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Effectiveness of GnRH agonist (leuprolide acetate) after surgical treatment of endometriosis: A systematic review

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ABSTRACT

Endometriosis may recur after surgery despite removal of visible lesions. Postoperative hormonal suppression is therefore used to control residual disease and symptoms. Gonadotropin-releasing hormone (GnRH) agonists, including leuprolide acetate, provide ovarian suppression, but their benefits after surgery remain uncertain. This study aimed to evaluate the effectiveness of postoperative GnRH agonist therapy, particularly leuprolide acetate, in reducing pain and recurrence and improving reproductive outcomes after endometriosis surgery. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework and searched PubMed, Scopus, Cochrane Library, and ScienceDirect for studies published from 2020 to 2026. Among 312 identified records, 54 duplicates were removed and 258 records were screened. Forty-four full-text articles were assessed, of which 41 were excluded, leaving 3 publications for qualitative synthesis. These comprised one randomized controlled trial (n=20), one comparative clinical study (n=158), and one review of 10 randomized controlled trials. In the randomized trial, pelvic pain decreased in the leuprolide group from 4.6 ± 0.84 at baseline to 0.2 ± 0.42 at week 12 ($p=0.003$), with no significant difference compared with dienogest ($p=1.000$). The comparative study reported lower recurrence and higher pregnancy rates with leuprorelin than the comparator (both $p<0.05$), although effect estimates and 95% confidence intervals were not reported. Adverse reactions did not differ significantly between groups (10.13% vs. 6.33%, $p>0.05$). Overall, evidence for pain was more supportive, whereas evidence for recurrence and reproductive outcomes remained limited and heterogeneous. Further randomized controlled trials are needed.

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INTRODUCTION

Endometriosis is a chronic gynecological condition characterized by the presence of tissue resembling the endometrium beyond the uterine cavity. These ectopic lesions are frequently found in the ovaries, pelvic peritoneal surfaces, uterosacral ligaments, and other pelvic structures. Their presence may result in dysmenorrhea, persistent pelvic pain, dyspareunia, infertility, and a reduced quality of life (Purwanto et al., 2020; Yu et al., 2022). Endometriosis involves complex hormonal, inflammatory, and immune mechanisms, in which estrogen promotes the proliferation and persistence of ectopic endometrial tissue, while inflammatory and immune dysregulation contribute to lesion persistence and associated pain (D'Alessandro et al., 2020; Veth et al., 2023). Consequently, endometriosis is considered a chronic and recurrent condition requiring long-term management.

Surgical treatment is an important therapeutic option, particularly for women presenting with severe symptoms, infertility, or advanced disease. Laparoscopic surgery allows the removal or ablation of visible endometriotic lesions, adhesiolysis, and restoration of pelvic anatomy, with potential benefits for both pain relief and fertility outcomes(Amirudin & Tjandra, 2025; Qing et al., 2024). However, surgery does not necessarily eliminate microscopic residual disease, and symptoms or lesions may recur during subsequent follow-up. Recurrence may result in the return of pelvic pain and dysmenorrhea, impair quality of life, and necessitate further medical or surgical intervention (Filindris et al., 2024; Surrey, 2022).

Postoperative medical therapy is therefore used to suppress ovarian estrogen production and inhibit the activity of residual endometriotic lesions. Hormonal management of endometriosis comprises oral contraceptives, progestins, danazol, and gonadotropin-releasing hormone (GnRH) agonists(Dick et al., 2025; Pinto da Costa Viana et al., 2025). Among these treatments, GnRH agonists, including leuprolide acetate, produce substantial suppression of ovarian function. With continuous administration, these agents cause pituitary GnRH receptor desensitization and downregulation, leading to reduced secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and, consequently, decreased ovarian estrogen production (Rzewuska et al., 2023; Wang et al., 2025). The resulting hypoestrogenic state may inhibit the growth and activity of residual endometriotic lesions and alleviate pain symptoms (Rzewuska et al., 2023; Wang et al., 2025).

Clinical studies have evaluated the use of postoperative GnRH agonists following surgical treatment of endometriosis, including leuprolide or leuprorelin-based regimens. In the randomized clinical trial by Purwanto et al., postoperative leuprolide acetate was associated with a reduction in pain following laparoscopic surgery, while the comparative cohort study by Yu et al. evaluated postoperative leuprorelin in relation to recurrence and pregnancy outcomes (Purwanto et al., 2020; Yu et al., 2022). These findings suggest potential benefits of postoperative GnRH agonist therapy across different clinical outcomes; however, the available primary studies differ in study design, patient characteristics, treatment regimens, and outcome assessment. GnRH agonist therapy may also cause hypoestrogenic adverse effects, including hot flashes, vaginal dryness, mood changes, and decreased bone mineral density, which may influence treatment tolerability and adherence (Taylor et al., 2021; Zondervan et al., 2020).

