriosis-related pain; they are well tolerated over the long term. Their main adverse effects are breakthrough bleeding, depression, decreased libido, breast tenderness, lipid alterations, weight gain and fluid retention.
- Combined contraceptives are a first-line treatment of endometriosis-related pain; their most common adverse effects are breakthrough bleeding, nausea, headaches, abdominal cramping, breast tenderness, and changes in vaginal discharge or libido. Most side effects of combined contraceptives are mild and often resolve with continued use or switching to a different formulation. The standard combined contraceptive regimen may slightly increase the risk of adverse events compared to the continuous regimen.
- Gonadotropin-releasing hormone agonists may cause several adverse effects such as alteration of lipid profile, depression, flushes, urogenital atrophying and loss of bone mineral density (BMD) that limit their long-term use. The intensity of these adverse effects can be decreased with the administration of an appropriate add-back therapy with norethindrone acetate or a low-dose combined contraceptive.
- Gonadotropin-releasing hormone antagonists may enhance long-term patient adherence to treatment because they effectively improve pain with minimal adverse effects, mainly hot flushing and loss of BMD.

1.0 Introduction

Endometriosis, affecting 5-15% of women of reproductive age, is a chronic inflammatory condition defined by the presence of endometriotic glands and stroma outside the uterine cavity (Figure 1). Endometriotic lesions can occur in various locations, most commonly on the pelvic peritoneum, ovaries, and uterosacral ligaments, as well as in the rectovaginal septum, rectosigmoid colon, and bladder detrusor. Rarely, endometriosis affects the diaphragm, umbilicus, pericardium and pleura [1] (Figure 2, Figure 3). Although endometriosis may occasionally be asymptomatic and diagnosed incidentally during surgery performed for other indications, more frequently, it causes pain symptoms (such as dysmenorrhea, deep dyspareunia, non-menstrual pelvic pain, dyschezia) and infertility.

Pain is the most debilitating symptom of endometriosis, significantly impairing quality of life, sexual function, work productivity, and social well-being. While surgical excision of endometriotic lesions can lead to substantial pain relief, it carries risks of intraoperative and postoperative complications. Moreover, pain recurrence following surgery is not uncommon. In particular, there is consistent evidence that the surgical management of ovarian endometriomas may compromise ovarian reserve [2]. Therefore, medical therapies are the first-line treatment of endometriosis-related pain.

Estradiol plays a role of paramount importance in the maintenance of endometriosis. Hormonal therapies currently used to treat endometriosis-related pain primarily act by suppressing ovulation and, thus, inducing a relatively hypoestrogenic state [3]. Estrogen promotes inflammation, angiogenesis, and neurogenesis within endometriotic lesions, all of which contribute to chronic pain. By suppressing estrogen production, hormonal therapies induce decidualization and atrophy of ectopic implants, reduce local cytokine release (e.g., IL-1β, TNF-α), and inhibit the growth of sensory nerve fibers, thereby reducing both inflammatory and neuropathic pain [4,5]. First-line hormonal therapies are combined with combined contraceptives (most frequently administered orally; COCs) and progestins. Second-line hormonal treatments include gonadotropin-releasing hormone analogues (GnRH-a) and gonadotropin-releasing hormone antagonists (GnRH-ant). While direct suppression of estrogen production is effective in reducing lesion activity and associated pain, such strategies—especially those that induce profound hypoestrogenism—are often poorly tolerated due to side effects such as hot flushes, mood alterations, and bone mineral density (BMD) loss. Therefore, therapeutic approaches aim to achieve a balance between sufficient estrogen suppression and acceptable long-term safety. Additionally, therapies for endometriosis improve symptoms, but they do not definitively “cure” the disease, which may not only persist but also progress despite the use of endocrine therapies and the improvement of pain symptoms [6]. Therefore, pain usually

recurs when patients discontinue the hormonal treatment either because of the adverse effects, the onset of contraindications (such as venous thrombosis) or because of the desire to conceive [5-7]. Consequently, when prescribing hormonal therapies to patients with moderate to severe pain caused by endometriosis, the physician must remember that the treatment will be used in the long term and, therefore, it is necessary to balance the efficacy of treatment with its safety and tolerability.

This review aims to provide a comprehensive evaluation of pharmacologic treatments for endometriosis, with a focus on their safety profiles, tolerability, and long-term management potential. The database of the National Library of Medicine (MEDLINE, 1950 - December 2024), EMBASE (1974 - December 2024) and the Cochrane Database (December 2024) were used to identify the papers that were published on this topic. The reference lists of all known primary and review articles were examined for additional relevant citations; recent book chapters were reviewed. The database of clinicaltrial.gov was investigated to evaluate ongoing clinical trials.

2.0 Non-steroidal anti-inflammatory drugs

2.1 Definition and mechanism of action

NSAIDs are a diverse class of drugs with analgesic, anti-inflammatory, and antipyretic properties, primarily achieved through inhibition of cyclooxygenase (COX) enzymes [8]. COX-1 is constitutively expressed and supports gastrointestinal, renal, and platelet homeostasis [9], whereas COX-2 is inducible at sites of inflammation and is primarily responsible for prostaglandin-mediated pain and fever [11,13].

2.2 Clinical efficacy

In endometriosis, NSAIDs are widely used to manage dysmenorrhea and pelvic pain. However, evidence supporting their efficacy is limited and inconsistent. This apparent paradox—where an inflammatory condition that shows only limited responsiveness to classic anti-inflammatory agents—may be explained by the complex pathophysiology of endometriosis, which involves estrogen-driven inflammation, altered immune responses, and cytokine-mediated neuroangiogenesis that extend beyond COX-mediated pathways [14]. While NSAIDs like tolfenamic acid (200 mg three times per day) and naproxen sodium (275 mg four times per day) have shown superiority to placebo for dysmenorrhea in some studies [10,12], no single agent has proven superior to others, and overall data on their impact in endometriosis-specific pain remain weak. Rofecoxib (25 mg per day), a COX-2 inhibitor, showed benefits in pelvic pain and dyspareunia but was withdrawn due to cardiovascular safety concerns [17].

2.1 Safety

While NSAIDs are often perceived as relatively safe for short-term use, their long-term administration can lead to a range of adverse effects, many of which are severe and potentially life-threatening.

The gastrointestinal tract is particularly vulnerable, with NSAID-related damage potentially affecting any segment, from the esophagus to the rectum [18-21]. However, the stomach and duodenum are most impacted. NSAID significantly increase the risk of gastrointestinal bleeding and perforation, with the risk amplifying in elderly patients or those with a history of peptic ulcers. In populations with high NSAID usage, these drugs are implicated in up to 30% of ulcer-related complications.

The renal system is another target of NSAID-related toxicity [20]. Functional renal impairment is a common side effect, potentially exacerbating conditions like cardiac failure and hyperkalemia. NSAIDs may also interfere with the actions of diuretics and antihypertensive medications, leading to fluid retention and necessitating additional medical interventions.

Respiratory complications, including acute bronchospasm, are particularly concerning in individuals with a history of aspirin sensitivity or asthma.

Rare but severe side effects, such as hepatocellular damage, acute interstitial nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, and aplastic anemia, underscore the need for caution in prescribing NSAIDs. Clinicians must maintain a high index of suspicion for NSAID-induced adverse effects, especially given the widespread use of these medications.

2.1.1 General Safety Considerations and Remarks

Overall, while NSAIDs are commonly used for the symptomatic management of endometriosis-related pain, particularly dysmenorrhea, their role is supportive rather than disease-modifying. Given the risk of gastrointestinal, renal, and cardiovascular adverse effects, their prolonged use requires careful patient selection and regular safety monitoring.

3.0 Progestins

3.1 Definition and mechanism of action

Progestins are synthetic derivatives of progesterone that exert their effects by binding to progesterone receptors and modulating hormonal activity in target tissues [22]. They decrease the frequency and increase the amplitude of GnRH pulses, thereby reducing the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As a result, the continuous

administration of progestins suppresses ovarian steroidogenesis, inducing anovulation and lowering circulating estrogen and progesterone levels.

The induced hypoestrogenic state leads to decidualization and atrophy of both eutopic and ectopic endometrial tissue. Moreover, recent evidence shows that progestins may exert direct anti-inflammatory effects, likely mediated through changes in cytokine mRNA expression and nuclear receptor protein levels [23].

Progestins can be classified based on chemical structure into 17-hydroxyprogesterone and 19-nortestosterone derivatives [3,7]. A wide range of progestins are available for the treatment of endometriosis, including norethindrone acetate (NETA), cyproterone acetate (CPA), medroxyprogesterone acetate (MPA), desogestrel (DSG), etonogestrel (ENG), levonorgestrel (LNG), and dienogest (DNG). These can be administered orally, subcutaneously (depot), via subdermal implants, or intrauterine devices.

3.2 Clinical efficacy

Progestins are particularly effective in managing dysmenorrhea and menstruation-related pain. In addition to their ovulation-suppressing effects, they counteract estrogen-driven inflammation and neuroangiogenesis, contributing to lesion regression and a reduction in nerve fiber density within ectopic implants, which correlates with improved pain control [4,5].

A Cochrane review published in 2012, including 13 randomized controlled trials (RCTs), investigated the use of progestins versus other drugs (placebo, COCs, danazol, and GnRH-a) to treat endometriosis-related pain. Only medroxyprogesterone acetate (MPA, 100 mg daily) was found to be superior to placebo, while other comparisons, including depot progestins, did not show a benefit over COCs or GnRH-a [23]. However, since this review, more robust evidence has emerged supporting the use of modern progestins.

3.2.1 Dienogest

Several systematic reviews with meta-analysis have evaluated the effectiveness of DNG, a fourth-generation selective progestin with anti-inflammatory properties, in managing endometriosis-related pain [25,26]. One review specifically addressed its role in the conservative, long-term treatment of deep infiltrating endometriosis [27], analyzing five studies involving 256 patients. DNG demonstrated significant efficacy in relieving dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and dyschezia, while also reducing lesion size.

Another systematic review and meta-analysis assessed DNG in the postoperative setting [28]. DNG was associated with a lower rate of endometrioma recurrence compared to placebo. In a subgroup of

191 patients, recurrence rates were similar between DNG and GnRH-a. Secondary endpoints suggested greater pain reduction with DNG versus placebo at six months.

