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TREATMENT OF ENDOMETRIOSIS: AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSES WITH ASSESSMENT OF EVIDENCE OVERLAP

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ABSTRACT

Background: Endometriosis is a chronic inflammatory disease associated with pain, infertility, and impaired quality of life. Numerous systematic reviews and meta-analyses have evaluated available treatments but overlapping evidence and methodological heterogeneity limit interpretability.
Objective: To synthesize secondary evidence on endometriosis management using an umbrella review with explicit assessment of evidence overlap.
Methods: Systematic reviews with quantitative meta-analyses published between 2019 and 2026 were identified through PubMed. Methodological quality was assessed using AMSTAR 2. Evidence was synthesized narratively across therapeutic domains and overlap of primary studies was quantified using the Corrected Covered Area (CCA).
Results: Forty-nine systematic reviews were included. Overall, methodological quality was moderate to high. Evidence overlap was generally low but high in selected domains, particularly hormonal pretreatment before assisted reproductive technologies. Progestins and gonadotropin-releasing hormone modulators consistently reduce endometriosis-related pain. Surgical excision of ovarian endometriomas reduced recurrence but impaired ovarian reserve, while postoperative hormonal suppression reduced recurrence risk.
Conclusions: This umbrella review supports selected hormonal and surgical strategies for endometriosis management while highlighting evidence redundancy and key knowledge gaps.

KEYWORDS
Endometriosis, Umbrella, Systematic, Treatment, Overlap, CCA

CITATION

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1. Introduction

1.1 Clinical and Biological Relevance

Endometriosis is a chronic, estrogen-dependent inflammatory disease defined by the presence of endometrial-like tissue outside the uterine cavity [1]. It affects approximately 10% of women of reproductive age and up to 30–50% of those presenting with chronic pelvic pain or infertility [2]. The disease is associated with a wide range of symptoms, including dysmenorrhea, chronic pelvic pain, dyspareunia, bowel and urinary complaints, fatigue, and reduced quality of life [1]. In addition to pain-related morbidity, endometriosis is a major contributor to infertility and subfertility, further amplifying its personal, social, and economic burden [3].

From a biological perspective, endometriosis is a heterogeneous condition involving complex interactions between hormonal dysregulation, chronic inflammation, immune dysfunction, angiogenesis, neurogenesis, and altered pain processing [4]. Lesions vary widely in location, depth of infiltration, fibrotic component, and biological behavior, ranging from superficial peritoneal disease to ovarian endometriomas and deep infiltrating endometriosis (DIE) affecting pelvic organs such as the bowel, bladder, and ureters [5]. This heterogeneity contributes to variability in symptom severity, disease progression, and treatment response, complicating both clinical management and evidence generation.

Clinically, endometriosis is characterized by a chronic and often recurrent course [1]. Treatment goals typically include pain control, preservation or restoration of fertility, prevention of disease progression or recurrence, and improvement of quality of life. Management strategies therefore span multiple domains, including pharmacological therapies, surgical interventions, assisted reproductive technologies (ART), expectant management, and non-pharmacological or complementary approaches. Treatment selection must be individualized, taking into account disease phenotype, symptom profile, reproductive goals, treatment tolerability, and patient preferences [6].

1.2 Rationale for Umbrella Review

Over the past two decades, the volume of research on endometriosis management has expanded substantially, accompanied by a rapid proliferation of systematic reviews and meta-analyses across virtually all therapeutic domains. These include reviews of hormonal therapies (such as progestins, GnRH agonists and antagonists), surgical techniques for ovarian and deep infiltrating disease, postoperative and perioperative medical strategies, fertility-oriented interventions, and a growing body of literature on lifestyle, nutritional, and complementary therapies.

While this growth reflects increasing clinical and scientific interest, it has also resulted in a fragmented and highly overlapping secondary evidence base. Many systematic reviews address similar clinical questions, often drawing on partially or fully overlapping sets of primary studies. This redundancy can obscure true evidence strength, inflate perceived certainty, and lead to discordant conclusions when differences in methodology, inclusion criteria, or analytical approaches are not explicitly acknowledged.