Thus, several clinically relevant questions remain unresolved: whether postoperative leuprolide acetate consistently reduces pain and delays recurrence after surgery, whether its potential reproductive benefit is reproducible across different patient populations, and how these outcomes vary according to treatment and follow-up characteristics. The available evidence is further complicated by variation in surgical approaches, disease characteristics, treatment duration, comparator therapies, outcome definitions, and follow-up periods. Consequently, the effectiveness of leuprolide acetate specifically after surgical treatment of endometriosis remains insufficiently characterized despite the increasing availability of postoperative evidence.

This systematic review was therefore conducted to synthesize the evidence published between 2020 and 2026 on the effectiveness of postoperative GnRH agonist therapy, with particular emphasis on leuprolide acetate, following surgical treatment of endometriosis. The review specifically evaluates three clinically relevant domains—pain, disease recurrence, and reproductive outcomes—to clarify the consistency of reported benefits, identify sources of heterogeneity, and define remaining evidence gaps.

RESEARCH METHOD

Study Design

This study was conducted as a systematic review to evaluate the effectiveness of postoperative gonadotropin-releasing hormone (GnRH) agonist therapy, particularly leuprolide acetate, in women with endometriosis who had undergone surgical treatment. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was not prospectively registered.

A systematic literature search was conducted in PubMed, Scopus, ScienceDirect, and the Cochrane Library for studies published from January 2020 to January 2026. The publication period was restricted to focus the review on recent evidence regarding postoperative hormonal management of endometriosis. The search strategy incorporated terms related to endometriosis, surgical treatment, GnRH agonists or leuprolide acetate, postoperative therapy, and clinical outcomes.

For PubMed, the search strategy used Medical Subject Headings (MeSH) and Title/Abstract field tags as follows: ("Endometriosis"[Mesh] OR endometriosis[tiab]) AND ("Surgical Procedures, Operative"[Mesh] OR surgery[tiab] OR "surgical treatment"[tiab] OR laparoscopy[tiab] OR "laparoscopic surgery"[tiab]) AND ("Gonadotropin-Releasing Hormone Agonists"[Mesh] OR "Leuprolide"[Mesh] OR "gonadotropin-releasing hormone agonist"[tiab] OR "GnRH agonist"[tiab] OR leuprolide[tiab] OR "leuprolide acetate"[tiab]) AND (postoperative[tiab] OR "post-surgical"[tiab] OR "postoperative therapy"[tiab]) AND (recurrence[tiab] OR pain[tiab] OR "pelvic pain"[tiab] OR dysmenorrhea[tiab] OR "clinical outcome"[tiab]) AND ("2020/01/01"[Date - Publication] : "2026/01/31"[Date - Publication]) AND English[Language].

For Scopus, the search strategy was applied using the Title, Abstract, and Keywords field: TITLE-ABS-KEY(endometriosis) AND TITLE-ABS-KEY(surgery OR "surgical treatment" OR laparoscopy OR "laparoscopic surgery") AND TITLE-ABS-KEY("gonadotropin-releasing hormone agonist" OR "GnRH agonist" OR leuprolide OR "leuprolide acetate") AND TITLE-ABS-KEY(postoperative OR "post-surgical" OR "postoperative therapy") AND TITLE-ABS-KEY(recurrence OR pain OR "pelvic pain" OR dysmenorrhea OR "clinical outcome") AND PUBYEAR > 2019 AND PUBYEAR < 2027 AND LIMIT-TO(LANGUAGE, "English").

For ScienceDirect, the search was conducted using the Title, Abstract, or Author-specified Keywords fields with the following search terms: (endometriosis) AND (surgery OR "surgical treatment" OR laparoscopy OR "laparoscopic surgery") AND ("gonadotropin-releasing hormone agonist" OR "GnRH agonist" OR leuprolide OR "leuprolide acetate") AND (postoperative OR "post-surgical" OR "postoperative therapy") AND (recurrence OR pain OR "pelvic pain" OR dysmenorrhea OR "clinical outcome").