An additional review of nine randomized trials confirmed that DNG is significantly better than placebo for pain relief, with comparable outcomes to GnRH-a and a beneficial effect on lesion regression [28]. A separate review comparing DNG with expectant management after conservative surgery demonstrated a striking difference in recurrence rates: 2 per 100 women with DNG versus 29 per 100 women in the expectant group over a mean 29–36 month follow-up [30].

3.2.2 Etonogestrel-Release Subdermal Implant

The ENG-release subdermal implant is a progestin-based, long-acting contraceptive option, especially suitable for patients seeking extended symptom control. In an Italian study involving 43 women with ultrasound-confirmed rectovaginal endometriosis treated with an ENG-releasing subdermal implant, follow-up at 6, 12, and 24 months showed significant reductions in pain scores and improvements in quality of life. Nodule volume decreased significantly within 6 months and continued to regress thereafter [31].

A systematic review encompassing 11 studies (335 patients) further confirmed that the ENG implant provides comparable pain relief to depot-MPA (DMPA) and LNG-IUD, with consistent improvements across physical and emotional health domains measured by validated questionnaires [31].

3.2.3 Levonorgestrel-Releasing Intrauterine Device

The LNG-IUD is an effective option for patients with dysmenorrhea and heavy menstrual bleeding, particularly in the presence of adenomyosis or fibroids [33]. However, its role in preventing endometrioma recurrence is controversial [33].

A randomized trial of 80 women following laparoscopic cystectomy and GnRH-a therapy found no significant difference in endometrioma recurrence, although pain symptoms and CA125 levels improved in the LNG-IUD group [34]. A non-inferiority RCT involving 103 women with chronic pelvic pain demonstrated that ENG implant and LNG-IUD were similarly effective in reducing pain and improving quality of life [35]. However, a Cochrane review (4 RCTs, 157 women) rated the evidence as low-quality, highlighting limited evidence for pain reduction at 12 months [36].

Despite this, a meta-analysis of seven studies (491 participants) reported that the LNG-IUD significantly reduced postoperative pain and had a recurrence rate comparable to COCs and danazol [37]. Patient satisfaction was higher for the LNG-IUD than for COCs.

3.2.4 Other Applications and Practical Considerations

Progestins have also shown efficacy in treating pain related to specific forms of endometriosis, including gastrointestinal symptoms in colorectal endometriosis [38,39], urinary symptoms in bladder disease [40], and endometrioma-related pelvic pain [41].

A practical limitation is that only selected progestins are approved for contraceptive use (e.g., DSG, ENG, LNG-IUD), which may affect patient preference. Additionally, oral progestins must be taken daily, and missed doses can reduce effectiveness — a relevant factor in long-term adherence.

3.3 Safety

3.3.1 General Tolerability of Progestins

Progestins are well tolerated over the long term, and their main related adverse effects are spotting, breakthrough bleeding, depression, decreased libido, breast tenderness, lipid alterations, weight gain, and fluid retention (Table 1). Irregular vaginal bleeding is a potential disadvantage of all progestin-only methods, particularly during the initial cycles after treatment initiation. However, amenorrhea rates are notably higher with the use of the LNG-IUD and DMPA [42].

3.3.2 Norethindrone Acetate

In an RCT including women with symptomatic rectovaginal endometriosis, administering low-dose NETA (2.5 mg/day) for 12 months resulted in weight gain in 26.7% of participants, with an average increase of 3.6 ± 2.3 kg. Additionally, 9% of participants reported decreased libido [43]. A retrospective study evaluating the efficacy and safety of a 5-year NETA treatment identified the most common adverse effects as weight gain (30.1%), vaginal bleeding (23.3%), and lipid alterations (11.6%) [44].

3.3.3 Dienogest

A retrospective study involving 83 patients evaluated the adverse effects of long-term DNG treatment [39]. Reported side effects included weight gain (30.1%), abnormal uterine bleeding (26.9%), headache (21.2%), depression (9.6%), decreased libido (3.8%), and acne (1.9%). A randomized controlled trial comparing DNG to continuous LNG/ethinylestradiol (EE) in patients with endometriosis found similar efficacy in pain relief, although side effect profiles differed; DNG was associated with more frequent bleeding irregularities, while COC users reported higher rates of nausea and breast tenderness. A systematic review and meta-analysis confirmed that DNG increases the risk of adverse effects compared to LNG-IUD and GnRH-a, especially vaginal bleeding and weight gain [45]. Another meta-analysis focusing on the adverse effects of DNG also reported

increased incidence of headaches and decreased libido. However, an advantage of DNG is its ability to maintain average estradiol serum levels within 20–50 pg/ml, sufficient to prevent BMD loss [25].

3.3.4 Desogestrel

DSG is associated with specific side effects such as acne flares and ovarian cysts. Irregular or altered menstrual bleeding is the most frequently reported issue with DSG. While DSG generally has fewer systemic side effects compared to COCs, it is more likely to cause menstrual irregularities [46].

An RCT evaluating the safety of DSG reported breakthrough bleeding in 20.0% of participants [47]. A multicenter RCT involving 1,190 participants found that DSG administration over nine cycles reduced cholesterol (total, HDL, LDL) and triglyceride levels, without significant changes in glucose metabolism, insulin, C-peptide, or bone remodeling markers. DSG did not impact coagulation parameters [48].

3.3.5 Long-Acting Progestins: LNG-IUD, ENG-Release Subdermal Implant, and DMPA

A systematic review analyzing bleeding patterns associated with DMPA included 13 studies involving 1,610 patients. The review found that 46% of users experienced amenorrhea within 90 days after the fourth dose [49]. A non-inferiority RCT comparing the ENG-releasing contraceptive implant and the LNG-IUD for managing endometriosis-associated pelvic pain showed that the most common bleeding patterns at 180 days were amenorrhea and infrequent bleeding for ENG implant users, and infrequent bleeding and spotting for LNG-IUD users [35]. A Cochrane review assessing the LNG-IUD as postoperative treatment for symptomatic endometriosis found fewer vasomotor symptoms than GnRH-a, but more irregular bleeding [36].

3.3.6 General Safety Considerations and Remarks

One notable advantage of progestins is their lower thrombotic risk compared to combined oral contraceptives (COCs). Users of DSG have no increased venous thromboembolism (VTE) risk compared to nonusers [51]. The LNG-IUD does not increase the risk of VTE compared to individuals without hormone exposure [51-53]. Compared to DSG and the LNG-IUD, MPA may have a higher thrombotic risk [51]. In a large database study evaluating the ENG implant, the adjusted relative risk of thrombosis was 1.4 compared to nonusers [53].

Another important aspect of safety is the suitability of progestins for patients with neurological contraindications to estrogens. Progestins can be safely prescribed to women with migraine with

aura and are better tolerated than COCs in patients under 35 years of age with migraines without aura [54-56].

In summary, progestins represent a safe and well-tolerated class of agents for the long-term treatment of endometriosis. Differences in bleeding patterns, metabolic impact, contraceptive indication, and thrombotic risk should guide personalized treatment selection. Appropriate counseling and careful monitoring improve adherence and optimize patient outcomes.

4.0 Combined Estrogen–Progestin Contraceptives

4.1 Definition and mechanism of Action

COCs disrupt the normal function of the hypothalamic–pituitary–gonadal axis by inhibiting LH (via progestogen) and FSH (via estrogen), thereby preventing ovulation [58]. Progestogen also contributes to contraceptive efficacy by inducing endometrial atrophy, thickening cervical mucus, and reducing tubal motility. Estrogens play a key role in stabilizing the endometrium to reduce breakthrough bleeding and enhances the activity of progestogens, enabling the use of lower doses for effective contraception [59].

COCs are widely used in the management of dysmenorrhea, dyspareunia, and non-menstrual pelvic pain in reproductive-aged women with endometriosis. They are available in oral, transdermal, or vaginal formulations, with oral use being the most common. In addition to providing long-term safety and effective contraception, COCs offer the benefit of regulating the menstrual cycle [59].

Depending on individual clinical needs, they can be prescribed cyclically or continuously. Continuous regimens, in particular, are preferred for patients whose symptoms worsen during menstruation.

4.2 Clinical efficacy

Numerous randomized controlled trials have investigated the efficacy of COCs in reducing endometriosis-associated pain. Early studies comparing COCs to GnRH agonists or danazol showed that both therapies reduced pain symptoms, although GnRH-a often led to faster or more profound relief. In a trial comparing cyclic low-dose COC (20 μg EE and 0.15 mg DSG) with monthly subcutaneous goserelin, both treatment arms showed reductions in deep dyspareunia and non-menstrual pelvic pain. However, symptoms tended to recur six months after treatment discontinuation, with no significant differences between groups [60]. Another trial compared a COC combined with danazol (50 mg/day) to depot MPA (150 mg every three months) for long-term pain

control. While both therapies led to symptom improvement, patient satisfaction was higher in the MPA group (72.5%) compared to the COC plus danazol group (57.5%) [61].

Further studies confirmed that COCs and GnRH-a are similarly effective in reducing pain, particularly dysmenorrhea and pelvic pain. A multicentre RCT compared 12 months of COC use (30 μg EE and 0.75 mg gestodene) to a four-month course of triptorelin followed by eight months of the same COC regimen. Both groups reported significant reductions in dysmenorrhea and non-menstrual pelvic pain, with no notable differences between the two [61]. Another randomized study in women with stage III–IV endometriosis evaluated COC, GnRH-a, dietary supplementation, and placebo. COC and GnRH-a were more effective than placebo in relieving dysmenorrhea, but all interventions were comparably effective for non-menstrual pelvic pain and dyspareunia [62].

A double-blind, placebo-controlled Japanese trial assessed a cyclic low-dose COC (35 μg EE and 1 mg NETA) for endometriosis-associated pain. After four months, patients receiving the COC experienced significant reductions in dysmenorrhea, but there was no significant effect on non-menstrual pain. However, a reduction in the volume of endometriomas >3 cm was observed [63]. Another trial compared continuous COC use to depot leuprolide (11.25 mg IM every 12 weeks) with NETA add-back therapy. Both treatment arms showed comparable reductions in pain and depressive symptoms over 48 weeks [65].

