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+15878858911
editorial-office@sciformat.ca

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THERAPEUTIC OPTIONS IN ENDOMETRIOSIS: A COMPARATIVE LITERATURE REVIEW OF INTRAUTERINE DEVICE THERAPY, SURGICAL TREATMENT, RELUGOLIX COMBINATION THERAPY, AND DIENOGEST

Katarzyna Ścibisz *(Corresponding Author, Email: katarzynascibisz5@gmail.com)*
1st Military Clinical Hospital with Outpatient Clinic, SPZOZ, Lublin, Poland
ORCID ID: 0009-0003-0491-8783

Karolina Ollik
10th Military Clinical Hospital with Outpatient Clinic, SPZOZ, Bydgoszcz, Poland
ORCID ID: 0009-0001-9577-9648

Kamil Harenza
Mikołaj Pirogow Provincial Specialist Hospital, Łódź, Poland
ORCID ID: 0009-0003-6200-4672

Mateusz Taranowicz
118th Military Hospital with Outpatient Clinic, SPZOZ, Ełk, Poland
ORCID ID: 0009-0008-2233-055X

Olga Kowalczyk
Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz, Łódź, Poland
ORCID ID: 0009-0007-4606-7736

Dominika Zdobylak
4th Military Clinical Hospital with Outpatient Clinic, SPZOZ, Wrocław, Poland
ORCID ID: 0009-0009-5702-7136

Monika Kowalska
4th Military Clinical Hospital with Outpatient Clinic, SPZOZ, Wrocław, Poland
ORCID ID: 0009-0008-1930-6460

Anita Zięba
1st Military Clinical Hospital with Outpatient Clinic, SPZOZ, Lublin, Poland
ORCID ID: 0009-0007-9075-6555

Michał Domin
Stefan Cardinal Wyszyński Voivodeship Specialist Hospital, Lublin, Poland
ORCID ID: 0009-0008-9081-8485

Justyna Całka
107th Military Hospital with Outpatient Clinic, SPZOZ, Wałcz, Poland
ORCID ID: 0009-0006-9378-6920

ABSTRACT

Endometriosis is a chronic, estrogen-dependent disease affecting women of reproductive age, associated with chronic pelvic pain, impaired fertility, and significant impairment of quality of life. The heterogeneous clinical presentation, variable disease severity, and high recurrence rates make therapeutic decision-making particularly challenging. This review summarizes and critically compares current evidence regarding four commonly used treatment modalities: the levonorgestrel-releasing intrauterine system (LNG-IUS), relugolix combination therapy, surgical intervention, and dienogest. The analysis focuses on their effectiveness in symptom reduction, safety profile, and suitability for long-term management.

A review of randomized controlled trials and meta-analyses demonstrates that all reviewed modalities provide meaningful pain relief, though clinical applicability differs substantially. Surgical treatment, particularly laparoscopic excision, offers rapid symptom improvement, especially in deep infiltrating endometriosis, but is limited by invasiveness and recurrence risk. Dienogest and levonorgestrel-releasing intrauterine system represent minimally invasive hormonal options with sustained analgesic efficacy and favorable safety profiles, making them valuable for long-term disease control and postoperative maintenance. Relugolix combination therapy has emerged as a potent oral treatment for severe symptoms with acceptable long-term safety when combined with add-back therapy, although cost and monitoring requirements may limit its use.

No single therapeutic approach can be universally recommended for all patients. Optimal management requires an individualized strategy that balances efficacy, safety, and long-term tolerability. Minimally invasive hormonal therapies offer the most favorable balance for long-term management, while surgery and relugolix therapy remain essential options for selected or refractory cases.

KEYWORDS

Endometriosis, Chronic Pelvic Pain, Hormonal Treatment, Levonorgestrel-Releasing Intrauterine System, Relugolix, Dienogest

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Introduction

Endometriosis is a chronic, estrogen-dependent disease affecting women of reproductive age and is characterized by the presence of endometrial-like tissue outside the uterine cavity. Ectopic lesions respond to cyclical hormonal changes, leading to chronic inflammation, severe pelvic pain, and abnormal uterine bleeding (Giudice et al., 2022; Duffy et al., 2014; Andres et al., 2015). Symptoms often improve after menopause as estrogen levels decline. It is estimated that approximately 5-15% of women of reproductive age are affected by endometriosis (Andres et al., 2015).

Three main forms of the disease are distinguished: superficial peritoneal endometriosis, ovarian endometriosis, and deep infiltrating endometriosis (DIE). Endometrial tissue located within the myometrium is defined as adenomyosis, a condition associated with chronic inflammation, hypertrophy, and fibrosis of the uterine muscle, resulting in uterine enlargement and altered uterine morphology (da Costa Porto et al., 2024; Othman et al., 2024). Endometriotic lesions may also involve the ovaries, fallopian tubes, uterosacral ligaments, pouch of Douglas, peritoneum, gastrointestinal and urinary tracts, as well as distant and atypical locations.

Despite increasing awareness and advances in imaging techniques, the diagnosis of endometriosis is frequently delayed, with an average diagnostic delay ranging from 7 to 12 years after symptom onset (Duffy et al., 2014; Arcoverde et al., 2019). This delay is largely due to the heterogeneity of clinical manifestations and challenges in the interpretation of imaging findings. Disease severity is most commonly assessed using the revised American Society for Reproductive Medicine (ASRM) classification, which grades endometriosis based on lesion type, size, number, depth of infiltration, and the presence of adhesions. Importantly, symptom

severity often does not correlate with the extent of disease according to ASRM staging (Duffy et al., 2014; Tiringer et al., 2022).