The ScienceDirect search was restricted to publications from 2020 to 2026 and English-language articles. For the Cochrane Library, the search strategy incorporated controlled vocabulary and text words as follows: (MeSH descriptor: [Endometriosis] explode all trees OR endometriosis,ab,kw) AND (MeSH descriptor: [Surgical Procedures, Operative] explode all trees OR surgery,ab,kw OR "surgical treatment",ab,kw OR laparoscopy,ab,kw OR "laparoscopic surgery",ab,kw) AND (MeSH descriptor: [Gonadotropin-Releasing Hormone Agonists] explode all trees OR leuprolide,ab,kw OR "leuprolide acetate",ab,kw OR "GnRH agonist",ab,kw) AND

(postoperative,ab,kw OR "post-surgical",ab,kw) AND (recurrence,ab,kw OR pain,ab,kw OR "pelvic pain",ab,kw OR dysmenorrhea,ab,kw OR "clinical outcome",ab,kw).

The search date, number of records retrieved from each database, and database-specific search settings were recorded to facilitate reproducibility. The retrieved records were managed using Mendeley Reference Manager for reference management and duplicate removal, while Microsoft Excel was used to document the screening and study-selection process. Following the screening process, eligible studies were assessed and synthesized using a narrative synthesis approach.

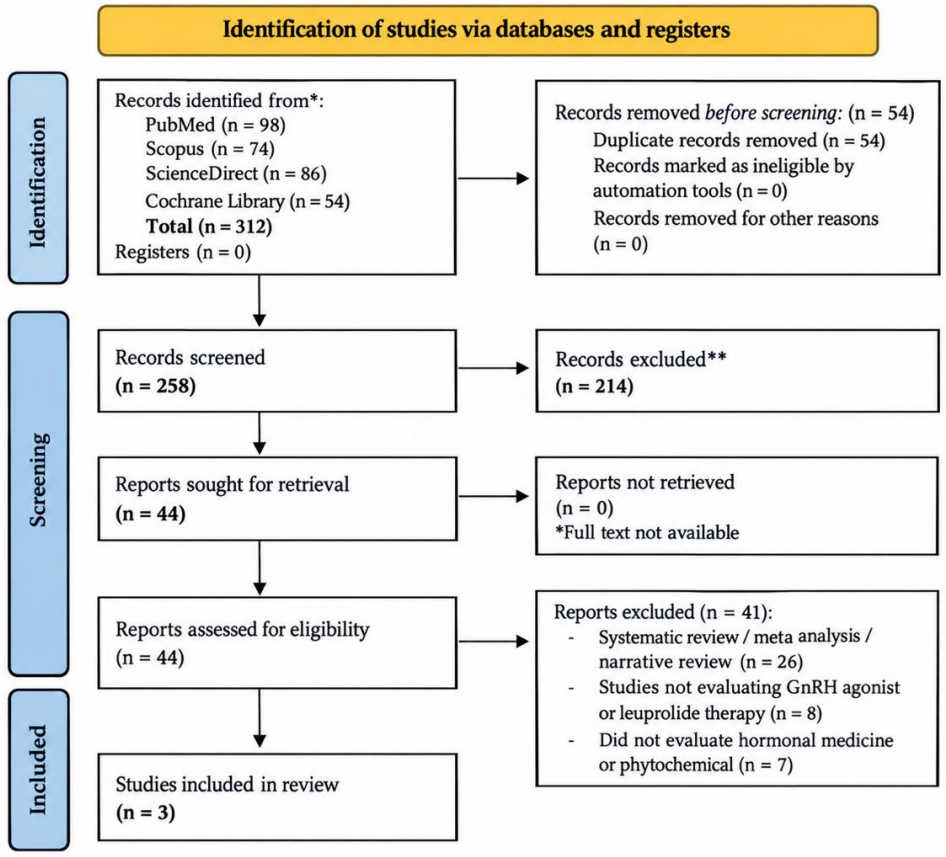


Figure 1. PRISMA search method

Study Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (1) primary clinical studies with randomized controlled trial, controlled clinical trial, prospective cohort, or retrospective cohort designs; (2) participants were women diagnosed with endometriosis who had undergone surgical treatment, including laparoscopy or laparotomy; (3) postoperative treatment included a GnRH agonist, particularly leuprolide or leuprolide acetate; (4) a comparison group received no hormonal therapy, placebo, oral contraceptives, progestins, or another postoperative hormonal treatment; and (5) reported outcomes included endometriosis recurrence, pelvic pain, dysmenorrhea, reproductive or pregnancy outcomes, quality of life, or adverse effects. Only full-text, peer-reviewed articles published in English between January 2020 and January 2026 were considered. Studies were excluded if they involved animals or in vitro experiments; evaluated GnRH agonists without postoperative treatment; or were systematic reviews, meta-analyses, narrative reviews, case reports, editorials, conference abstracts, commentaries, or studies with incomplete outcome data or unclear methodology. Systematic reviews, meta-analyses, and case

reports identified during the literature search were therefore not considered eligible studies for the qualitative synthesis, although relevant publications could be retained as supporting references for contextual discussion.