COCs have also been compared directly to progestins. A prospective patient-preference study evaluated continuous NETA (2.5 mg/day) versus extended-cycle COC (30 μg EE and 150 μg LNG for 84 days followed by 10 μg EE for 7 days). Satisfaction at 12 months was similar between the two groups (82.2% for NETA vs. 68.4% for COC), with both significantly alleviating pain symptoms. Unscheduled bleeding was more frequent in the COC group during the first cycle [65]. In a surgical context, an RCT comparing continuous COC (30 μg EE and 0.75 mg gestodene) to depot MPA following conservative endometriosis surgery found a greater reduction in dysmenorrhea in the COC group, with similar discontinuation rates due to persistent pain [66].

A multicenter phase 3, double-blind RCT assessed the efficacy and safety of a flexible extended COC regimen (FlexibleMIB) for endometriosis-associated pelvic pain. In 312 patients, FlexibleMIB significantly reduced severe pelvic pain compared to placebo and showed comparable effectiveness to DNG over 52 weeks [68]. Multiple other trials comparing COCs to DNG in symptomatic women and postoperative patients found that both therapies provided significant and similar reductions in pelvic pain, dyspareunia, and improvements in quality of life, with no statistically significant differences between groups [68].

Although no RCTs have specifically evaluated the use of vaginal rings or transdermal patches for the treatment of endometriosis-related pain, prospective cohort studies suggest that these

formulations may be effective. One study compared a vaginal ring (15 µg EE and 120 µg ENG monthly) with a transdermal patch (60 µg EE and 6 mg 17-deacetylnorgestimate monthly), reporting reductions in pain with both treatments. The vaginal ring appeared more effective in reducing symptoms [73]. Another study confirmed the usefulness of the vaginal ring in the treatment of deep infiltrating endometriosis, with comparable results to continuous oral DSG (75 µg/day) [73].

4.3 Safety

Some women using COCs may experience side effects related to estrogen and progestin exposure. However, these adverse effects are significantly less frequent with modern low-dose formulations compared to older COCs. The most common side effect is breakthrough bleeding, followed by nausea, headaches, abdominal cramping, breast tenderness, and changes in vaginal discharge or libido (Table 2) [42]. In most cases, these symptoms are mild, self-limiting, and improve over time or after switching formulations. Nausea, in particular, can often be mitigated by taking the pill at bedtime.

The risk of irregular bleeding appears to be higher with standard COC regimens than with continuous regimens [74]. Nevertheless, there is insufficient evidence to determine whether continuous regimens differ from standard ones in terms of serious adverse events, headaches, or nausea. Irregular bleeding patterns tend to vary depending on the COC formulation and timing of use. Breakthrough bleeding affects 10% to 30% of users in the first month, decreasing to approximately 10% by the third month [76-78]. Bleeding that occurs later in treatment is often associated with progestin-induced endometrial decidualization, inconsistent pill use, or smoking.

Weight gain is frequently reported as a concern among users and is one of the most cited reasons for discontinuation. However, clinical trials have not demonstrated a causal link, and weight changes are comparable between COC and placebo groups [79]. The impact of COCs on libido remains controversial. While some studies report a decrease in libido, others describe improvements in sexual satisfaction and enjoyment. A well-designed prospective study showed that a low-dose drospirenone-containing COC was associated with improved sexual satisfaction and no change in libido [80].

The risk of VTE and arterial events such as ischemic stroke or myocardial infarction is increased with COC use, but remains rare in healthy reproductive-aged women. According to a Cochrane review, VTE incidence in non-users ranges from 0.19 to 0.37 per 1,000 person-years. COC use increases VTE risk approximately 3.5-fold, and the risk is influenced by both estrogen dose and progestin type [81]. COCs containing 30–35 µg EE in combination with gestodene,

desogestrel, cyproterone acetate, or drospirenone confer a 50% to 80% higher risk than COCs containing LNG. A dose-dependent relationship was observed for several progestins, with higher EE doses correlating with increased risk.

For arterial events, a meta-analysis of 28 studies reported that COC users had an increased risk of ischemic stroke (RR 1.7) and myocardial infarction (RR 1.6) compared to non-users [82]. These risks were more pronounced with EE doses >50 µg, which are rarely used in modern formulations. Today's lower estrogen content COCs substantially reduce thrombotic risk, and the use of LNG-containing preparations at 30 µg EE is preferred to minimize cardiovascular complications.

COCs may also impact glucose metabolism in the first months of use. Women with diabetes may require adjustments to insulin or oral medications to maintain glycemic control. Moreover, hypertension may be induced in 4–5% of healthy women and worsened in up to 16% of women with pre-existing hypertension [84].

Finally, there is emerging concern that COCs might attenuate bone mineral density (BMD) accrual in adolescents, particularly with formulations containing 30 µg EE. Although the clinical relevance of this finding remains uncertain, it warrants attention in long-term users starting in adolescence [84,85].

4.3.1 General Safety Considerations and Remarks

Despite the association with rare but serious vascular events, modern low-dose COCs remain safe for the majority of women when appropriately selected and monitored. The overall risk profile is strongly influenced by individual susceptibility, comorbidities, smoking status, age, and hormonal formulation. The selection of COCs containing lower EE doses (≤30 µg) and second-generation progestins such as LNG is advisable in women with increased thrombotic risk [81].

In conclusion, COCs represent a well-tolerated and effective first-line therapy for endometriosis-associated pain. Their safety profile is favorable in most users, and adverse effects can be minimized by careful patient selection, education, and individualized management.

5.0 Gonadotropin-Releasing Hormone Analogues (GnRH-a)

5.1 Definition and mechanism of Action

GnRH-a, such as buserelin, goserelin, leuprorelin acetate, nafarelin, and triptorelin, are typically prescribed when first-line hormonal therapies fail to adequately relieve pain in patients with endometriosis [87]. These decapeptides differ from native GnRH by one or more amino acid substitutions, leading to their high affinity for GnRH receptors. Their primary mechanism involves desensitization of pituitary GnRH receptors, resulting in suppressed LH and FSH secretion,

ultimately inhibiting ovarian estrogen production. The resulting hypoestrogenic state induces amenorrhea and regression of endometriotic lesions.

Although not traditionally categorized as anti-inflammatory drugs, GnRH-a have been shown to reduce peritoneal inflammation by decreasing local estrogen levels and downregulating pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and VEGF. Moreover, they promote apoptosis and inhibit neuroangiogenesis within ectopic implants, which contributes to pain relief and lesion regression [87,88].

5.2 Clinical efficacy

A 2010 Cochrane review including 41 RCTs (4935 women) evaluated the efficacy of GnRH-a for the treatment of endometriosis-related pain [89]. Compared to placebo or no treatment, GnRH-a significantly improved pain symptoms. The review also found greater efficacy of GnRH-a compared to danazol, although the difference in dysmenorrhea was not statistically significant. No significant difference in overall pain reduction was observed between GnRH-a and the LNG-IUD. Notably, the review highlighted a lack of conclusive evidence regarding optimal duration, dose, and route of administration for GnRH-a.

Additional RCTs supported these findings. Among these, Fedele et al. showed that a six-month course of intranasal buserelin was superior to expectant management in improving pain in infertile women with endometriosis [90]. Four placebo-controlled trials involving leuprorelin and triptorelin consistently demonstrated superiority of GnRH-a in reducing pain and improving quality of life [94,95].

Although no RCTs have directly compared GnRH-a to NSAIDs, comparisons with other hormonal therapies are available. Two multicenter RCTs compared subcutaneous depot MPA to intramuscular leuprolide over six months. Both therapies effectively reduced pain, with benefits persisting at 12-month follow-up [96,97]. DNG was compared to buserelin and leuprolide in two RCTs; all treatments led to significant pain improvement, with no significant differences between groups [98-100].

Three RCTs compared the LNG-IUD to GnRH-a. Two six-month studies comparing LNG-IUD to leuprolide found comparable efficacy in reducing pain [98,99], while a third RCT found goserelin and LNG-IUD similarly effective over 24 weeks [100]. In a trial by Vercellini et al., subcutaneous goserelin was compared with low-dose COC (20 μg EE and 0.15 mg DSG); both reduced non-menstrual pelvic pain, but goserelin showed greater improvement in dyspareunia [60]. Two additional RCTs comparing COCs with GnRH-a also found equivalent pain reductions [61]. However, no RCTs have compared GnRH-a to NETA monotherapy.

A randomized trial also assessed the use of goserelin combined with the aromatase inhibitor anastrozole versus goserelin alone after conservative surgery for severe endometriosis. The combination therapy led to greater pain reduction and a longer recurrence-free interval during a two-year follow-up [61].

Concerning treatment duration, one RCT compared three versus six months of nafarelin therapy. Both groups experienced similar reductions in pain, with recurrence rates comparable at 12 months post-treatment [103].

5.3 Safety

The tolerability profile of GnRH-a is generally less favorable than that of first-line hormonal therapies. Approximately 75% of women develop signs of hypoestrogenism within four weeks of initiating therapy, with nearly all patients affected by the eighth week [104]. Serum estradiol levels during treatment are typically <20 pg/mL, resembling postmenopausal values. This profound hypoestrogenic state accounts for many of the adverse effects associated with GnRH-a, including amenorrhea, vasomotor symptoms, decreased libido, and mood changes. Over 80% of patients report vasomotor symptoms; vaginal dryness and headaches affect approximately 30% of users [92]. These symptoms negatively impact quality of life and often lead to treatment discontinuation [105].

5.3.1 Bone Mineral Density Loss

Among the most concerning adverse effects is the reduction in BMD. Estrogen are important for inhibiting osteoclastic bone resorption and promoting osteoblastic bone formation. GnRH-a therapy disrupts this balance, leading to accelerated bone loss, particularly at trabecular-rich sites such as the lumbar spine and femoral neck. Studies have shown BMD reductions of 2% to 6% after six months of therapy [106,107]. This decline can exceed 1% per month during the early phase of treatment.

Recovery of BMD after treatment cessation is often incomplete, especially after longer courses. Some studies report persistent deficits even 6–24 months after stopping therapy, with partial recovery at best [91]. Adolescents and young women, who have not yet reached peak bone mass, are particularly vulnerable. Monitoring BMD with DEXA scans and ensuring adequate calcium and vitamin D intake, alongside weight-bearing exercise, are recommended for patients receiving GnRH-a, especially those with preexisting risk factors for osteoporosis [112].