Umbrella reviews offer a structured approach to synthesizing evidence across multiple systematic reviews and meta-analyses, allowing comparison across interventions and outcomes within a unified framework. However, the validity of umbrella-level conclusions depends critically on understanding the degree of overlap among included reviews. The Corrected Covered Area (CCA) provides a quantitative measure of overlap between reviews and is increasingly recognized as an essential tool for assessing redundancy and independence of evidence. Despite this, CCA is infrequently applied systematically in endometriosis research, particularly across broad therapeutic domains.

Given the clinical heterogeneity of endometriosis, the diversity of available treatments, and the methodological challenges posed by overlapping evidence, a comprehensive umbrella review that integrates clinical synthesis with explicit overlap assessment is warranted.

1.3 Objective

The primary objective of this umbrella review is to systematically synthesize and evaluate the existing systematic reviews and meta-analyses addressing the management of endometriosis across pharmacological, surgical, reproductive, and non-pharmacological interventions.

Secondary objectives are:

- To structure the available evidence according to key clinical domains, including pain management, fertility outcomes, disease recurrence, and quality of life.
- To quantify the degree of overlap among systematic reviews using the CCA within relevant sections.
- To contextualize the strength, consistency, and limitations of the evidence considering overlap, study design, and outcome heterogeneity.
- To identify areas of robust evidence, evidence gaps, and priorities for future research.

Through this approach, the review aims to provide clinicians, researchers, and guideline developers with a coherent, transparent, and methodologically informed overview of the current evidence base for endometriosis management.

2. Methods

2.1 Protocol and Reporting

This umbrella review was conducted in accordance with established methodological guidance for overviews of systematic reviews and meta-analyses. The reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [7], with adaptations relevant to umbrella review methodology. Where applicable, additional guidance for overlap assessment and synthesis of systematic reviews was applied.

A formal protocol was developed a priori, defining the objectives, eligibility criteria, outcomes of interest, and analytical framework, including assessment of overlap using the Corrected Covered Area (CCA). The protocol was not prospectively registered in an international database; however, all methodological decisions were prespecified and applied consistently throughout the review process.

2.2 Eligibility Criteria

Types of studies

This umbrella review included systematic reviews published within a predefined time frame, that reported at least one quantitative meta-analysis evaluating therapeutic interventions for endometriosis. Eligible reviews were required to describe a systematic search strategy, clearly defined inclusion criteria, and pooled effect estimates derived using formal meta-analytic methods.

As a single, predefined exception, one Cochrane systematic review without a completed meta-analysis was included. In this review, a quantitative synthesis was planned a priori but could not be performed because only one primary study fulfilled the eligibility criteria. Given the methodological rigor of the Cochrane process, transparent reporting, and clinical relevance of the research question, this review was retained and its findings were synthesized narratively.

All other systematic reviews without meta-analysis, as well as narrative reviews, scoping reviews, overviews, primary studies, conference abstracts, editorials, clinical guidelines, and commentaries were excluded.

Population

Women of reproductive age with a diagnosis of endometriosis, established by surgical, imaging, or clinical criteria, irrespective of disease phenotype (superficial peritoneal endometriosis, ovarian endometrioma, or deep infiltrating endometriosis).

Interventions

All therapeutic strategies for endometriosis management were considered eligible, including:

- Pharmacological treatments
- Surgical interventions
- Combined medical–surgical approaches

- Assisted reproductive technologies (ART)
- Expectant management
- Non-pharmacological, lifestyle, and complementary therapies

Outcomes

Eligible systematic reviews reported at least one clinically relevant outcome, including:

- Endometriosis-associated pain (e.g. dysmenorrhea, dyspareunia, chronic pelvic pain)
- Quality of life and patient-reported outcomes
- Fertility and reproductive outcomes
- Disease progression or recurrence
- Adverse events or treatment discontinuation

2.3 Information Sources and Search Strategy

A comprehensive literature search was conducted in PubMed to identify relevant systematic reviews and meta-analyses. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords related to endometriosis, treatment, and systematic review methodology.

The initial search was performed without filters. Subsequently, predefined filters were applied, including publication date, language (English), and article type (systematic reviews and meta-analyses) (Fig.1).