Study Selection

A total of 312 records were identified from PubMed, Scopus, ScienceDirect, and the Cochrane Library. After removing 54 duplicate records, 258 records remained for title and abstract screening. Of these, 214 records were excluded because they did not meet the predefined eligibility criteria. The remaining 44 reports were retrieved and assessed for eligibility through full-text review. Following full-text assessment, 41 reports were excluded, comprising 26 systematic reviews, meta-analyses, or narrative reviews; 8 studies that did not evaluate GnRH agonist or leuprolide therapy; and 7 studies that did not evaluate hormonal medicine or phytochemical interventions. Consequently, 3 primary clinical studies met all eligibility criteria and were included in the qualitative synthesis. The study selection process is presented in the PRISMA 2020 flow diagram.

Data Extraction and Synthesis

Data were extracted from the three included primary clinical studies using a predefined data-extraction framework. The extracted information included author and year of publication, country, study design, sample size, type of surgical treatment, postoperative GnRH agonist regimen, comparator intervention, treatment duration, follow-up period, and reported clinical outcomes. Particular attention was given to numerical data related to recurrence, pain or dysmenorrhea, reproductive outcomes, quality of life, and adverse effects. The extracted data were organized in a summary table and compared across studies according to their study characteristics and reported outcomes. Because of differences in study design, treatment regimens, follow-up periods, and outcome measures among the included studies, a meta-analysis was not performed. The findings were therefore synthesized narratively to describe the effects of postoperative GnRH agonist therapy, particularly leuprolide acetate, on clinical and reproductive outcomes following endometriosis surgery.

Risk of Bias Assessment

The risk of bias of the included studies was assessed according to their respective study designs. Purwanto et al. (2020), as a randomized controlled trial, was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, while Yu et al. (2022), as a non-randomized cohort study, was assessed using the Methodological Index for Non-Randomized Studies (MINORS). D'Alessandro et al. (2020), which was included as a review of randomized controlled trials, was assessed according to the methodological quality of the primary studies reported in the review. The assessment considered relevant methodological domains, including the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results for randomized studies, as well as methodological characteristics relevant to non-randomized studies.

Table 1. Risk of bias assessment

Study	Design	Instrument	Risk of Bias Level
Purwanto 2020	Randomized Clinical Trial	RoB 2	Moderate
Yu 2022	Cohort comparative study	MINORS	Moderate
D'Alessandro 2020	Review of RCTs	RoB 2 (review-level)	Moderate

The results of the risk of bias assessment were presented descriptively and were considered when interpreting the findings of the qualitative synthesis.

RESULTS AND DISCUSSIONS

Result

A total of 312 records were retrieved from PubMed, Scopus, Cochrane Library, and ScienceDirect for studies published between 2020 and 2026. Following the removal of 54 duplicate records, 258 unique records were available for title and abstract screening. Among these, 214 records were subsequently excluded as they failed to fulfill the predefined eligibility criteria. Forty-four reports were assessed for eligibility by full-text review, of which 41 were excluded, resulting in three primary clinical studies included in the qualitative synthesis. The three included studies consisted of one randomized clinical trial, one comparative cohort study, and one review of randomized controlled trials. However, because the review by D'Alessandro et al. (2020) summarizes evidence from primary randomized trials, its findings were not treated as additional independent patient-level evidence to avoid double-counting. The quantitative results reported below therefore distinguish findings from primary clinical studies from evidence summarized by the review.

Table 2. Characteristics of included studies

Author, Year	Study Design	Sample	Intervention	Comparator	Follow-up	Outcomes Assessed	DOI / Identifier
Purwanto et al., 2020	Randomized controlled trial	20 (10/group)	Leuprolide acetate 3.75 mg IM every 4 weeks for 12 weeks after laparoscopic surgery	Dienogest 2 mg/day	12 weeks	Pain (VAS), adverse effects	10.32771/INAJOG.V8I1.1110
Yu et al., 2022	Comparative clinical study	158 (79/group)	Leuprorelin 3.75 mg every menstrual cycle for 3 months after laparoscopic surgery	Dydrogesterone 10 mg for 3 months	12 months	Recurrence, pregnancy, hormone levels, adverse reactions	10.3389/fsurg.2022.873698; PMID: 35521431
D'Alessandro et al., 2020	Review of randomized controlled trials	10 RCTs	Postoperative GnRH analogues	Various control/postoperative treatments	6–36 months	Recurrence after surgery	10.21037/gpm-20-31