5.3.2 Metabolic and Other Adverse Effects

GnRH-a treatment has also been associated with adverse metabolic effects. Increases in LDL cholesterol and unfavorable changes in the LDL/HDL ratio have been reported compared to COCs or progestins [113].

The range of other side effects includes hot flushes (19.6% to 90%), headaches (8.5% to 68%), stiff shoulders (12.8%), vaginal dryness (28–37%), decreased libido (19–24%), fatigue (58%), irritability (47%), depression (32%), sleep disturbances (11%), acne (26%), and other physical and emotional discomforts. These adverse effects often resolve after treatment cessation but can significantly affect adherence and patient satisfaction.

5.3.3 Add-Back Therapy and Long-Term Safety Considerations

Due to these safety concerns, especially related to bone and vasomotor symptoms, the use of add-back therapy is recommended for any treatment course exceeding six months. Add-back regimens such as low-dose NETA or tibolone have been shown to reduce the severity of hypoestrogenic symptoms while preserving the efficacy of GnRH-a in pain control [114]. This approach enables longer treatment durations, improves patient adherence, and mitigates long-term risks associated with estrogen deprivation.

5.3.4 General Safety Considerations and Remarks

GnRH-a are effective second-line treatments for endometriosis-associated pain, with mechanisms that extend beyond ovulation suppression to include anti-inflammatory and neuroangiogenesis-inhibiting effects. However, their use is constrained by a less favorable safety profile, particularly regarding bone health and vasomotor symptoms. When prolonged treatment is needed, the addition of hormone add-back therapy is essential to reduce adverse effects and allow for sustained symptom control. Close monitoring of patients receiving GnRH-a, especially those at risk for osteoporosis or cardiovascular complications, is critical to ensure a favorable risk–benefit ratio.

6.0 Gonadotropin-Releasing Hormone Antagonists

6.1 Definition and mechanism of Action

GnRH-ant represent a more recent addition to the therapeutic arsenal for endometriosis and offer distinct pharmacological advantages over GnRH agonists. In contrast to GnRH-a, which cause an initial flare-up of gonadotropin secretion before receptor downregulation occurs, GnRH-ant produce immediate pituitary suppression, thereby avoiding the transient exacerbation of symptoms. This contributes to more rapid pain relief and a more favorable side effect profile.

GnRH-ant provide dose-dependent suppression of the hypothalamic–pituitary–gonadal axis: lower doses partially suppress estrogen production, while higher doses induce full ovarian suppression. Their effects are fully reversible upon discontinuation, as endogenous GnRH rapidly displaces the antagonist at receptor sites. Among the most widely studied antagonists are elagolix (ELX), relugolix (RLX), and linzagolix (LGX). Differences in half-life and tissue distribution determine their pharmacokinetics and dosing regimens. RLX and ELX require daily administration and typically necessitate add-back therapy at therapeutic doses. In contrast, LGX has a longer half-life and offers flexible dosing strategies, reducing the need for add-back therapy at lower doses, and making it suitable for both short- and long-term management strategies .

6.2 Clinical efficacy

6.2.1 Elagolix

ELX is an orally administered GnRH-ant that is rapidly absorbed and quickly suppresses gonadotropins and estradiol levels [115]. The pivotal Elaris Endometriosis I and II trials were two large, multicenter, double-blind, phase 3 RCTs evaluating the efficacy of ELX over a six-month treatment period in women with moderate-to-severe endometriosis-associated pain [116]. Treatment with ELX (150 mg once daily and 200 mg twice daily) significantly improved dysmenorrhea in 42.1–46.2% and 75.3–76.9% of participants, respectively. Improvements in non-menstrual pelvic pain were reported by 45.7–51.6% of those on the 150 mg dose and 62.1–62.2% on the 200 mg dose. The higher dose was also associated with improved outcomes in dyspareunia, reduced opioid use, and decreased reliance on rescue analgesics. Sustained benefit was observed in the extension studies (Elaris III–IV) [116].

A subsequent 12-month double-blind phase 3 trial confirmed that ELX 200 mg twice daily combined with add-back therapy significantly improved dysmenorrhea (62.8% vs. 23.7%), non-menstrual pelvic pain (51.3% vs. 36.8%), and fatigue, compared to placebo [118]. These benefits were maintained through month 12, supporting the long-term utility of ELX with hormonal add-back therapy.

6.2.2 Relugolix

Two large, multicenter phase 3 RCTs—SPIRIT 1 and SPIRIT 2—evaluated the effectiveness of RLX in combination with estrogen and NETA add-back therapy for the treatment of moderate-to-severe endometriosis-related pain [118]. After 24 weeks, RLX combination therapy significantly reduced dysmenorrhea (75%) and non-menstrual pelvic pain (58–66%) compared to placebo (27–43%). Reductions in opioid consumption were also documented.

These results were confirmed in the SPIRIT extension study, which followed patients for an additional 80 weeks [120]. Sustained improvements were observed in all treatment arms, with 84.8% of women reporting resolution of dysmenorrhea and 75.8% reporting relief of non-menstrual pelvic pain at 104 weeks. The study also reported reductions in dyspareunia, improved quality of life, and decreased opioid use, establishing RLX combination therapy as a viable long-term option for endometriosis-associated pain.

6.2.3 Linzagolix

LGX is another oral GnRH-ant evaluated for its efficacy in managing endometriosis-associated pain [121]. A dose-ranging multinational, double-blind RCT assessed four daily doses (50, 75, 100, 200 mg) over 24 weeks [122]. Doses ≥75 mg significantly reduced dysmenorrhea and non-menstrual pelvic pain at 12 and 24 weeks, with additional benefits including improved quality of life and amenorrhea rates.

The Edelweiss III trial, a placebo-controlled, double-blind RCT, evaluated 75 mg LGX monotherapy and 200 mg LGX with add-back therapy [123]. At 3 months, the response rate for dysmenorrhea was 72.9% with 200 mg plus add-back, 44.0% with 75 mg monotherapy, and 23.5% with placebo. For non-menstrual pelvic pain, response rates were 47.3%, 38.9%, and 30.9%, respectively. These improvements were maintained through six months. The 75 mg dose achieved statistical significance for non-menstrual pelvic pain only after month three.

6.3 Safety

GnRH antagonists have demonstrated a generally favorable safety profile, with most adverse effects being mild, dose-dependent, and related to hypoestrogenism. In clinical trials of ELX, hot flushes were the most commonly reported adverse event, occurring in 24% of patients taking 150 mg daily and 48% of those receiving 200 mg twice daily. BMD loss was also dose-dependent: reductions exceeded 3.5% at the higher dose, while remaining closer to 1% at 150 mg. Importantly, studies using add-back therapy reported substantially lower incidence of hypoestrogenic symptoms and no significant impact on BMD [118].

In the SPIRIT-1 and SPIRIT-2 trials, RLX combination therapy was associated with minimal changes in BMD, with mean percentage reductions at the lumbar spine of only 0.70% and 0.78%, respectively. The incidence of hot flushes was low and comparable to placebo (10.4% and 13.6%) [119].

Similarly, LGX was well tolerated. In clinical trials, hot flushes were reported by only 7.5% of patients on the 75 mg dose and 6.8% on the 200 mg dose with add-back therapy. BMD reductions were mild and averaged less than 1% (Table 3) [123].

6.3.1 General Safety Considerations and Remarks

GnRH-ant are effective and well-tolerated options for the medical management of moderate to severe endometriosis-associated pain. They provide rapid symptom relief, offer dose-adjustable estrogen suppression, and avoid the initial flare effect associated with GnRH-a. When used with appropriate add-back therapy, these agents can be administered safely over the long term without significant impacts on bone health or metabolic parameters. Their oral administration, flexible dosing, and favorable safety profiles make GnRH-ant valuable alternative to traditional hormonal therapies in selected patients.

7.0 Conclusion

Endometriosis is a chronic, estrogen-dependent condition that requires long-term, often cyclical, management. Hormonal therapy should be initiated at symptom onset or diagnosis and continued throughout the reproductive years, with temporary discontinuation only when pregnancy is desired. Achieving an optimal balance between efficacy and safety is essential, particularly for long-term use. First-line therapies, including progestins and COCs, offer favorable safety profiles and are suitable for most patients. GnRH-a and -ant are reserved for refractory cases due to their hypoestrogenic side effects and the risk of BMD loss. Treatment choice should be individualized, considering age, comorbidities, reproductive plans, and tolerability. Future research should focus on identifying biomarkers predictive of treatment response, developing better-tolerated agents with targeted mechanisms of action, and integrating personalized algorithms into clinical practice. Tailoring therapy to the individual patient remains the cornerstone of effective endometriosis care.

8.0 Expert opinion

Most hormonal therapies currently available for endometriosis are suppressive rather than curative, leading to a high likelihood of symptom recurrence upon discontinuation. Additionally, most treatments for endometriosis-related pain, excluding NSAIDs, have contraceptive effects, making them unsuitable for young patients wishing to conceive.

The limited efficacy of NSAIDs likely stems from their inability to modulate the underlying hormonal and immune dysregulation that sustains chronic inflammation in endometriosis. This

limitation underscores the need for therapies that act upstream of prostaglandin synthesis or through alternative pathways.

Among traditional first-line treatments, estroprogestins (administered orally, via transdermal patches, or as vaginal rings) and progestins (administered orally, as depot injections, implants, or through LNG-IUDs) effectively manage pain in most patients. These options provide satisfactory pain relief with minimal adverse effects, long-term safety, and affordability. The efficacy of these therapies in pain reduction is largely attributable to the suppression of estrogenic activity, which otherwise supports a pro-inflammatory and neurotrophic environment within endometriotic lesions. Reducing estrogen not only limits lesion growth but also downregulates pain-generating molecular pathways and peripheral nerve activation. While COCs have long been the primary treatment for symptomatic endometriosis, the use of progestins as monotherapy has been increasingly recognized as effective. However, it remains debated whether progestins are superior to COCs. Concerns exist that COCs, which induce supraphysiologic estrogen levels, could exacerbate estrogen dominance in cases of progesterone resistance, potentially leading to disease progression.