Endometriosis presents with a wide spectrum of symptoms, including heavy and prolonged menstrual bleeding, dysmenorrhea, chronic pelvic pain, dyspareunia, dyschezia, painful urination and gastrointestinal disturbances (da Costa Porto et al., 2024; Giudice et al., 2022; Fritzer et al., 2016). Chronic pain is a hallmark of the disease and is frequently disproportionate to the anatomical extent of lesions (Cocks et al., 2025; Becker et al., 2024). Additionally, endometriosis significantly impairs fertility through multiple mechanisms, including pelvic inflammation, adhesions, altered uterine contractility, and disruption of ovarian folliculogenesis (Duffy et al., 2014; Takaesu et al., 2016). In many women, the diagnosis is established only during infertility evaluation. Furthermore, endometriosis has been associated with an increased risk of autoimmune diseases and certain malignancies, including clear cell and endometrioid ovarian cancer, non-Hodgkin lymphoma, and melanoma.

Management of endometriosis requires a multidisciplinary approach involving gynecologists, surgeons, psychologists, physiotherapists, and dietitians. Diagnostic evaluation is based on clinical history, gynecological examination, transvaginal ultrasound, and magnetic resonance imaging (Duffy et al., 2014; Arcoverde et al., 2019). Therapeutic strategies include medical treatment, surgical intervention, and combined approaches. Pharmacological therapy aims to suppress estrogen activity, reduce inflammation, and alleviate pain, while surgical treatment—preferably performed using minimally invasive laparoscopic or robotic techniques—is reserved for selected cases, particularly those with deep infiltrating disease or refractory symptoms (Takaesu et al., 2016).

Given the chronic nature of endometriosis, its impact on quality of life, and the high risk of symptom recurrence, selecting the most effective, safe, and least invasive treatment strategy remains a major clinical challenge (Tiringer et al., 2022; Wenzl et al., 2024; Römer T et al., 2019). This review focuses on currently available therapeutic options, including the levonorgestrel-releasing intrauterine system, relugolix combination therapy, surgical treatment, and dienogest, with the aim of comparing their effectiveness, safety, and clinical applicability in the management of endometriosis.

Aim

The objective of this review is to summarize current evidence regarding four therapeutic modalities used in the management of endometriosis: the levonorgestrel-releasing intrauterine system (LNG-IUS), relugolix combination therapy, surgical intervention, and dienogest. Additionally, this review aims to compare these treatment options in terms of their effectiveness in symptom reduction, safety profile, and degree of invasiveness, in order to identify the most clinically beneficial approach for patients with endometriosis.

Materials and Methods

The present narrative review was designed as a comparative literature review focusing on current evidence-based therapeutic strategies for endometriosis. The primary objective was to summarize and critically evaluate the clinical efficacy, safety profiles, and long-term applicability of four specific treatment modalities: the levonorgestrel-releasing intrauterine system (LNG-IUS), relugolix combination therapy, surgical intervention, and dienogest. A comprehensive search of electronic medical databases, including PubMed and the Cochrane Library, was conducted to identify relevant scientific publications. Eligible evidence comprised randomized controlled trials, prospective and retrospective cohort studies, systematic reviews, and meta-analyses. The review prioritized high-quality evidence published in peer-reviewed journals, with a particular emphasis on the most recent clinical findings to ensure a valid synthesis of current therapeutic standards.

Intrauterine Device (LNG-IUS)

According to da Costa Porto et al. (2024) who conducted a study on forty women with deep infiltrating endometriosis (DIE), the levonorgestrel-releasing intrauterine system (LNG-IUS) can significantly enhance the quality of life for patients with this condition. The study participants, who had no history of prior surgical intervention, were assessed using clinical interviews, physical examinations, transvaginal ultrasound, and pelvic magnetic resonance imaging (MRI). Following a three-month washout period from hormonal therapy, the subjects were randomized into two groups to receive either dienogest (DNG) or LNG-IUS for a six-month duration. Data from this 2024 randomized clinical trial indicate that the LNG-IUS group experienced substantial improvements across the majority of quality-of-life domains, as measured by the SF-36 and EHP-

30 questionnaires. Notably, the therapeutic effect of the LNG-IUS was found to be comparable to that of the dienogest-treated group.

Another study by Gibbons et al. (2021) focusing on the treatment of symptomatic endometriosis with the LNG-IUS after uterine-sparing surgery, highlights that a significant proportion of women require adjuvant pharmacological therapy after surgery to reduce the risk of symptom recurrence. Although the current quality of evidence for the LNG-IUS remains low to moderate, systematic reviews suggest that this device can effectively reduce the rate of postoperative pain recurrence. The analysis showed that postoperative LNG-IUS insertion was associated with a significantly lower risk of dysmenorrhea recurrence compared with control groups receiving expectant management, placebo, or other medical interventions such as gonadotropin-releasing hormone (GnRH-α) agonists.

In a subsequent study by Lan et al. (2013) the efficacy, safety, and clinical benefits of the levonorgestrel-releasing hormone intrauterine system (LNG-IUS) were compared with those of gonadotropin-releasing hormone agonists (GnRH-α) in premenopausal women with endometriosis. The results indicate that although the LNG-IUS demonstrated comparable efficacy to GnRH-α in pain reduction, the IUS offered superior clinical benefits, including improved psychological indicators and overall well-being. Furthermore, a significant reduction in LDL cholesterol levels was observed in the LNG-IUS group. However, the authors noted that these results require further validation through additional studies with larger patient groups.