Supplementary Material – Search Strategy

Database: PubMed

Search strategy: ("Endometriosis"[Mesh] OR endometriosis[tiab]) AND (pathogenesis[tiab] OR pathophysiology[tiab] OR etiology[tiab] OR mechanism*[tiab] OR immunolog*[tiab] OR inflamm*[tiab] OR angiogenesis[tiab] OR neurogenesis[tiab] OR epigenetic*[tiab] OR genetic*[tiab] OR microbiome[tiab] OR therapy[tiab] OR treatment[tiab] OR management[tiab] OR surgery[tiab] OR "hormonal therapy"[tiab] OR progestin*[tiab] OR "GnRH antagonist*"[tiab] OR "GnRH agonist*"[tiab])

Filters applied:

- Article type: Clinical Trial, Observational Study, Randomized Controlled Trial, Systematic Review
- Text availability: Free full text
- Species: Humans
- Language: English
- Publication date: 1 January 2019 to 6 January 2026

The search was initially performed without filters. Filters were subsequently applied to restrict results to recent, human, English-language publications relevant to the objectives of this umbrella review, in accordance with PRISMA 2020 recommendations.

Fig. 1. *Search Strategy*

2.4 Study Selection

All records identified through the search were imported into a reference management software, and duplicate records were removed. Study selection was performed in two stages.

First, titles and abstracts were screened independently by two reviewers to exclude clearly irrelevant records. Second, full texts of potentially eligible articles were retrieved and assessed independently for inclusion based on the predefined eligibility criteria.

Disagreements at either stage were resolved through discussion and, when necessary, consultation with a third reviewer. Reasons for exclusion at the full-text stage were documented. The study selection process is summarized in a PRISMA flow diagram.

2.5 Data Extraction

Data extraction was performed independently by two reviewers using a standardized, piloted extraction form. Extracted data included:

- Bibliographic details (author, year, journal)

- Review objectives and scope
- Number and type of included primary studies
- Total sample size
- Interventions and comparators
- Outcomes assessed
- Methods of synthesis (qualitative, pairwise meta-analysis, network meta-analysis)
- Key findings and effect estimates
- Authors' conclusions
- Limitations noted by the review authors

For overlap assessment, detailed lists of included primary studies were extracted from each systematic review whenever available. Discrepancies in extracted data were resolved by consensus.

2.6 Methodological Quality Assessment

The methodological quality of included systematic reviews was assessed using the AMSTAR 2 instrument [8]. AMSTAR 2 evaluates 16 domains related to protocol registration, literature search adequacy, risk-of-bias assessment, appropriateness of meta-analytic methods, and consideration of publication bias.

Each review was rated as having high, moderate, low, or critically low confidence in the results, according to AMSTAR 2 guidance. Quality assessment was performed independently by two reviewers, with disagreements resolved through discussion.

Methodological quality assessments were used to contextualize findings but did not serve as exclusion criteria.

2.7 Assessment of Overlap of Primary Studies

To quantify overlap of primary studies across included systematic reviews, the Corrected Covered Area (CCA) [9] was calculated for relevant sections of the umbrella review.

CCA values were interpreted using established thresholds:

- 0–5%: slight overlap
- 6–10%: moderate overlap
- 11–15%: high overlap
- 15%: very high overlap

CCA was calculated separately for major domains to avoid artificial inflation of overlap due to clinically heterogeneous evidence bases. Results were reported numerically, graphically, and narratively.