Abnormal vaginal bleeding is a common side effect of continuous hormonal therapy, particularly with progestins. Bleeding patterns often relate to the estrogen-to-progestin ratio in COC formulations or the absence of estrogen in progestin monotherapy. Breakthrough bleeding is frequent in women using long-acting progestins such as depot MPA or LNG-IUD [124]. A pooled analysis of DNG (2 mg/day) revealed an initial increase in bleeding days, followed by a reduction over time, with amenorrhea rates improving [124]. In clinical practice, treatment adherence improves when patients are informed about potential bleeding side effects, particularly at the start of therapy. Between 25% and 30% of women undergoing first-line treatments for endometriosis experience inadequate responses [5]. This lack of efficacy may result from molecular mechanisms, such as imbalances in estrogen receptors or cell adhesion molecules, which are implicated in progestin resistance. However, no definitive conclusions or biomarkers for resistance have been established. Dynamic monitoring of treatment response is crucial, enabling timely treatment changes or surgical considerations.

These limitations have stimulated interest in directly antagonizing estrogenic activity at the receptor level. However, selectively blocking estrogen action in endometriosis has proven challenging. Approaches involving selective estrogen receptor modulators (SERMs) or aromatase inhibitors have not translated into broadly applicable therapies. In premenopausal women, these agents are often poorly tolerated and may require complex hormonal add-back regimens to counteract hypoestrogenic side effects. Moreover, the differential expression of estrogen receptor subtypes (e.g., ERα and ERβ) in endometriotic lesions complicates the development of receptor-targeted

strategies [126,127]. As result, despite a strong mechanistic rationale, the clinical viability of selective estrogen blockade remains limited, and further research is required to identify more effective and better tolerated alternatives.

Patients receiving long-term hormonal treatment must be periodically evaluated to timely diagnose the progression of endometriosis, which may not always correlate with clinical symptoms, particularly in patients under hormonal treatment. This follow-up can be performed by transvaginal ultrasonography, which has good performance in diagnosing not only ovarian endometrioma but also deep endometriosis [125].

GnRH-a and GnRH-ant are second-line therapies that are prescribed when first-line therapies fail to alleviate pain, are poorly tolerated, or are contraindicated. While effective, long-term use of GnRH-a is limited by hypoestrogenic side effects (e.g., vaginal dryness, hot flashes, and bone mineral density loss). Therefore, treatment exceeding six months often requires add-back therapy, such as COCs or NETA. Oral GnRH-ant such as ELX, RLX, and LGX represent a major advancement in managing endometriosis-associated pain, offering an alternative to traditional treatments with the benefit of dose flexibility to mitigate side effects. However, the hypoestrogenic side effects, particularly those impacting bone mineral density, remain a key challenge. These limitations underscore that while estrogen suppression is mechanistically effective, its clinical application requires careful dose modulation and the use of add-back therapies to mitigate adverse effects. The advent of oral GnRH antagonists with dose-dependent suppression profiles represents a promising strategy to optimize this balance between efficacy and tolerability.

Careful monitoring and limitations in treatment duration are essential to optimize outcomes while minimizing risks. Comparative studies of GnRH-ant with estro-progestins or progestins would be valuable in determining whether GnRH-ant offer significant advantages over first-line therapies. No such studies exist, and available comparisons are limited to GnRH-a.

Funding

This paper was not funded.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

[1] Ferrero S, Racca A, Leone Roberti Maggiore U. Endometriosis. In: Woodward B, Mehta J, editors. Female Infertilty: Core Principles and Clinical Management: Jaypee Brothers Medical Publishers (P) Ltd.; 2020.

[2] Zhang Y, Zhang S, Zhao Z, et al. Impact of cystectomy versus ablation for endometrioma on ovarian reserve: a systematic review and meta-analysis. Fertility and sterility. 2022;118(6):1172-1182.

[3] Ferrero S, Remorgida V, Venturini PL. Current pharmacotherapy for endometriosis. Expert Opin Pharmacother. 2010;11(7):1123-34.

[4] Ferrero S, Camerini G, Venturini P, et al. Progression of bowel endometriosis during treatment with the oral contraceptive pill. Gynecol Surg. 2011;8(3):311-313.

[5] Ferrero S, Evangelisti G, Barra F. Current and emerging treatment options for endometriosis. Expert Opin Pharmacother. 2018;19(10):1109-1125.

[6] Ferrero S, Barra F, Leone Roberti Maggiore U. Current and Emerging Therapeutics for the Management of Endometriosis. Drugs. 2018;78(10):995-1012.

[7] Tafi E, Leone Roberti Maggiore U, Alessandri F, et al. Advances in pharmacotherapy for treating endometriosis. Expert Opin Pharmacother. 2015;16(16):2465-83.

[8] Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int. 2012;32(6):1491-502.

[9] Piper P, Vane J. The release of prostaglandins from lung and other tissues. Ann N Y Acad Sci. 1971;180:363-85.

[10] Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med. 1998;104(3A):2S-8S; discussion 21S-22S.

[11] Davies NM, Good RL, Roupe KA, et al. Cyclooxygenase-3: axiom, dogma, anomaly, enigma or splice error?--Not as easy as 1, 2, 3. J Pharm Pharm Sci. 2004;7(2):217-26.

[12] Vane JR. The fight against rheumatism: from willow bark to COX-1 sparing drugs. J Physiol Pharmacol. 2000;51(4 Pt 1):573-86.

[13] Brown J, Crawford TJ, Allen C, et al. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev. 2017;1:CD004753.

* Systematic review on the effects of anti-inflammatory drugs for treating endometriosis-related pain

[14] Kauppila A, Puolakka J, Ylikorkala O. Prostaglandin biosynthesis inhibitors and endometriosis. Prostaglandins. 1979;18(4):655-61.

[15] Kauppila A, Ronnberg L. Naproxen sodium in dysmenorrhea secondary to endometriosis. Obstet Gynecol. 1985;65(3):379-83.

[16] Cobellis L, Razzi S, De Simone S, et al. The treatment with a COX-2 specific inhibitor is effective in the management of pain related to endometriosis. Eur J Obstet Gynecol Reprod Biol. 2004;116(1):100-2.

[17] Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352(11):1092-102.

[18] Tai FWD, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clin Med (Lond). 2021;21(2):131-134.

[19] Bjarnason I, Scarpignato C, Holmgren E, et al. Mechanisms of Damage to the Gastrointestinal Tract From Nonsteroidal Anti-Inflammatory Drugs. Gastroenterology. 2018;154(3):500-514.

[20] Henry D, McGettigan P. Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. Int J Clin Pract Suppl. 2003(135):43-9.

[21] Carson JL, Willett LR. Toxicity of nonsteroidal anti-inflammatory drugs. An overview of the epidemiological evidence. Drugs. 1993;46 Suppl 1:243-8.

[22] Ferrero S. Progesterone and progestin mimics. In: Wexler P, editor. Encyclopedia of Toxicology. Vol. 7. Oxford (UK): Elsevier; 2024. p. 903-909.

* Entensive review on the use of progestins in gynecology

[23] Grandi G, Mueller M, Bersinger NA, et al. Does dienogest influence the inflammatory response of endometriotic cells? A systematic review. Inflamm Res. 2016;65(3):183-92.

[24] Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev. 2012(3):CD002122.

[25] Bizzarri N, Remorgida V, Leone Roberti Maggiore U, et al. Dienogest in the treatment of endometriosis. Expert Opin Pharmacother. 2014;15(13):1889-902.

[26] Ferrero S, Remorgida V, Venturini PL, et al. Endometriosis: the effects of dienogest. BMJ Clin Evid. 2015;2015.

[27] Wu H, Liu JJ, Ye ST, et al. Efficacy and safety of dienogest in the treatment of deep infiltrating endometriosis: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2024;297:40-49.

[28] Muzii L, Di Tucci C, Galati G, et al. The Efficacy of Dienogest in Reducing Disease and Pain Recurrence After Endometriosis Surgery: a Systematic Review and Meta-Analysis. Reprod Sci. 2023;30(11):3135-3143.

[29] Andres MP, Lopes LA, Baracat EC, et al. Dienogest in the treatment of endometriosis: systematic review. Arch Gynecol Obstet. 2015.

[30] Zakhari A, Edwards D, Ryu M, et al. Dienogest and the Risk of Endometriosis Recurrence Following Surgery: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2020;27(7):1503-1510.

[31] Ferrero S, Scala C, Ciccarelli S, et al. Treatment of rectovaginal endometriosis with the etonogestrel-releasing contraceptive implant. Gynecol Endocrinol. 2020;36(6):540-544.

[32] Ambacher K, Secter M, Sanders AP. The use of progestin subdermal implants in the management of endometriosis-related pain symptoms and quality of life: a systematic review. Curr Med Res Opin. 2022;38(3):479-486.

[33] Etrusco A, Barra F, Chiantera V, et al. Current Medical Therapy for Adenomyosis: From Bench to Bedside. Drugs. 2023;83(17):1595-1611.

[34] Chen YJ, Hsu TF, Huang BS, et al. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. Am J Obstet Gynecol. 2017;216(6):582 e1-582 e9.

[35] Carvalho N, Margatho D, Cursino K, et al. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. Fertility and sterility. 2018;110(6):1129-1136.

[36] Gibbons T, Georgiou EX, Cheong YC, et al. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database Syst Rev. 2021;12(12):CD005072.

* Systematic review on the use of the levonorgestrel-releasing intrauterine device for treating endometriosis-related pain

[37] Song SY, Park M, Lee GW, et al. Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2018;231:85-92.

[38] Ferrero S, Camerini G, Ragni N, et al. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. Hum Reprod. 2010;25(1):94-100.

[39] Barra F, Scala C, Maggiore ULR, et al. Long-Term Administration of Dienogest for the Treatment of Pain and Intestinal Symptoms in Patients with Rectosigmoid Endometriosis. J Clin Med. 2020;9(1).

[40] Leone Roberti Maggiore U, Ferrero S, Candiani M, et al. Bladder Endometriosis: A Systematic Review of Pathogenesis, Diagnosis, Treatment, Impact on Fertility, and Risk of Malignant Transformation. Eur Urol. 2017;71(5):790-807.