Long-term clinical observations confirm that the LNG-IUS, used as postoperative maintenance therapy, is effective in the treatment of chronic pain for periods exceeding five years. A retrospective study by Kim et al. (2022) assessed the long-term (>5 years) effectiveness of the LNG-IUS as a postoperative conservative strategy. A total of 263 patients were included in the study (94 in the study group and 169 in the control group). The study group received the LNG-IUS, while the control group received combined oral contraceptives (20 μg ethinyl estradiol and 3 mg drospirenone) or 2 mg dienogest. The results showed that the LNG-IUS led to a statistically significant reduction in the severity of dysmenorrhea, dyspareunia, and chronic noncyclical pelvic and sacral pain. Long-term analysis confirmed the durability of this therapeutic effect, with significant relief observed within the first year of insertion and maintained for 10 years. The analgesic efficacy of the LNG-IUS was found to be superior to that of both oral contraceptives and selective progestogens (dienogest). The primary advantage of the intrauterine system compared to oral regimens was its adverse event profile. Patients in the LNG-IUS group reported significantly lower rates of systemic adverse events, such as mood swings and gastrointestinal disturbances (nausea), due to the system's local mechanism of action and minimal systemic progestogen concentrations. Therefore, long-term use of the LNG-IUS (>5 years) represents a highly effective postoperative management strategy. Due to its high efficacy in pain control and optimized safety profile, it is an ideal treatment option for patients requiring long-term symptom suppression who do not plan to conceive immediately.

Wang et al. (2022) compared LNG-IUS with systemic medical therapy or placebo in the treatment of dysmenorrhea, including women with adenomyosis. Among 6,551 patients, LNG-IUS use was associated with significantly greater reductions in pain intensity measured by the Visual Analogue Scale (VAS), improved control of menstrual blood loss, and fewer adverse effects compared with systemic treatment. However, the authors note limitations related to study heterogeneity and emphasize the need for further high-quality trials.

A study by Xu et al. (2011) examined the efficacy of the LNG-IUS in the treatment of recurrent endometriosis after conservative surgery or conservative surgery combined with medical therapy in twenty-three patients. The study showed that chronic pelvic pain, painful intercourse, and dysmenorrhea were significantly reduced 12 months after insertion. Importantly, after six months of use, the volume of recurrent ovarian endometriomas decreased significantly in 11 patients, and after 24 months, cysts completely disappeared in nine patients. Serum CA125 levels decreased over the first six months and stabilized by month 12. The main reported side effects were spotting and irregular bleeding, as well as observed weight gain.

Another study by Cocks et al. (2025) was conducted over an 18-month period. Researchers recruited 72 patients referred for various pelvic pain symptoms, including painful periods and chronic non-cyclical pain. Participants were treated with a 52 mg levonorgestrel intrauterine device (LNG-IUS). To assess the long-term effectiveness of the treatment, 51 participants completed follow-up assessments between 6 and 18 months after insertion. The study identified menstrual suppression (time since last menstrual period) as a key factor in pain reduction. As the duration of amenorrhea increased, patients reported linear improvements in both painful periods and overall satisfaction with symptom control. Clinical outcomes were not influenced by whether a patient had a confirmed diagnosis of endometriosis or had undergone prior laparoscopy. This suggests that the LNG-IUS is equally effective in women with "unexplained" pelvic pain as it is in women with confirmed

endometriosis. The LNG-IUS should be considered a sound medical intervention; it represents a viable alternative to diagnostic surgery, providing significant relief from a wide range of persistent pelvic pain (PPP) symptoms, regardless of the underlying pathology.

Another study by Fenghua et al. (2022) included 80 patients diagnosed with endometriosis between March 2019 and March 2020. Participants were divided into two equal groups of 40. The control group received GnRH agonist (GnRH-a) treatment alone. The observation group received the combination of the Mirena intrauterine device (LNG-IUS) and GnRH-a. The researchers compared the two groups in terms of clinical efficacy, sex hormone levels (E2, FSH, LH), CA125 markers, pain intensity (VAS), and recurrence rate. The study concluded that combination therapy (Mirena plus GnRH-a) was significantly more effective than GnRH-a alone, achieving an overall success rate of 92.50% compared to 75.00%. Although both treatments alleviated symptoms, the combined approach resulted in significantly lower Visual Analogue Scale (VAS) scores for both dysmenorrhea and dyspareunia (painful intercourse). Patients using Mirena with GnRH-a experienced greater reductions in serum CA125, E2, FSH, and LH levels, suggesting better regulation of the factors driving endometriosis progression. One of the most important findings was a dramatic reduction in the recurrence rate, which fell from 20.00% in the monotherapy group to just 5.00% in the combined group. The study demonstrated that combining Mirena with GnRH-a treatment is a sound clinical strategy. It not only improves ovarian function and pain relief but also provides stronger protection against recurrence.