Regarding pain outcomes, Purwanto et al. (2020) conducted a randomized clinical trial involving 20 postoperative endometriosis patients comparing leuprolide acetate with dienogest. Both treatment groups demonstrated significant reductions in visual analogue scale (VAS) pain scores at 4, 8, and 12 weeks after laparoscopic surgery. The study also reported no statistically significant difference in safety outcomes between the two treatment groups. However, the available data in the current study extraction did not provide sufficient numerical information to calculate a mean difference (MD), standardized mean difference (SMD), or 95% confidence interval; therefore, these effect estimates are not reported here.

Table 3. Quantitative findings of included studies

Study	Outcome	Quantitative Findings	Statistical Result
Purwanto et al., 2020	Pain (VAS)	Leuprolide: baseline 4.6 ± 0.84, week 4 2.7 ± 0.82, week 8 0.9 ± 0.74, week 12 0.2 ± 0.42. Dienogest: baseline 4.9 ± 0.88, week 4 2.4 ± 1.26, week 8 1.0 ± 1.33, week 12 0.2 ± 0.42.	Within-group: p=0.004, 0.004, and 0.003 for leuprolide; p=0.004 at all time points for dienogest. Between-group: week 4 p=0.476; week 8 p=0.810; week 12 p=1.000.
Purwanto et al., 2020	Adverse effects	Adverse effects were compared between the two treatment groups.	p=0.238, indicating no statistically significant difference.
Yu et al., 2022	Recurrence	At 12-month follow-up, the recurrence rate was	p<0.05

Study	Outcome	Quantitative Findings	Statistical Result
		lower in the leuprorelin group than in the dydrogesterone group.	
Yu et al., 2022	Pregnancy	At 12-month follow-up, the pregnancy rate was higher in the leuprorelin group than in the dydrogesterone group.	p<0.05
Yu et al., 2022	Adverse reactions	10.13% in the leuprorelin group vs 6.33% in the dydrogesterone group.	p>0.05
Yu et al., 2022	Hormonal profile	LH, FSH, and estradiol levels were lower after treatment in the leuprorelin group.	p<0.05
D'Alessandro et al., 2020	Recurrence	The review included 10 RCTs. Reported recurrence results varied according to GnRH analogue, comparator, outcome definition, and follow-up. Examples included objective recurrence of 10% vs 15% at 6 months (Shaw et al.), 26.9% vs 30.8% at 24–36 months (Acién et al.), and 10.3% vs 15.0–17.8% at 18 months in Sesti et al.	Findings across RCTs were not uniformly statistically significant; the review characterized the evidence as controversial and suggested that treatment duration may influence recurrence.

For reproductive and recurrence outcomes, Yu et al. (2022) evaluated 158 women with endometriosis-associated infertility who underwent laparoscopic surgery followed by postoperative hormonal treatment. The leuprorelin group was reported to have a lower recurrence rate and a higher pregnancy rate than the dydrogesterone group. However, the current extracted data do not provide the corresponding event counts, effect estimates, 95% confidence intervals, or p-values. Therefore, the findings are presented descriptively rather than as calculated relative risks (RR) or odds ratios (OR). D'Alessandro et al. (2020) reviewed randomized controlled trial evidence concerning postoperative GnRH analogue therapy and recurrence of endometriosis. Because this publication is a review rather than an independent primary clinical study, its findings were used as supporting evidence and were not counted as an additional independent study population. The biological mechanisms underlying pain reduction and recurrence suppression are addressed in the Discussion section rather than the Results.

Table 4. Summary of main findings

Outcome	Findings from Included Publications
Pain	Purwanto et al. reported substantial reductions in VAS scores in both leuprolide and dienogest groups. However, no significant between-group difference was observed at weeks 4, 8, or 12.
Recurrence	Yu et al. reported a significantly lower 12-month recurrence rate with leuprorelin compared with dydrogesterone (p<0.05). D'Alessandro et al. reported variable recurrence findings across 10 RCTs, with effects differing according to comparator and follow-up duration.
Pregnancy	Yu et al. reported a significantly higher pregnancy rate at 12 months in the leuprorelin group (p<0.05).
Hormonal outcomes	Yu et al. reported significantly lower LH, FSH, and estradiol levels following leuprorelin treatment (p<0.05).
Adverse effects/reactions	Purwanto et al. found no significant difference between leuprolide and dienogest (p=0.238). Yu et al. likewise reported no significant difference between leuprorelin and dydrogesterone (10.13% vs 6.33%; p>0.05).