[41] Ferrero S, Remorgida V, Venturini PL, et al. Norethisterone acetate versus norethisterone acetate combined with letrozole for the treatment of ovarian endometriotic cysts: a patient preference study. Eur J Obstet Gynecol Reprod Biol. 2014;174:117-22.

[42] Ferrero S, Alessandri F, Racca A, et al. Treatment of pain associated with deep endometriosis: alternatives and evidence. Fertility and sterility. 2015;104(4):771-92.

[43] Vercellini P, Pietropaolo G, De Giorgi O, et al. Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate. Fertility and sterility. 2005;84(5):1375-87.

[44] Morotti M, Venturini PL, Biscaldi E, et al. Efficacy and acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis. Eur J Obstet Gynecol Reprod Biol. 2017;213:4-10.

[45] Liu Y, Gong H, Gou J, et al. Dienogest as a Maintenance Treatment for Endometriosis Following Surgery: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;8:652505.

[46] Scala C, Leone Roberti Maggiore U, Remorgida V, et al. Drug safety evaluation of desogestrel. Expert Opin Drug Saf. 2013;12(3):433-44.

[47] Razzi S, Luisi S, Ferretti C, et al. Use of a progestogen only preparation containing desogestrel in the treatment of recurrent pelvic pain after conservative surgery for endometriosis. Eur J Obstet Gynecol Reprod Biol. 2007;135(2):188-90.

[48] Palacios S, Colli E, Regidor PA. Metabolic and laboratory effects of a progestin-only pill containing drospirenone 4 mg in comparison to desogestrel 75 microg: a double-blind, double-dummy, prospective, randomised study. Eur J Contracept Reprod Health Care. 2021;26(6):454-461.

[49] Hubacher D, Lopez L, Steiner MJ, et al. Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: systematic review and evidence-based comparisons. Contraception. 2009;80(2):113-8.

[50] Skeith L, Bates SM. Estrogen, progestin, and beyond: thrombotic risk and contraceptive choices. Hematology Am Soc Hematol Educ Program. 2024;2024(1):644-651.

[51] Mantha S, Karp R, Raghavan V, et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ. 2012;345:e4944.

* Meta-analysis on the impact of progestins on the risk of venous thromboembolism

[52] Lidegaard O, Nielsen LH, Skovlund CW, et al. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. BMJ. 2012;344:e2990.

[53] Tepper NK, Whiteman MK, Marchbanks PA, et al. Progestin-only contraception and thromboembolism: A systematic review. Contraception. 2016;94(6):678-700.

[54] Tepper NK, Dragoman MV, Gaffield ME, et al. Nonoral combined hormonal contraceptives and thromboembolism: a systematic review. Contraception. 2017;95(2):130-139.

[55] Morotti M, Remorgida V, Buccelli E, et al. Comparing treatments for endometriosis-related pain symptoms in patients with migraine without aura. J Comp Eff Res. 2012;1(4):347-57.

[56] Morotti M, Remorgida V, Venturini PL, et al. Progestogen-only contraceptive pill compared with combined oral contraceptive in the treatment of pain symptoms caused by endometriosis in patients with migraine without aura. Eur J Obstet Gynecol Reprod Biol. 2014;179:63-8.

[57] Morotti M, Remorgida V, Venturini PL, et al. Progestin-only contraception compared with extended combined oral contraceptive in women with migraine without aura: a retrospective pilot study. Eur J Obstet Gynecol Reprod Biol. 2014;183:178-82.

[58] Crosignani PG, Testa G, Vegetti W, et al. Ovarian activity during regular oral contraceptive use. Contraception. 1996;54(5):271-3.

[59] Dragoman MV. The combined oral contraceptive pill -- recent developments, risks and benefits. Best Pract Res Clin Obstet Gynaecol. 2014;28(6):825-34.

[60] Leone Roberti Maggiore U, Ferrero S. An overview of early drug development for endometriosis. Expert Opin Investig Drugs. 2016;25(2):227-47.

[61] Vercellini P, Trespidi L, Colombo A, et al. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertility and sterility. 1993;60(1):75-9.

[62] Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol. 1996;175(2):396-401.

[63] Parazzini F, Di Cintio E, Chatenoud L, et al. Estroprogestin vs. gonadotrophin agonists plus estroprogestin in the treatment of endometriosis-related pelvic pain: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Eur J Obstet Gynecol Reprod Biol. 2000;88(1):11-4.

[64] Sesti F, Pietropolli A, Capozzolo T, et al. Hormonal suppression treatment or dietary therapy versus placebo in the control of painful symptoms after conservative surgery for

endometriosis stage III-IV. A randomized comparative trial. Fertility and sterility. 2007;88(6):1541-7.

[65] Harada T, Momoeda M, Taketani Y, et al. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertility and sterility. 2008;90(5):1583-8.

[66] Guzick DS, Huang LS, Broadman BA, et al. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertility and sterility. 2011;95(5):1568-73.

[67] Scala C, Leone Roberti Maggiore U, Barra F, et al. Norethindrone acetate versus extended-cycle oral contraceptive (Seasonique((R))) in the treatment of endometriosis symptoms: A prospective open-label comparative study. Eur J Obstet Gynecol Reprod Biol. 2018;222:89-94.

[68] Cheewadhanaraks S, Choksuchat C, Dhanaworavibul K, et al. Postoperative depot medroxyprogesterone acetate versus continuous oral contraceptive pills in the treatment of endometriosis-associated pain: a randomized comparative trial. Gynecol Obstet Invest. 2012;74(2):151-6.

[69] Harada T, Kosaka S, Elliesen J, et al. Ethinylestradiol 20 mug/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial. Fertility and sterility. 2017;108(5):798-805.

[70] El Taha L, Abu Musa A, Khalifeh D, et al. Efficacy of dienogest vs combined oral contraceptive on pain associated with endometriosis: Randomized clinical trial. Eur J Obstet Gynecol Reprod Biol. 2021;267:205-212.

[71] Mehdizadeh Kashi A, Niakan G, Ebrahimpour M, et al. A randomized, double-blind, placebo-controlled pilot study of the comparative effects of dienogest and the combined oral contraceptive pill in women with endometriosis. Int J Gynaecol Obstet. 2022;156(1):124-132.

[72] Caruso S, Cianci A, Iraci Sareri M, et al. Randomized study on the effectiveness of nomegestrol acetate plus 17beta-estradiol oral contraceptive versus dienogest oral pill in women with suspected endometriosis-associated chronic pelvic pain. BMC Womens Health. 2022;22(1):146.

[73] Vercellini P, Barbara G, Somigliana E, et al. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertility and sterility. 2010;93(7):2150-61.

[74] Leone Roberti Maggiore U, Remorgida V, Scala C, et al. Desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis

infiltrating the rectum: a prospective open-label comparative study. Acta Obstet Gynecol Scand. 2014;93(3):239-47.

[75] Schroll JB, Black AY, Farquhar C, et al. Combined oral contraceptive pill for primary dysmenorrhoea. Cochrane Database Syst Rev. 2023;7(7):CD002120.

[76] Endrikat J, Muller U, Dusterberg B. A twelve-month comparative clinical investigation of two low-dose oral contraceptives containing 20 micrograms ethinylestradiol/75 micrograms gestodene and 30 micrograms ethinylestradiol/75 micrograms gestodene, with respect to efficacy, cycle control, and tolerance. Contraception. 1997;55(3):131-7.

[77] Rosenberg MJ, Meyers A, Roy V. Efficacy, cycle control, and side effects of low- and lower-dose oral contraceptives: a randomized trial of 20 micrograms and 35 micrograms estrogen preparations. Contraception. 1999;60(6):321-9.

[78] Westhoff C, Morroni C, Kerns J, et al. Bleeding patterns after immediate vs. conventional oral contraceptive initiation: a randomized, controlled trial. Fertility and sterility. 2003;79(2):322-9.

[79] Gallo MF, Lopez LM, Grimes DA, et al. Combination contraceptives: effects on weight. Cochrane Database Syst Rev. 2014;2014(1):CD003987.

[80] Davis AR, Castano PM. Oral contraceptives and libido in women. Annu Rev Sex Res. 2004;15:297-320.

[81] Caruso S, Agnello C, Intelisano G, et al. Prospective study on sexual behavior of women using 30 microg ethinylestradiol and 3 mg drospirenone oral contraceptive. Contraception. 2005;72(1):19-23.

[82] de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014;2014(3):CD010813.

** Systematic review on the impact of combined oral contraceptives on the risk of thrombosis

[83] Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev. 2015;2015(8):CD011054.

* Systematic review on the impact of combined oral contraceptives on the risk of myocardial infarction and ischemic stroke

[84] de Souza IS, Laporta GZ, Zangirolami-Raimundo J, et al. Association between the use of oral contraceptives and the occurrence of systemic hypertension: A systematic review with statistical comparison between randomized clinical trial interventions. Eur J Obstet Gynecol Reprod Biol X. 2024;22:100307.

[85] Orsolini LR, Goldberg TBL, Caldeirao TD, et al. Bone impact after two years of low-dose oral contraceptive use during adolescence. PLoS One. 2023;18(6):e0285885.

[86] Warholm L, Petersen KR, Ravn P. Combined oral contraceptives' influence on weight, body composition, height, and bone mineral density in girls younger than 18 years: a systematic review. Eur J Contracept Reprod Health Care. 2012;17(4):245-53.

[87] Della Corte L, Barra F, Mercorio A, et al. Tolerability considerations for gonadotropin-releasing hormone analogues for endometriosis. Expert Opin Drug Metab Toxicol. 2020;16(9):759-768.

* Review on the safety of gonadotropin-releating hormone analogues for the treatment of endometriosis

[88] Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev. 2010(12):CD008475.

[89] Fedele L, Bianchi S, Bocciolone L, et al. Buserelin acetate in the treatment of pelvic pain associated with minimal and mild endometriosis: a controlled study. Fertility and sterility. 1993;59(3):516-21.

[90] Bergqvist A, Bergh T, Hogstrom L, et al. Effects of triptorelin versus placebo on the symptoms of endometriosis. Fertility and sterility. 1998;69(4):702-8.

[91] Dlugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. Lupron Study Group. Fertility and sterility. 1990;54(3):419-27.