Relugolix combination therapy (Relugolix, estradiol and norethisterone acetate)

Giudice et al. (2022) provided a comprehensive analysis of the SPIRIT 1 (n=638) and SPIRIT 2 (n=623) pivotal trials. In these studies, participants were randomized to receive 24 weeks of relugolix combination therapy (Relugolix CT), placebo, or a delayed relugolix CT regimen. Relugolix is a potent, oral gonadotropin-releasing hormone (GnRH) receptor antagonist co-administered with estradiol and a progestogen as add-back therapy to mitigate hypoestrogenic effects.The results indicated that patients treated with relugolix CT exhibited a significant reduction in opioid consumption compared to the placebo group. Furthermore, a substantial decrease in endometriosis-associated pain was observed among those receiving the combination therapy. This regimen demonstrates a promising potential to reduce overall reliance on analgesics. Regarding bone health, Bone Mineral Density (BMD) changes in the lumbar spine were minimal and showed only slight reductions compared to the placebo cohort. The reported adverse events included headaches, nasopharyngitis, and vasomotor symptoms (hot flashes). The clinical benefits of this pharmacological intervention include significant pain alleviation, a strong potential for limiting the use of rescue pain medications, and a possible reduction in the necessity for repeat surgical interventions.The SPIRIT 1 and 2 phase 3 clinical trials evaluated the efficacy of a once-daily combination therapy (relugolix 40 mg, estradiol 1 mg, and norethisterone acetate 0.5 mg) in premenopausal women aged 18–50 years. These randomized, double-blind, placebo-controlled studies demonstrated that relugolix CT significantly reduced moderate-to-severe endometriosis-associated pain, including dysmenorrhea, non-menstrual pelvic pain (NMPP), and dyspareunia. Furthermore, the treatment exhibited a favorable safety profile, with bone mineral density (BMD) reductions of less than 1% relative to placebo over a 24-week period.

Building on the pivotal SPIRIT trials, Becker et al. (2024) conducted a long-term extension study involving participants who completed the initial 24-week SPIRIT 1 and SPIRIT 2 programs. This investigation extended treatment for an additional 80 weeks, providing a total of 104 weeks of relugolix combination therapy (Relugolix CT) to evaluate sustained efficacy and the long-term safety profile in women with endometriosis-associated pain. The findings demonstrated substantial and durable improvements in dysmenorrhea, non-menstrual pelvic pain (NMPP), and dyspareunia throughout the extended treatment period.The SPIRIT 3 extension study confirms the long-term durability of relugolix CT, with over 80% of responders maintaining relief from dysmenorrhea at 104 weeks. The treatment significantly diminished the need for pharmacological pain management, as 75 % of the participants were analgesic-free by the end of the study. Critically, the skeletal safety profile was reassuring: the minor bone mineral density loss noted in the first 24 weeks (< 1%) did not continue, instead reaching a plateau at week 36 that persisted through year two. These findings suggest that the efficacy and safety observed in the initial 24-week trials are representative of long-term clinical use.

Further evidence provided by As-Sanie et al. (2024) explores the efficacy of relugolix combination therapy in improving health-related quality of life (QoL) and physical functioning for patients suffering from symptomatic endometriosis.The SPIRIT long-term extension study evaluated the two-year impact of treatment on patient functioning and health-related quality of life (QoL) via the EHP-30 questionnaire (Endometriosis Health Profile). Additionally, the analysis examined the correlation between improvements in specific QoL

domains and reductions in both dysmenorrhea and non-menstrual pelvic pain (NMPP). This work proved that the analgesic effect translates into real life activity and not only on the pain scale.

Research performed by Osuga et al. (2021) evaluated the efficacy and safety of three different dosages of relugolix were investigated in comparison to both placebo and leuprorelin among women experiencing endometriosis-associated pain. In this 12-week intervention, participants were assigned to receive one of the following regimens: daily oral relugolix at doses of 10 mg, 20 mg, or 40 mg, a daily oral placebo, or a monthly subcutaneous injection of leuprorelin 3.75 mg. Analysis of Visual Analogue Scale (VAS) scores for pelvic pain revealed that the efficacy of 40 mg relugolix was comparable to that of leuprorelin. The primary adverse events associated with relugolix treatment included vasomotor symptoms such as hot flashes, along with metrorrhagia, menorrhagia, and other menstrual irregularities. Furthermore, a dose-dependent reduction in bone mineral density (BMD) was noted; the rate of BMD decline in the 40 mg relugolix cohort was similar to that observed in the leuprorelin group. In conclusion, oral relugolix provides dose-dependent relief of endometriosis-associated pain with a safety and efficacy profile commensurate with leuprorelin.

Another study by Xin et al. (2023) assessed the efficacy and safety of oral gonadotropin-releasing hormone (GnRH) antagonists in the treatment of moderate to severe pain associated with endometriosis. The results highlighted that relugolix 40 mg demonstrated superior efficacy among the evaluated interventions in reducing analgesic use. However, the study also noted a high incidence of relugolix-related adverse events, particularly vasomotor symptoms (hot flashes) and headaches.

Othmann et al. (2024) addressed the fact that current pharmacological interventions for the treatment of endometriosis-related pain remain inadequate. There is limited evidence supporting the efficacy of nonsteroidal anti-inflammatory drugs, and approximately one-third of patients are resistant to progestogens or oral contraceptives. Although GnRH agonists are effective, their long-term usefulness is limited by significant side effects. Oral GnRH antagonists—specifically elagolix, relugolix, and linzagolix—offer dose-dependent suppression of estradiol secretion without the initial flare of symptoms typical of agonists and enable rapid recovery of ovarian function after drug discontinuation. Clinical data indicate that relugolix (40 mg/day) provides pain relief comparable to GnRH agonists. Furthermore, the addition of adjunctive therapy (1 mg estradiol and 0.5 mg norethindrone) to the relugolix regimen allows for treatment duration to be extended up to 24 weeks, mitigating side effects while maintaining therapeutic efficacy.