A meta-analysis was not performed because the three included sources differed substantially in study design, intervention and comparator characteristics, outcome definitions, and reported outcome measures. In particular, the available primary studies did not provide sufficiently comparable numerical data for a valid pooled effect estimate. The evidence also included a randomized trial and a non-randomized cohort study, while D'Alessandro et al. (2020)

represented a secondary synthesis of randomized trials. Therefore, pooling these data would risk combining non-equivalent populations and potentially double-counting evidence. A narrative synthesis was consequently considered more appropriate for the available evidence.

Discussion

a. Overview of Endometriosis and Its Management

Endometriosis is a chronic gynecological disorder in which endometrial-like tissue occurs beyond the uterine cavity. It primarily affects women of reproductive age and may manifest clinically as pelvic pain, dysmenorrhea, dyspareunia, and infertility (Zondervan et al., 2020). The disease affects approximately 6–10% of women worldwide, with substantially higher rates reported among those with infertility or chronic pelvic pain (Burney & Giudice, 2012).

Its pathogenesis involves complex interactions between hormonal, inflammatory, and immune mechanisms (Burney & Giudice, 2012; Chapron et al., 2019). Estrogen has a central role in promoting the growth and persistence of ectopic lesions and maintaining the inflammatory environment associated with the disease (Vercellini et al., 2018). Consequently, hormonal therapies for endometriosis primarily aim to reduce ovarian estrogen production and suppress the activity of endometriotic implants.

Treatment generally combines surgical and medical approaches. Laparoscopic excision or ablation is commonly performed to remove visible lesions, restore pelvic anatomy, and relieve pain; however, postoperative recurrence remains a significant concern (D'Alessandro et al., 2020; Veth et al., 2023). Postoperative hormonal therapy has therefore been investigated as an adjunct to surgery, particularly to control symptoms and potentially delay recurrence (Chiu et al., 2022; Zakhari et al., 2020).

b. Role of GnRH Agonists in Postoperative Endometriosis Treatment

Gonadotropin-releasing hormone (GnRH) agonists, including leuprolide and leuprorelin acetate, are established options for the medical management of endometriosis and are frequently used after surgery (Becker et al., 2022; Surrey, 2022). These agents initially stimulate pituitary GnRH receptors, causing a transient increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Continuous exposure subsequently induces receptor desensitization and downregulation, resulting in sustained suppression of LH and FSH and, consequently, reduced ovarian estrogen production (Becker et al., 2022; Surrey, 2022).

The hypoestrogenic state produced by GnRH agonists suppresses the growth and activity of residual endometriotic lesions after surgery(Chapron et al., 2019; Vercellini et al., 2018). Estrogen contributes to cellular proliferation, angiogenesis, and inflammatory signaling within ectopic lesions, while estrogen suppression reduces these processes and may decrease the production of inflammatory mediators involved in pelvic pain and dysmenorrhea (Chapron et al., 2019; Vercellini et al., 2018). Therefore, postoperative GnRH agonist therapy may provide both symptomatic control and suppression of microscopic residual disease, potentially delaying its reactivation.

GnRH agonists are generally administered by intramuscular or subcutaneous injection at regular intervals, commonly for three to six months, depending on the clinical context and treatment goals (Surrey, 2022). However, because prolonged hypoestrogenism may cause menopausal symptoms and other adverse effects, treatment duration and the need for add-back therapy should be individualized.

In the present review, the clinical effects of postoperative GnRH agonists were not uniform across outcomes. The available evidence was strongest for short-term pain reduction, whereas evidence regarding recurrence and reproductive outcomes was less consistent and more difficult to interpret because of differences in outcome definitions, comparators, treatment duration, and follow-up. Therefore, the findings support a potential role for postoperative GnRH agonist therapy

but do not establish a definitive treatment effect for all clinical outcomes (Patel, 2024; Vercellini et al., 2018).

c. Pain Reduction Following GnRH Agonist Therapy

Pain reduction is an important outcome of postoperative endometriosis treatment, as chronic pelvic pain and dysmenorrhea substantially impair daily activities, sexual function, productivity, and quality of life (D'Alessandro et al., 2020; Purwanto et al., 2020; Yu et al., 2022). Persistent symptoms may also occur despite surgical removal of visible lesions because microscopic residual disease can remain and contribute to symptom recurrence. Therefore, postoperative hormonal suppression remains an important strategy for maintaining pain control.