[92] Miller JD. Leuprolide acetate for the treatment of endometriosis. Prog Clin Biol Res. 1990;323:337-41.

[93] Miller JD. Quantification of endometriosis-associated pain and quality of life during the stimulatory phase of gonadotropin-releasing hormone agonist therapy: a double-blind, randomized, placebo-controlled trial. Am J Obstet Gynecol. 2000;182(6):1483-8.

[94] Crosignani PG, Luciano A, Ray A, et al. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod. 2006;21(1):248-56.

[95] Schlaff WD, Carson SA, Luciano A, et al. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertility and sterility. 2006;85(2):314-25.

[96] Harada T, Momoeda M, Taketani Y, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis--a randomized, double-blind, multicenter, controlled trial. Fertility and sterility. 2009;91(3):675-81.

[97] Strowitzki T, Marr J, Gerlinger C, et al. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. Hum Reprod. 2010;25(3):633-41.

[98] Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod. 2005;20(7):1993-8.

[99] Ferreira RA, Vieira CS, Rosa ESJC, et al. Effects of the levonorgestrel-releasing intrauterine system on cardiovascular risk markers in patients with endometriosis: a comparative study with the GnRH analogue. Contraception. 2010;81(2):117-22.

[100] Bayoglu Tekin Y, Dilbaz B, Altinbas SK, et al. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertility and sterility. 2011;95(2):492-6.

[101] Soysal S, Soysal ME, Ozer S, et al. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod. 2004;19(1):160-7.

[102] Hornstein MD, Yuzpe AA, Burry KA, et al. Prospective randomized double-blind trial of 3 versus 6 months of nafarelin therapy for endometriosis associated pelvic pain. Fertility and sterility. 1995;63(5):955-62.

[103] Kumar P, Sharma A. Gonadotropin-releasing hormone analogs: Understanding advantages and limitations. J Hum Reprod Sci. 2014;7(3):170-4.

[104] Geukes M, van Aalst MP, Nauta MC, et al. The impact of menopausal symptoms on work ability. Menopause. 2012;19(3):278-82.

[105] Revilla R, Revilla M, Hernandez ER, et al. Evidence that the loss of bone mass induced by GnRH agonists is not totally recovered. Maturitas. 1995;22(2):145-50.

[106] Berlanda N, Somigliana E, Vigano P, et al. Safety of medical treatments for endometriosis. Expert Opin Drug Saf. 2016;15(1):21-30.

[107] Gallagher JS, Missmer SA, Hornstein MD, et al. Long-Term Effects of Gonadotropin-Releasing Hormone Agonists and Add-Back in Adolescent Endometriosis. J Pediatr Adolesc Gynecol. 2018;31(4):376-381.

[108] Sagsveen M, Farmer JE, Prentice A, et al. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Cochrane Database Syst Rev. 2003;2003(4):CD001297.

[109] Fogelman I. Gonadotropin-releasing hormone agonists and the skeleton. Fertility and sterility. 1992;57(4):715-24.

[110] Hornstein MD, Surrey ES, Weisberg GW, et al. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Lupron Add-Back Study Group. Obstet Gynecol. 1998;91(1):16-24.

[111] Pierce SJ, Gazvani MR, Farquharson RG. Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. Fertility and sterility. 2000;74(5):964-8.

[112] Al-Omari WR, Nassir UN, Izzat B. Estrogen 'add-back' and lipid profile during GnRH agonist (triptorelin) therapy. Int J Gynaecol Obstet. 2001;74(1):61-2.

[113] Abu Hashim H. Gonadotrophin-releasing hormone analogues and endometriosis: current strategies and new insights. Gynecol Endocrinol. 2012;28(4):314-21.

[114] Barra F, Scala C, Ferrero S. Elagolix sodium for the treatment of women with moderate to severe endometriosis-associated pain. Drugs Today (Barc). 2019;55(4):237-246.

[115] Taylor HS, Giudice LC, Lessey BA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med. 2017;377(1):28-40.

** Randomized controlled trial investigating the use of elagolix in the treatment of endometriosis

[116] Surrey E, Taylor HS, Giudice L, et al. Long-Term Outcomes of Elagolix in Women With Endometriosis: Results From Two Extension Studies. Obstet Gynecol. 2018;132(1):147-160.

[117] Miller CE, Kim JH, Kroll R, et al. Efficacy, tolerability, and bone density outcomes of elagolix with add-back therapy for endometriosis-associated pain: twelve months of an ongoing randomized phase 3 trial. Am J Obstet Gynecol. 2024;231(6):630 e1-630 e13.

[118] Giudice LC, As-Sanie S, Arjona Ferreira JC, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2). Lancet. 2022;399(10343):2267-2279.

** Randomized controlled trial investigating the use of relugolix in the treatment of endometriosis

[119] Becker CM, Johnson NP, As-Sanie S, et al. Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study. Hum Reprod. 2024;39(3):526-537.

[120] Dababou S, Garzon S, Lagana AS, et al. Linzagolix: a new GnRH-antagonist under investigation for the treatment of endometriosis and uterine myomas. Expert Opin Investig Drugs. 2021;30(9):903-911.

[121] Donnez J, Taylor HS, Taylor RN, et al. Treatment of endometriosis-associated pain with linzagolix, an oral gonadotropin-releasing hormone-antagonist: a randomized clinical trial. Fertility and sterility. 2020;114(1):44-55.

[122] Donnez J, Becker C, Taylor H, et al. Linzagolix therapy versus a placebo in patients with endometriosis-associated pain: a prospective, randomized, double-blind, Phase 3 study (EDELWEISS 3). Hum Reprod. 2024;39(6):1208-1221.

** Randomized controlled trial investigating the use of linzagolix in the treatment of endometriosis

[123] Barra F, Scala C, Ferrero S. Current understanding on pharmacokinetics, clinical efficacy and safety of progestins for treating pain associated to endometriosis. Expert Opin Drug Metab Toxicol. 2018;14(4):399-415.

[124] Strowitzki T, Faustmann T, Gerlinger C, et al. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. Int J Womens Health. 2015;7:393-401.

[125] Guerriero S, Condous G, Van den Bosch T, et al. Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol. 2016.

Tables

Table 1. Adverse effects of progestins used in the treatment of endometriosis

Progestin therapy	Most frequently reported side effects	Notes on tolerability
Medroxyprogesterone acetate	Weight gain, edema, spotting/amenorrhea, acne, mood changes, decreased libido	Long-acting formulation; higher rates of amenorrhea and fluid retention
Dienogest	Irregular bleeding (especially in early treatment), headaches, weight changes, mood alterations	Generally well tolerated; maintains stable estradiol levels
Norethindrone acetate	Weight gain, acne, breast tenderness, libido reduction, lipid profile changes	Common in continuous low-dose regimens
Desogestrel	Breakthrough bleeding, acne, ovarian cysts	Often used as progestin-only pill; fewer systemic effects
Levonorgestrel-intrauterine device	Irregular bleeding, acne, pelvic discomfort, ovarian cyst formation, mood changes	High local (endometrial) progestin activity with minimal systemic exposure
Etonogestrel implant	Bleeding disturbances, weight gain, decreased libido, headaches	Suitable for long-term contraception and symptom control

Table 2. Adverse effects of COCs used in the treatment of endometriosis

Formulation	Typical adverse effects	Additional considerations
Oral combined contraceptives	Nausea, headache, breakthrough bleeding, breast tenderness, mood changes	Side effects often resolve with continued use or formulation change
Vaginal ring	Headache, vaginal irritation, breast pain, nausea	Cyclic estrogen-progestin release; lower systemic estrogen peaks
Transdermal patch	Skin irritation, breast discomfort, mood alterations, irregular bleeding	Delivers hormones through the skin; avoids first-pass metabolism

Table 3. Impact of GnRH antagonist on mineral bone density and hot flushes

		SPIRIT I-II			**ELARIS-EM I-II**			**EDELWEISS III**		
	Trial	Placebo	RLX / ABT	Delayed RLX	Placebo	ELX 150 mg 1/days	ELX 200 mg 2/days	Placebo	LGX 75 mg	LGX 200 mg/ABT
BMD (% change from baseline in lumbar spine)	I	0.20	-0.70	-1.99	NA	NA	NA	0.77	-0.87	-0.804
	II	0.02	-0.78	-1,92	NA	NA	NA	0.77	-0.87	-0.804
Hot flushes (%)	I	10	10	34	7	23.7	42.3	2.5	7.5	6.8
	II	3	14	35	10.3	22.6	47.6			

NA: not available; ABT: add-back therapy; BMD: bone mineral density; RLX: relugolix; ELX: elagoix

Legend to Figures

Figure 1. Microscopic image of a rectosigmoid endometriotic nodule (hematoxylin and eosin staining)