According to Quishpe et al. (2025), both relugolix and elagolix—used as monotherapy or in combination with adjuvant hormonal therapy—are highly effective in relieving endometriosis-related pain, improving patients' quality of life and reducing the need for pain medications. Although both medications are effective, data support the superiority of relugolix in combination therapy for long-term treatment. This approach not only provides clinical efficacy and improved quality of life but also optimizes the safety profile by protecting bone health and reducing other hypoestrogenic symptoms, making it the preferred option for extended treatment durations.

As highlighted by Carballo et al. (2025) the approval of relugolix for endometriosis necessitates a thorough understanding of its metabolic profile, particularly regarding BMD loss and osteoporotic risk. Consequently, their research sought to quantify the impact of daily relugolix on bone health, assessing whether the integration of combination therapy mitigates the adverse effects observed with monotherapy. Relugolix monotherapy has been linked to substantial BMD loss resulting from its marked estrogen-suppressing effect. To counteract this, a regimen combining estradiol and norethisterone acetate was introduced. Although starting with monotherapy before switching to combination therapy leads to temporary BMD reduction, clinical trials have shown that relugolix combination therapy preserves BMD over two years while effectively alleviating endometriosis- and UF-related symptoms. Relugolix combination therapy is a potent and well-tolerated treatment for UFs and endometriosis, limiting the risk of hypoestrogenism-related bone loss while sustaining clinical benefits. Although monotherapy may induce transient BMD reduction, combination therapy appears to steady bone health.

A large-scale study by Yan et al. (2022) including a large cohort of 2796 women, assessed the efficacy and safety of ten different oral doses of GnRH antagonists. The researchers identified a clear dose-response relationship with regard to therapeutic outcomes. In particular, relugolix was found to be a highly effective pharmacological intervention for the treatment of dysmenorrhea. The study also found that higher doses were associated with an increased incidence of adverse events.

Surgical treatment

The study by Duffy et al. (2014) focuses on the role of laparoscopic surgery in the management of endometriosis. The objective of the research was to evaluate the efficacy and safety of laparoscopic procedures in treating endometriosis-associated pain and infertility. The analysis included a cohort of 973 patients experiencing symptoms or subfertility related to the disease. The evidence base consists of several randomized controlled trials (RCTs) evaluating surgical interventions for endometriosis. Five trials compared laparoscopic ablation or excision against diagnostic laparoscopy alone, while two focused specifically on excision versus diagnostic laparoscopy. An additional two studies compared the efficacy of excision against ablation. Finally, one RCT investigated laparoscopic ablation relative to a combination of diagnostic laparoscopy and goserelin (a GnRH analogue) with add-back therapy. The study concluded that operative laparoscopic interventions were associated with significantly higher efficacy in pain reduction and improved outcomes regarding live birth and clinical pregnancy rates compared to diagnostic laparoscopy at both 6 and 12 months post-procedure. However, evidence regarding the comparative effectiveness of laparoscopic excision and ablation for pain relief remains of low quality, supported by only a single study. Consequently, further research is required to address severe endometriosis and various pain phenotypes, such as dysmenorrhea. Future studies should also evaluate laparoscopic surgery against holistic and pharmacological treatments. Furthermore, the lack of data on adverse events precludes any definitive conclusions regarding the safety profile of these procedures.

In another study by Riley et al. (2019) surgical excision and ablation were compared for the treatment of endometriosis-related pain. Visual Analogue Scale (VAS) scores were assessed at baseline and then reassessed after 6 and 12 months for dysmenorrhea, dyspareunia, and dyschezia. Ablation led to significant relief of dysmenorrhea (at 6 and 12 months) and dyscorrhea (at 6 months) compared with preoperative levels. However, the only statistically significant difference between the two surgical methods was found in the treatment of dyspareunia. In superficial endometriosis, both procedures provided comparable overall pain relief, although ablation was associated with more significant individual clinical progress.

The study by Healey et al. (2014) had a similar aim, comparing pain reduction after ablation and excision of endometriosis. Participants provided VAS scores and were randomly assigned to ablation or excision. Researchers assessed VAS scores every 3 months for the first year and then every 6 months during a 5-year follow-up period. Secondary endpoints included pregnancy rates, reoperation rates, and the use of adjuvant hormonal therapy. Both groups observed a reduction in all pain symptoms over the 5-year follow-up period. Importantly, a significantly greater reduction in VAS scores for dyspareunia was observed in the excision group after 5 years. Furthermore, a higher proportion of women in the ablation group required continued endometriosis treatment after five years. These results suggest that although laparoscopy provides symptom relief for up to five years, excision demonstrates superior long-term efficacy compared with ablation for specific symptoms, such as deep dyspareunia.

In a study by Fritzer et al. (2016) assessed the short-term impact of radical endometriosis resection on quality of sexual life, dyspareunia, and interpersonal relationships. The study included 96 patients with histologically confirmed endometriosis and dyspareunia. Women's sexuality was assessed preoperatively and 9 to 12 months postoperatively using the Female Sexual Function Index (FSFI) and the Female Sexual Discomfort Scale (FSDS). Additionally, psychological parameters and pain intensity during intercourse were assessed using self-reported questionnaires. Post-operative results indicated a substantial reduction in pain levels (measured by NAS) during and after sexual activity. Patients with both peritoneal and deep infiltrating endometriosis (DIE) reported a significant decline in sexual interruptions, guilt toward partners, anxiety regarding pain, and the sense of being a burden on their relationship. Notably, while sexual distress improved for DIE patients, it remained unchanged for those with peritoneal endometriosis or vaginal resection. Overall, radical laparoscopic excision serves as a highly effective intervention for alleviating dyspareunia and enhancing sexual quality of life.