2.8 Data Synthesis

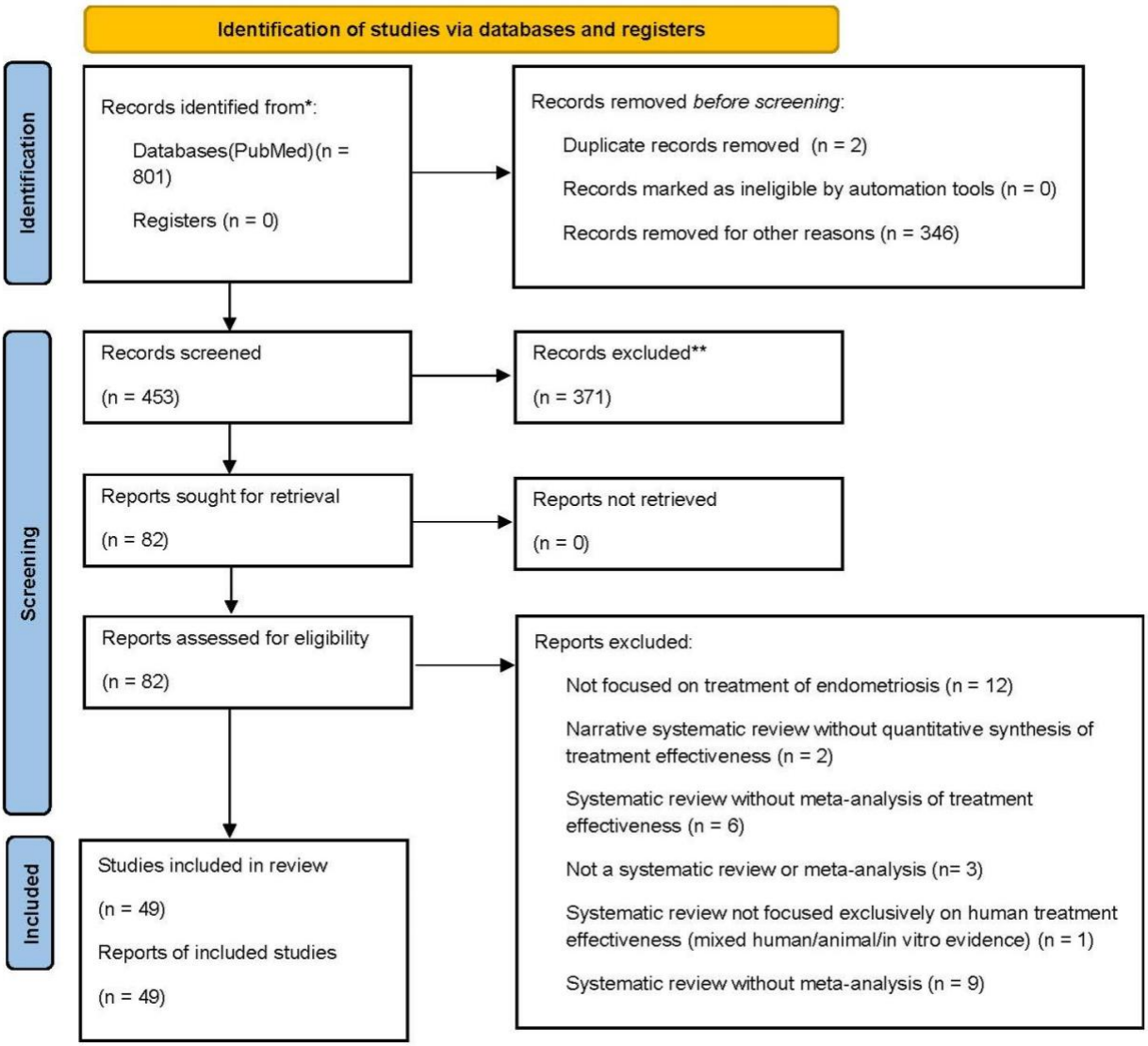
Given the heterogeneity of interventions, outcomes, and review methodologies, a primarily narrative synthesis was undertaken. Findings were organized by therapeutic domain and outcome category, with emphasis on consistency of results, magnitude of effects, and certainty of evidence.

Quantitative results from meta-analyses and network meta-analyses were summarized descriptively; no de novo meta-analyses were performed. Where multiple reviews addressed the same question, results were interpreted in light of methodological quality and degree of overlap.

Overlap-adjusted interpretation was applied throughout the synthesis, particularly in domains with high or very high CCA values. Evidence gaps, inconsistencies, and areas requiring further primary research were identified.

3. Results

3.1 Study Selection



A total of 801 records were identified through database searching (PubMed), with no additional records retrieved from study registers. After removal of 2 duplicate records and exclusion of 346 records for other reasons prior to screening, 453 records remained for title and abstract screening.

During the screening phase, 371 records were excluded based on title and abstract review. The remaining 82 reports were sought for full-text retrieval, all of which were successfully obtained and assessed for eligibility.

Of the 82 full-text articles assessed, 33 reports were excluded (Table 1)

Ultimately, 49 systematic reviews with meta-analyses met the predefined eligibility criteria and were included in the umbrella review. Each included review contributed a single report, resulting in 49 reports of included studies.