Figure 2. Retrocervical endometriotic lesions

Figure 3. Endometriotic cyst of the left ovary

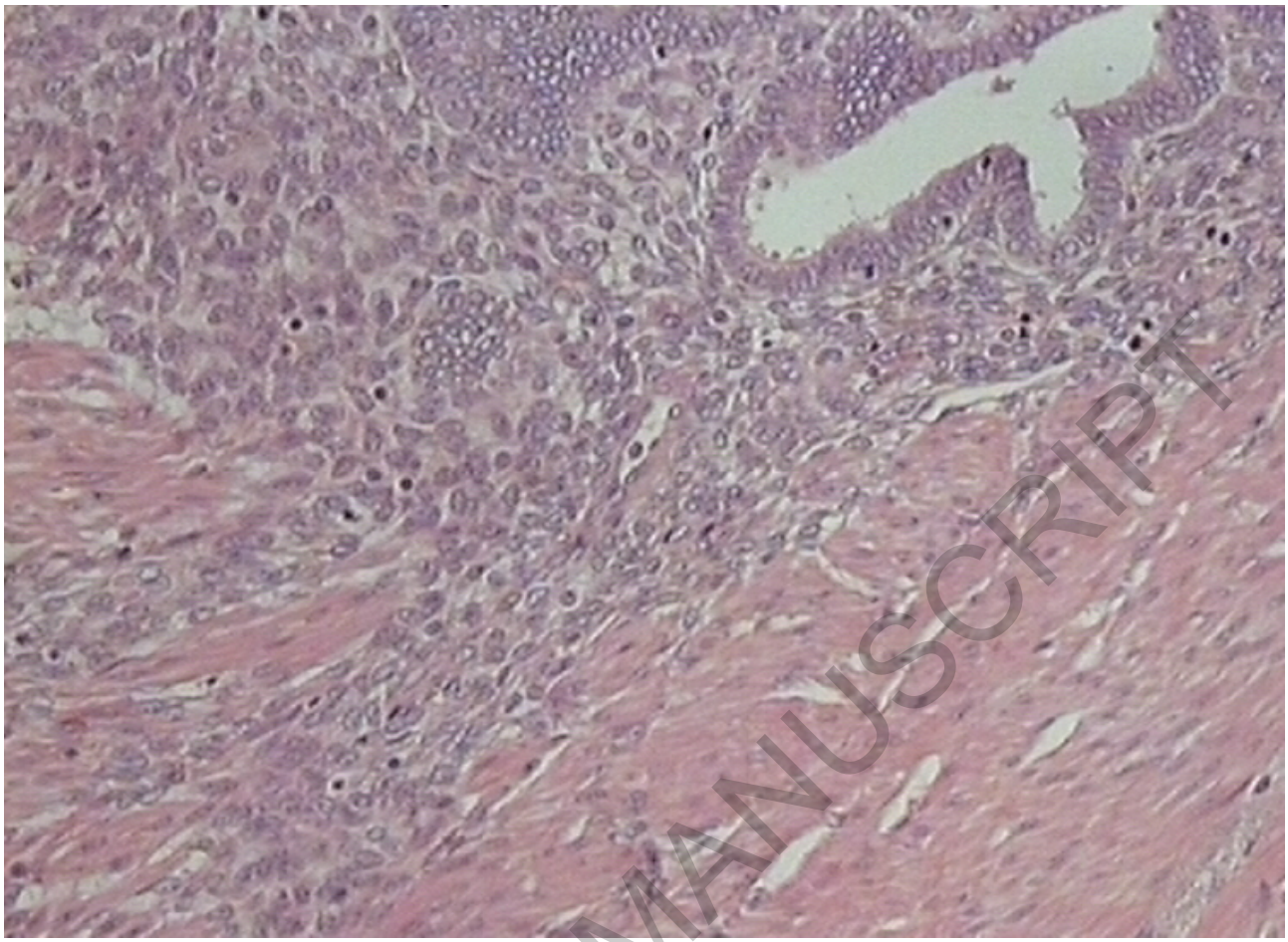

Fig 1

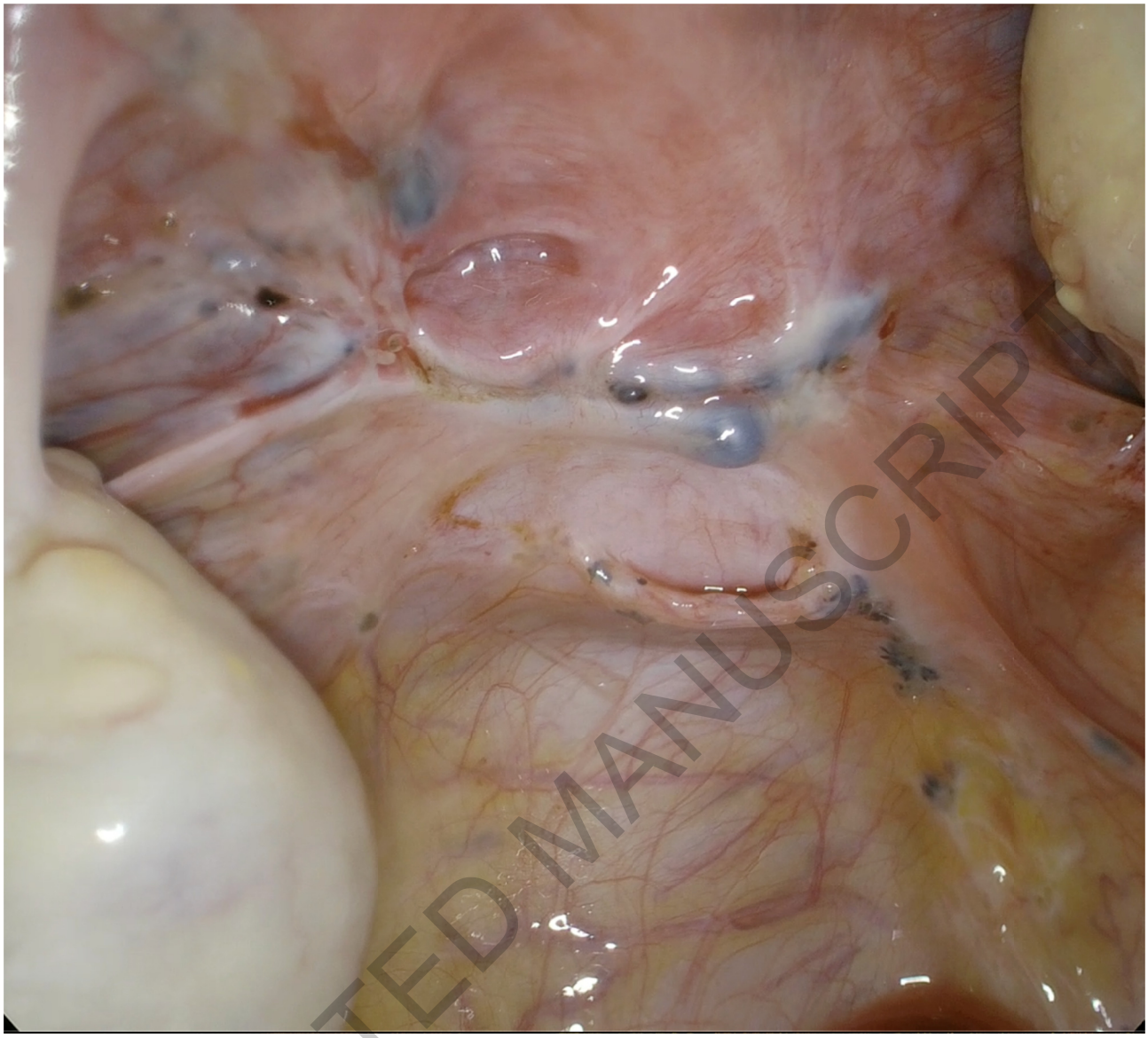

Fig 2

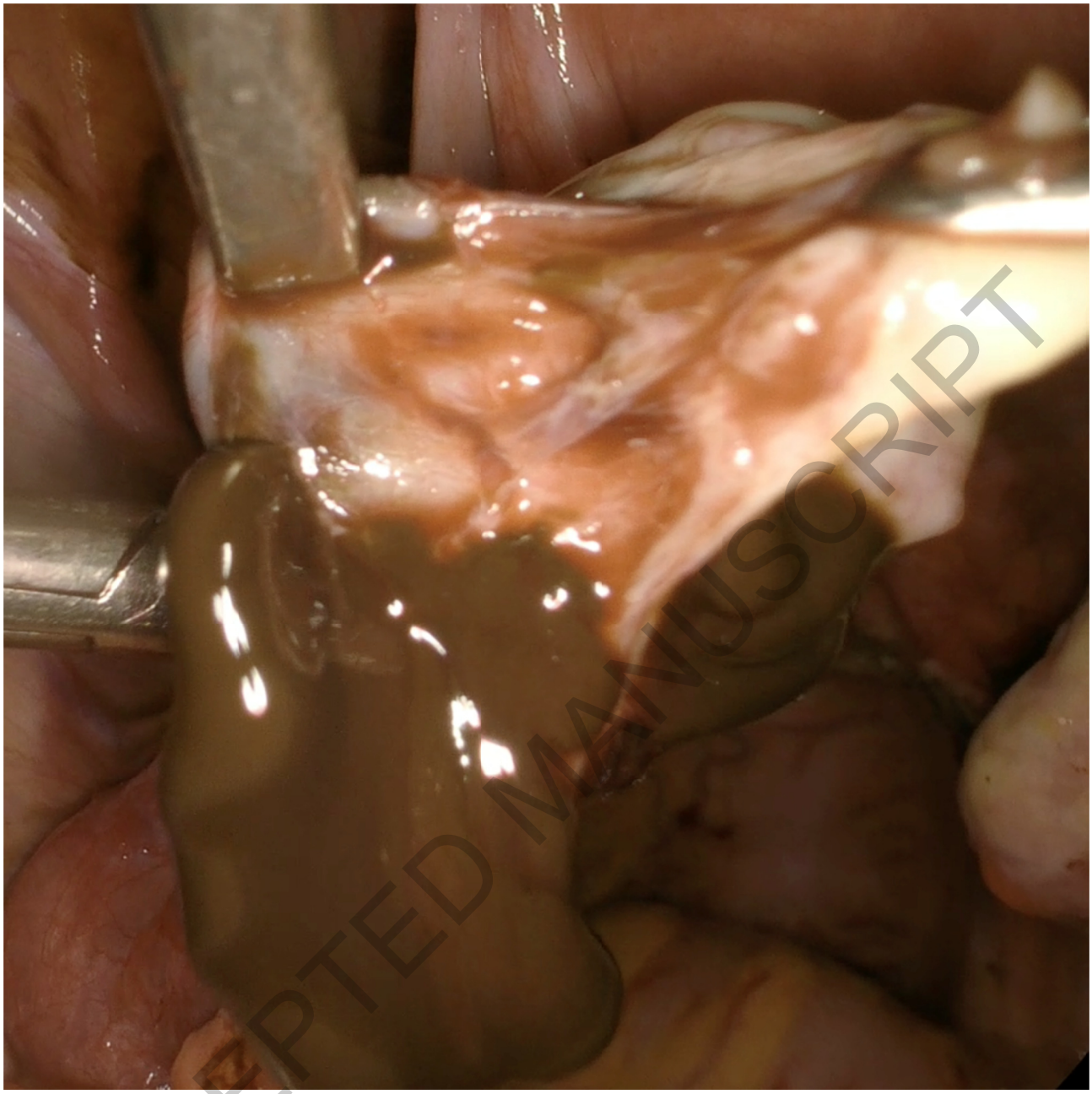

Fig 3