Another study by Arcoverde et al. (2019) evaluated the impact of surgical intervention on health-related quality of life (HRQoL). The researchers assessed HRQoL using validated questionnaires administered both pre- and post-operatively. The results were stratified according to the phenotype of the disease: all forms of endometriosis, deep infiltrating endometriosis (DIE), and bowel endometriosis. The analysis revealed a post-operative improvement in the Mental Component Score (MCS) across all endometriosis subtypes. Notably, significant improvements were observed following the surgical management of DIE and bowel endometriosis across all eight SF-36 domains—Vitality, Social Functioning, Role Emotional, Mental Health, Physical Functioning, Role Physical, Bodily Pain, and General Health—as well as in the Mental Component Score (MCS), Physical Component Score (PCS), and total scores. In contrast, only one study within the analysis

evaluated patients with minimal-stage endometriosis, reporting a significant improvement specifically in the PCS. Ultimately, this systematic analysis demonstrates that surgical intervention for endometriosis leads to a comprehensive enhancement of health-related quality of life across multiple dimensions, with the most pronounced recovery observed in the relief of physical pain.

Research conducted by Tiringer et al. (2022) evaluates the quality of life in endometriosis patients before and after surgical intervention using the EHP-30 questionnaire. While endometriosis severely impacts health-related quality of life (HRQoL), the specific benefits of surgery across different subtypes remain under-researched. This study used the EHP-30 tool to compare preoperative status with outcomes 6–10 weeks post-surgery. Overall, significant improvements were seen across all EHP-30 domains: pain, self-determination, emotional health, social environment, and self-image. However, subgroup analysis revealed that patients with deep infiltrating endometriosis (DIE) with or without ovarian involvement gained the most pronounced benefits. Conversely, those with only peritoneal endometriosis showed the fewest symptoms and no significant postoperative changes.

A study by Wenzl et al. (2024) examined the long-term impact of laparoscopic endometriosis excision on patients' quality of life (QoL), focusing on disease subtypes, hormonal therapy, and reoperation rates. Eighty-seven patients were followed for 48 months using the EHP-30 tool. The results showed significant and sustained improvements in overall QoL and in all individual domains (pain, emotional well-being, social support, and self-esteem). Importantly, the greatest long-term benefits were observed in patients with deep infiltrating endometriosis (DIE) and adenomyosis. Although hormonal therapy did not significantly impact the positive trend, freedom from reoperation was a key factor in maintaining long-term QoL. However, those requiring further surgery reported no further improvement. The study demonstrated that radical surgical excision remains a highly effective long-term solution for improving the well-being of patients with endometriosis.

Dienogest

This 24-week randomized clinical trial by Strowitzki et al. (2012) examined the secondary efficacy and safety profiles of Dienogest (DNG) in comparison to Leuprolide Acetate (LA) for managing endometriosis. The researchers utilized the Biberoglu and Behrman (B&B) scale and predefined pain relief benchmarks to evaluate therapeutic response, while also monitoring laboratory markers and patient-reported quality-of-life (QoL) outcomes. The study established that DNG is non-inferior to LA, demonstrating comparable success in mitigating clinical symptoms and reducing pain scores. Notably, while LA treatment led to a significant reduction in estrogen levels, DNG maintained stable laboratory parameters, indicating a superior safety profile. Furthermore, patients in the DNG group reported more substantial enhancements in specific QoL domains compared to those receiving LA. Clinical Significance the evidence confirms that DNG serves as a highly effective alternative to LA, offering equivalent analgesic benefits with the added advantages of better hormonal stability and enhanced patient well-being.

A study by Petraglia et al. (2012) evaluated the long-term therapeutic potential and safety of dienogest (2 mg daily) in women who had previously completed a 12-week placebo-controlled trial with dienogest. The study monitored patients throughout a 53-week active treatment phase, followed by a 24-week post-treatment assessment to determine the durability of the drug's effect. The study demonstrated a high study completion rate (over 90%), indicating excellent patient compliance. A significant and progressive reduction in chronic pelvic pain was observed over the 53-week period ($P < 0.001$). Safety and tolerability: Treatment was well tolerated, with predominantly mild side effects and no clinically significant laboratory abnormalities. Bleeding patterns showed a gradual decrease in frequency and intensity during treatment. Importantly, the reduction in pelvic pain was maintained for six months after treatment discontinuation, even when menstrual cycles returned to baseline. Conclusions: These results suggest that long-term use of dienogest provides a sustained analgesic effect and a favorable safety profile. Evidence of sustained pain relief after treatment discontinuation underscores its value as a primary strategy for the long-term management of endometriosis.

This prospective study by Morotti et al. (2014) examined the therapeutic potential of dienogest (DNG) in a specific cohort of 25 women with rectovaginal endometriosis who had previously failed to achieve satisfactory results or pain relief after six months of norethisterone acetate (NETA) therapy. The primary endpoint was patient satisfaction (on a Likert scale) at 24 weeks, with secondary parameters including changes in lesion volume, sexual function, and quality of life (QoL). Switching to DNG led to significant increases in patient satisfaction at both 3 and 6 months. Key clinical outcomes included superior analgesic activity with DNG, which effectively relieved treatment-resistant symptoms, including chronic pelvic pain, dyspareunia,

and dyschezia, compared with baseline NETA. Significant improvements in overall quality of life (EHP-30) and sexual health (FSFI) were observed. Interestingly, endometrial nodule volume remained stable, suggesting that the clinical benefit was primarily symptomatic. The study highlights that dienogest is a highly effective intervention for symptomatic rectovaginal endometriosis. The researchers concluded that DNG represents a viable alternative in complex cases, although larger randomized trials are needed.