Table. 1. Excluded Studies

DOI	Title	Reason for Exclusion
10.1007/s11701-025-02973-3	The Hugo™ RAS system in gynecologic robotic surgery: a systematic review of current applications	Not focused on treatment of endometriosis
10.3389/fendo.2025.1613334	Endometriosis-associated infertility: Multi-omics insights into pathogenesis and precision therapeutics.	Not focused on treatment of endometriosis
10.1007/s00404-025-08137-w	Endometriosis as a risk factor: impact on IVF outcomes and reproductive parameters: a systematic review and meta-analysis.	Not focused on treatment of endometriosis
10.1097/MD.0000000000041692	Impact of combining laparoscopy with traditional Chinese medicine on oxidative stress in endometriosis-related infertility: A systematic review and meta-analysis.	Not focused on treatment of endometriosis
10.1007/s00404-025-07957-0	The efficacy of progestins in managing pain associated with endometriosis, fibroids and pre-menstrual syndrome: a systematic review.	Not focused on treatment of endometriosis
10.1186/s12958-024-01273-z	Molecular regulation of DNA damage and repair in female infertility: a systematic review.	Not focused on treatment of endometriosis
10.1080/13625187.2024.2373143	Assessing the impact of hormonal contraceptive use on menstrual health among women of reproductive age - a systematic review.	Not focused on treatment of endometriosis
10.1007/s00384-024-04669-w	Role of robot-assisted laparoscopy in deep infiltrating endometriosis with bowel involvement: a systematic review and application of the IDEAL framework.	Not focused on treatment of endometriosis
10.26355/eurrev_202405_36182	Effects of herbal compounds on various aspects of endometriosis treatment: a systematic review.	Narrative systematic review without quantitative synthesis of treatment effectiveness
10.1093/bjr/tqae075	Safety and efficacy of cryoablation of soft-tissue tumours: a systematic review.	Not focused on treatment of endometriosis
10.1055/s-0043-1772596	Sexual Function of Patients with Deep Endometriosis after Surgical Treatment: A Systematic Review.	Systematic review without meta-analysis of treatment effectiveness
10.3390/ijms242115967	Diminished Ovarian Reserve in Endometriosis: Insights from In Vitro, In Vivo, and Human Studies-A Systematic Review.	Not focused on treatment effectiveness
10.5603/gpl.97573	The effect of two anti-inflammatory dietary components, omega-3 and resveratrol, on endometriosis.	Systematic review without meta-analysis of treatment effectiveness
10.1136/bmjopen-2022-063188	Substituting a randomised placebo control group with a historical placebo control in an endometriosis pain trial: a case study re-evaluating trial data using historical control data from another trial.	Not a systematic review or meta-analysis
10.1016/j.ctim.2023.102963	Acupuncture and moxibustion for endometriosis: A systematic review and analysis.	Systematic review without meta-analysis of treatment effectiveness
10.1002/npr2.12348	Pain-focused psychological interventions in women with endometriosis: A systematic review.	Systematic review without meta-analysis of treatment effectiveness
10.1186/s12958-022-01051-9	Effects of vitamin D supplementation in endometriosis: a systematic review.	Systematic review not focused exclusively on human treatment effectiveness (mixed human/animal/in vitro evidence)