In the randomized clinical trial by Purwanto et al., both leuprolide acetate and dienogest produced significant reductions in VAS pain scores at 4, 8, and 12 weeks after laparoscopic surgery(Purwanto et al., 2020). The magnitude of the reduction was substantial in both groups. In the leuprolide group, mean VAS decreased from 4.6 ± 0.84 at baseline to 2.7 ± 0.82 at week 4, 0.9 ± 0.74 at week 8, and 0.2 ± 0.42 at week 12. In the dienogest group, VAS decreased from 4.9 ± 0.88 to 2.4 ± 1.26, 1.0 ± 1.33, and 0.2 ± 0.42 at the same time points. Although the within-group reductions were statistically significant, the between-group differences were not significant at week 4 ($p=0.476$), week 8 ($p=0.810$), or week 12 ($p=1.000$). These findings are important because statistical improvement within each treatment group does not demonstrate superiority of leuprolide over dienogest. The comparable final VAS values also indicate that the observed pain improvement cannot be attributed specifically to leuprolide when compared with dienogest in this study. Thus, the evidence supports postoperative pain improvement with both regimens rather than a specific advantage of leuprolide.

The analgesic effect of GnRH agonists is closely related to estrogen suppression. Estrogen promotes the growth of ectopic endometrial tissue and contributes to the production of prostaglandins, cytokines, and other inflammatory mediators involved in nociceptive signaling (Burney & Giudice, 2012; Zondervan et al., 2020). Continuous GnRH agonist administration suppresses ovarian estrogen production, thereby reducing the activity of residual endometriotic lesions and the associated inflammatory response (Burney & Giudice, 2012; Zondervan et al., 2020). This hormonal effect may also influence the local neural environment within endometriotic implants, further contributing to symptom relief (Burney & Giudice, 2012; Richard et al., 2022; Zondervan et al., 2020).

From a clinical perspective, the findings suggest that postoperative GnRH agonist therapy can be considered in the context of symptom control, but the available comparative evidence does not demonstrate that leuprolide provides greater pain relief than an alternative postoperative hormonal regimen. In addition, the small sample size of the Purwanto et al. trial ($n=20$) limits the precision and generalizability of this finding.

d. Effect of GnRH Agonists on Recurrence of Endometriosis

Recurrence remains a major challenge after surgical treatment of endometriosis. Although laparoscopic excision or ablation can remove visible lesions, microscopic implants may persist and subsequently become active under continued estrogenic stimulation (D'Alessandro et al., 2020). Recurrence may manifest as recurrent pelvic pain, dysmenorrhea, or endometriotic cysts and can lead to repeated medical or surgical treatment (D'Alessandro et al., 2020; Qing et al., 2024; Veth et al., 2023).

The recurrence findings in the present review should be interpreted according to how recurrence was defined. Yu et al. evaluated recurrence at 12 months using ultrasonographic evidence of a new ovarian cyst measuring at least 2 cm that persisted over several menstrual cycles, with or without accompanying clinical or laboratory findings. The study reported a lower recurrence rate in the leuprorelin group than in the dydrogesterone group ($p<0.05$). This finding

suggests a potential reduction in structural/ovarian recurrence with postoperative leuprorelin, but the study did not report a risk ratio, odds ratio, or 95% confidence interval, limiting the ability to quantify the magnitude and precision of the effect. (Yu et al., 2022)

The findings from D'Alessandro et al. provide additional contextual evidence but should not be interpreted as an independent patient-level study because the publication was a review of randomized controlled trials. Across the RCTs summarized in that review, recurrence findings varied according to whether recurrence was defined objectively by imaging or subjectively by recurrent symptoms, as well as according to treatment duration and comparator. Some trials reported lower recurrence with postoperative GnRH analogues, whereas others did not demonstrate statistically significant differences. Therefore, the available evidence suggests a possible delay or reduction in recurrence, but does not establish a consistent effect across all forms of recurrence. (D'Alessandro et al., 2020)

Differences between Yu et al. and the RCTs summarized by D'Alessandro et al. may partly reflect differences in recurrence definitions, GnRH analogues used, comparator treatments, disease characteristics, surgical procedures, and follow-up duration. Consequently, the recurrence findings should not be pooled qualitatively as though all studies measured the same clinical outcome.