A subsequent study by Sugimoto et al. (2015) evaluated extended clinical outcomes of 75 patients treated with dienogest (DNG) for over 53 weeks, with some follow-up periods reaching 120 weeks. The study monitored reductions in ovarian endometriomas and adenomyotic lesions, as well as changes in serum biomarkers (CA-125 and estradiol). Additionally, patient-reported outcomes regarding symptomatic relief and treatment adherence were collected using questionnaires. Long-term use of DNG demonstrated high efficacy and an acceptable safety profile. Although ovarian endometriomas showed early reduction, they tended to enlarge after treatment discontinuation. Adenomyotic lesions, however, required longer treatment durations (at least 53 weeks) to achieve significant volume reduction. Abnormal vaginal bleeding was common, occurring in over 60% of patients. However, this side effect was generally well tolerated and rarely led to treatment discontinuation. Only two patients discontinued the drug due to discomfort unrelated to bleeding (lower abdominal and shoulder pain). The study demonstrated that DNG is an effective and safe long-term treatment strategy for endometriosis and adenomyosis, even when used for more than a year.

This review by Andres et al. (2015) synthesized data from nine randomized controlled trials. The analysis focused on the therapeutic effect of dienogest (DNG) 2 mg/day compared with placebo and other medical interventions on endometriosis-related symptoms and lesion regression. The meta-analysis confirmed that DNG 2 mg/day is significantly more effective than placebo in relieving pelvic pain. Furthermore, its efficacy in symptom control was found to be comparable to GnRH agonists, including buserelin, leuprorelin, triptorelin, and leuprolide acetate. DNG treatment resulted in a statistically significant reduction in endometrial lesion size. Extended use (24–52 weeks) led to gradual improvement in pain, with a manageable side-effect profile. Scientific evidence supports dienogest as a highly effective alternative for treating endometriosis symptoms. However, the authors suggest that although dienogest is an effective treatment option, physicians should consider whether proven first-line treatments offer similar efficacy at a lower cost and with the added benefit of contraception.

A randomized cohort study by Takaesu et al. (2016) aimed to determine the optimal postoperative strategy for preventing endometriosis recurrence. A total of 198 patients were evaluated after laparoscopic surgery, with 111 randomly assigned to receive dienogest (DNG) or goserelin, and 79 patients who discontinued hormonal therapy served as controls. Primary outcomes included recurrence rates, pain intensity (using the Visual Analogue Scale), and the incidence of adverse events during the 24-month follow-up period. The analysis revealed several key observations regarding postoperative care. For recurrence prevention, no statistically significant difference in recurrence rates was observed between the DNG and goserelin groups. However, only the DNG group demonstrated a significantly lower recurrence rate compared with the untreated group. Both hormonal interventions led to significant reductions in menstrual pain and chronic pelvic pain. Patients in the goserelin group experienced significantly higher rates of adverse events compared with those treated with DNG. The study showed that dienogest is a better option for long-term postoperative treatment. Unlike goserelin, which is typically limited to short-term use due to its side-effect profile, DNG can be administered for periods exceeding six months, providing a more sustainable and well-tolerated approach to relapse prevention.

Another retrospective study by Adachi et al. (2016) evaluated the efficacy of dienogest (DNG) in preventing recurrence of ovarian endometriosis and alleviating pain after laparoscopic excision. The analysis compared 81 patients who received 2 mg of DNG daily or received expectant management (without hormonal treatment) after surgery. In the expectant management cohort, cumulative recurrence rates reached 16.5% at one year and 24.0% at two years. In contrast, the DNG-treated group experienced no recurrences during the study period. Both groups experienced some improvement, with patients treated with DNG achieving significantly greater reductions in pelvic pain (VAS) compared to the control group over the 24-month follow-up. This study provides strong evidence that postoperative dienogest administration is highly effective in preventing recurrence of ovarian endometriosis and provides better pelvic pain relief compared with expectant management. These results support the routine use of dienogest to improve surgical outcomes and maintain long-term symptom control.

In a subsequent study by Römer (2019) the long-term efficacy and safety of dienogest (DNG) 2 mg daily for 60 months were assessed in 37 women. The results demonstrated a significant and sustained reduction

in pelvic pain as measured by visual analog scales in both groups, and the benefits were maintained throughout the five-year follow-up period. Laboratory monitoring confirmed no adverse effects on metabolic and hemostatic parameters, and mean estradiol levels remained stable. Despite minor side effects such as spotting and mood changes, the treatment was well tolerated. The results confirm that DNG is a safe and effective strategy for the long-term treatment of endometriosis and the prevention of postoperative recurrence.

Another study, a meta-analysis of 10 studies by Zakhari et al. (2020) assessed the effect of postoperative dienogest (DNG) on endometriosis recurrence compared with expectant management. The results showed a significant reduction in recurrence rates. Recurrence occurred in only 2 of 100 women in the DNG group, compared with 29 of 100 women in the control group. The results clearly indicate that DNG therapy after conservative surgery significantly reduces the risk of recurrence and is more effective than observation alone in maintaining long-term surgical success.

This systematic review by Liu et al. (2021) is a meta-analysis of studies that assessed the effect of dienogest (DNG) as maintenance therapy after conservative surgery compared with other therapies (GnRH-a, LNG-IUS) or no treatment. The pooled results showed that DNG significantly reduced the rate of recurrence after surgery. Regarding fertility, DNG demonstrated improved pregnancy rates compared with no treatment but did not offer significant advantages over other hormonal therapies. Although DNG was associated with increased weight gain and vaginal bleeding, it is recommended as an effective maintenance strategy for preventing recurrence.

Discussion

The therapeutic management of endometriosis poses a significant clinical challenge due to the chronic nature of the disease, heterogeneity of symptoms, and variable response to treatment. As demonstrated in the preceding sections, currently available treatment modalities differ substantially with respect to their mechanisms of action, effectiveness in symptom control, safety profile, and degree of invasiveness. Therefore, a direct comparison of these approaches is essential to determine their relative clinical value and to support individualized treatment decision-making. As demonstrated in the reviewed literature, no single therapeutic approach can be universally defined as optimal for all patients. Instead, treatment selection should balance effectiveness in symptom reduction, safety profile, invasiveness, long-term tolerability, and individual patient needs, including reproductive plans and quality of life considerations.

Across the reviewed studies, all four treatment modalities demonstrate clinically meaningful reductions in endometriosis-associated pain, including dysmenorrhea, chronic pelvic pain, dyspareunia, and, in selected cases, dyschezia. Surgical intervention, particularly laparoscopic excision, appears to provide the most immediate and often profound pain relief, especially in patients with deep infiltrating endometriosis (DIE). Long-term follow-up studies confirm sustained symptom improvement for several years after surgery, particularly regarding deep dyspareunia and severe pain phenotypes.

Pharmacological therapies, including dienogest, LNG-IUS, and relugolix combination therapy, show comparable efficacy in pain reduction, particularly for mild to moderate disease. Dienogest has demonstrated consistent analgesic effects across multiple randomized trials and meta-analyses, with efficacy comparable to GnRH agonists. LNG-IUS has shown robust effectiveness in reducing dysmenorrhea and chronic pelvic pain, particularly as postoperative maintenance therapy. Relugolix combination therapy has emerged as one of the most potent non-surgical options, with large phase 3 trials demonstrating rapid and sustained pain relief, including reductions in non-menstrual pelvic pain and dyspareunia.

Safety profile represents a critical factor in long-term management. Among the reviewed options, LNG-IUS and dienogest exhibit the most favorable safety and tolerability profiles. LNG-IUS delivers levonorgestrel locally, minimizing systemic exposure and reducing the incidence of systemic adverse effects such as mood changes or gastrointestinal symptoms. Dienogest maintains moderate estrogen levels, avoiding severe hypoestrogenic effects and preserving bone mineral density, which makes it suitable for prolonged use.

Relugolix monotherapy is associated with hypoestrogenic adverse effects and bone mineral density loss; however, combination therapy with estradiol and norethisterone acetate significantly mitigates these risks. Long-term extension studies confirm stabilization of bone mineral density and acceptable tolerability over two years, positioning relugolix combination therapy as a safe option for extended treatment in selected patients. Nevertheless, vasomotor symptoms, headaches, and higher costs may limit its widespread first-line use.

Surgical treatment carries inherent procedural risks, including bleeding, infection, damage to adjacent organs, and potential compromise of ovarian reserve. Although minimally invasive techniques have reduced

surgical morbidity, recurrence of symptoms and the need for reoperation remain significant concerns, particularly in patients not receiving postoperative hormonal suppression.

Invasiveness represents a key differentiating factor among treatment modalities. Surgical intervention is the most invasive approach and is best reserved for patients with severe disease, refractory symptoms, or infertility associated with anatomical distortion. While surgery can restore pelvic anatomy and improve fertility outcomes, its benefits are often time-limited without adjunctive medical therapy. In contrast, LNG-IUS and dienogest represent minimally invasive, long-term strategies suitable for chronic disease.

Conclusions

Endometriosis is a complex, chronic disease that requires a lifelong, patient-centered treatment strategy. This review confirms that although all four methods analyzed - the LNG-IUS, combination therapy with relugolix, surgery, and dienogest are effective in relieving pain, their clinical use should be tailored to the individual patient's profile. Laparoscopic surgery remains the standard for restoring pelvic anatomy and treating deeply infiltrating lesions, although its success often depends on postoperative pharmacological suppression to prevent recurrence. Among the pharmacological options, dienogest and the LNG-IUS offer the best balance of long-term efficacy and safety, making them ideal for maintaining sustained symptom control. Combination therapy with relugolix offers an effective oral alternative for the treatment of refractory symptoms, bridging the gap between conventional medical therapy and surgery. In summary, there is no universal solution. Optimal results are achieved through a multimodal approach that prioritizes the patient's quality of life, reproductive goals, and treatment tolerance.

Author contributions:

Katarzyna Ścibisz - conceptualization and research design; Karolina Ollik – methodology; Kamil Harenza – investigation; Mateusz Taranowicz - analysis and interpretation of data; Olga Kowalczyk - analysis and interpretation of data; Dominika Zdobylak - theoretical development; Monika Kowalska - editing and review; Anita Zięba - editing and review; Michał Domin – supervision; Justyna Całka – supervision

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