The preventive effect of GnRH agonists is biologically consistent with the estrogen-dependent nature of endometriosis. Estrogen suppression can inhibit cellular proliferation, angiogenesis, and inflammatory activity within residual lesions, thereby limiting their subsequent reactivation (Chapron et al., 2019; Vercellini et al., 2018). This effect may be especially relevant in advanced disease, in which complete removal of all endometriotic implants can be challenging (Chapron et al., 2019; Vercellini et al., 2018). Nevertheless, the magnitude of recurrence reduction should be interpreted cautiously because differences in treatment duration, disease severity, surgical completeness, and follow-up among studies may contribute to variation in reported outcomes (D'Alessandro et al., 2020; Qing et al., 2024; Veth et al., 2023).

e. Impact of GnRH Agonists on Fertility Outcomes

Infertility is a major concern in women with endometriosis and may result from pelvic adhesions, chronic inflammation, and impaired ovarian function (Yu et al., 2022). In a study by Yu et al., laparoscopic surgery followed by leuprorelin therapy was associated with higher pregnancy rates and lower recurrence rates than alternative postoperative hormonal treatment in women with endometriosis-associated infertility (Yu et al., 2022).

However, pregnancy rate should not be interpreted as equivalent to improved fertility, live-birth rate, or cumulative reproductive success. Yu et al. reported a higher pregnancy rate at 12 months in the leuprorelin group ($p<0.05$), but the study did not establish whether this difference translated into a higher live-birth rate. In addition, the absence of a reported risk ratio, odds ratio, and 95% confidence interval limits assessment of the magnitude and precision of the observed association (Yu et al., 2022).

The reproductive finding should therefore be interpreted as evidence of an association with pregnancy occurrence within the study follow-up rather than definitive evidence that postoperative leuprorelin improves fertility or live-birth outcomes. Factors such as age, ovarian reserve, disease severity, previous infertility duration, surgical findings, and use of assisted reproductive treatment may also influence pregnancy outcomes.

The systematic review and meta-analysis by Qing et al. was not treated as an additional independent clinical study in the present synthesis because systematic reviews may contain the same primary studies already represented in the included evidence. It was retained as supporting literature rather than as additional patient-level evidence (Qing et al., 2024)

Accordingly, the current evidence provides a signal of potential reproductive benefit but remains insufficient to establish a causal effect of leuprorelin on fertility or live birth. Future

studies should report pregnancy, clinical pregnancy, ongoing pregnancy, live birth, and time to conception separately to allow more clinically meaningful interpretation.

f. Limitations and Clinical Implications

Several limitations need to be taken into account when interpreting the findings of this systematic review. The number of eligible studies was limited, with differences in study design, sample size, treatment regimen, comparator, outcome definitions, and follow-up duration, resulting in substantial heterogeneity. The inclusion of a review of randomized controlled trials also required careful consideration to avoid double counting of evidence. A meta-analysis was therefore not performed because the available studies were not sufficiently homogeneous and did not consistently report effect estimates and 95% confidence intervals. Publication bias, language bias, and database bias could not be formally assessed because of the small number of eligible studies and the use of four databases. Selective reporting also could not be excluded because several outcomes were incompletely reported. Furthermore, the review protocol was not prospectively registered and a formal certainty-of-evidence assessment was not performed, limiting the ability to determine the overall certainty of the evidence. The hypoestrogenic effects of GnRH agonists, including vasomotor symptoms, vaginal dryness, mood changes, and reduced bone mineral density, should also be considered when determining treatment duration and the need for add-back therapy (Vercellini et al., 2018).

Despite these limitations, the findings indicate that postoperative GnRH agonist therapy may have a role in postoperative symptom management, particularly pain control. However, the evidence does not establish that leuprolide is superior to other postoperative hormonal treatments, and findings regarding recurrence and pregnancy should be interpreted cautiously rather than as definitive evidence of improved fertility or live birth. Clinical decisions should therefore consider disease characteristics, reproductive goals, previous treatment, tolerability, and patient preferences. Further randomized controlled trials with larger populations, standardized treatment regimens and outcome definitions, longer follow-up, and complete reporting of effect estimates with 95% confidence intervals are needed to strengthen the evidence and facilitate future quantitative synthesis.

CONCLUSION

The evidence suggests that postoperative GnRH agonist therapy, particularly leuprolide or leuprorelin acetate, may provide benefit for postoperative pain control in women with endometriosis, although the certainty of evidence remains limited. Evidence regarding recurrence is uncertain and insufficient to support a definitive conclusion on recurrence prevention, while findings on pregnancy outcomes are promising but remain insufficient to support clinical recommendations regarding improved fertility. Adverse effects should also be considered when evaluating treatment. Overall, the available evidence is heterogeneous and its certainty is low to moderate; therefore, further well-designed randomized controlled trials with standardized treatment regimens, outcome definitions, and longer follow-up are needed to establish the effectiveness and clinical role of postoperative GnRH agonist therapy.

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