10.3390/medicina58060792	The Use of near Infra-Red Radiation Imaging after Injection of Indocyanine Green (NIR-ICG) during Laparoscopic Treatment of Benign Gynecologic Conditions: Towards Minimalized Surgery. A Systematic Review of Literature.	Not focused on treatment of endometriosis
10.1111/aogs.14379	Different segmental resection techniques and postoperative complications in patients with colorectal endometriosis: A systematic review.	Systematic review without meta-analysis
10.3390/medicina58040552	Update of Robotic Surgery in Benign Gynecological Pathology: Systematic Review.	Systematic review without meta-analysis of treatment effectiveness
10.1590/S0004-2803.202100000-97	SURGICAL TECHNIQUES FOR THE TREATMENT OF RECTAL ENDOMETRIOSIS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES.	Systematic review without meta-analysis
10.1186/s12905-021-01500-4	Effect of physical activity and exercise on endometriosis-associated symptoms: a systematic review.	Systematic review without meta-analysis
10.1111/aogs.14169	Impact of exercise on pain perception in women with endometriosis: A systematic review.	Systematic review without meta-analysis
10.1002/med.21802	Pharmaceuticals targeting signaling pathways of endometriosis as potential new medical treatment: A review.	Narrative systematic review without quantitative synthesis of treatment effectiveness
10.1007/s43032-020-00418-w	Effectiveness of Dietary Interventions in the Treatment of Endometriosis: a Systematic Review.	Systematic review without meta-analysis
10.1111/aogs.13971	Indocyanine green in the surgical management of endometriosis: A systematic review.	Systematic review without meta-analysis of treatment effectiveness
10.1016/j.jogc.2019.08.004	Surgical Outcomes in Patients With Endometriosis: A Systematic Review.	Systematic review without meta-analysis
10.1016/j.aohep.2019.08.006	Diagnosis, surgical treatment and postoperative outcomes of hepatic endometriosis: A systematic review.	Systematic review without meta-analysis
10.1002/14651858.CD011422.pub2	Robot-assisted surgery in gynaecology.	Not focused on treatment effectiveness
10.1016/j.rbmo.2018.11.021	Ovarian stimulation and endometriosis progression or recurrence: a systematic review.	Systematic review without meta-analysis
10.3389/fendo.2025.1612899	Ethanol sclerotherapy for management of endometriomas: an overview of systematic reviews	Not a systematic review or meta-analysis
10.3390/ijms25021337	The Efficacy and Safety of Transvaginal Ethanol Sclerotherapy in the Treatment of Endometrial Cysts—A Systematic Review	Systematic review without meta-analysis
10.2147/DDDT.S315726	A Systematic Review of Systematic Reviews on the Use of Aromatase Inhibitors for the Treatment of Endometriosis: The Evidence to Date	Not a systematic review or meta-analysis

3.2 Characteristics of Included Reviews

A total of 49 systematic reviews with meta-analyses, published between 1 January 2019 and 6 January 2026, were included in this umbrella review (Table 2). This publication window was selected to capture contemporary evidence reflecting current diagnostic standards, pharmacological options, surgical techniques, and reproductive technologies in endometriosis management.

The included reviews addressed a broad spectrum of therapeutic strategies for endometriosis, encompassing pharmacological treatments, surgical management, combined medical–surgical approaches, assisted reproductive technologies, expectant management, and non-pharmacological or complementary interventions. Several reviews focused on specific disease phenotypes, such as ovarian endometrioma or deep infiltrating endometriosis, while others included mixed populations irrespective of lesion location.

Pain-related outcomes, including dysmenorrhea, dyspareunia, and chronic pelvic pain, were the most frequently reported endpoints across reviews. Additional commonly assessed outcomes included quality of life, recurrence or progression of disease, fertility and reproductive outcomes, and treatment-related adverse events. Outcome definitions and measurement instruments varied substantially between reviews, contributing to clinical and methodological heterogeneity.

The majority of included systematic reviews synthesized evidence from randomized controlled trials, although many also incorporated non-randomized comparative studies or prospective cohort data, particularly in surgical and assisted reproduction–related domains. Sample sizes of pooled analyses varied widely across reviews, ranging from meta-analyses of a small number of trials to large-scale syntheses incorporating several thousand participants.

Table. 2. Included Studies

Bibliographic details (author, year, journal)	**Review objectives and scope**	**Total sample size**	**Key findings / effect estimates**
Xie, 2025, Frontiers in Endocrinology	To evaluate the impact of relugolix on endometriosis-associated pain and health-related quality of life measured by EHP-30	Approximately 1,038 participants contributing to pooled analyses	Relugolix improved EHP-30 pain scores overall (MD 6.77, 95% CI 3.15–10.39; I^2 90.7%); superior to placebo (MD 15.31) and placebo-matched CT (MD 8.86) but less effective than leuprorelin (MD −3.79); increased pain responders (OR 3.25); significant improvements in emotional well-being (MD 5.71), social support (MD 6.40), and self-image (MD 6.00)
Gu, 2025, BMC Women's Health	To compare the short-term effects of dienogest versus oral contraceptives on pain and quality of life in women with endometriosis	714 participants (356 dienogest; 358 OCPs)	Dienogest improved overall VAS pain vs OCPs (SMD −1.46, 95% CI −2.33 to −0.59); superior to mifepristone and Yasmin; inferior to OCPs for pelvic pain (SMD 0.42) and dyspareunia (SMD 0.70); improved several QoL domains (EHP-5, EHP-30 subscales, SF-12 PCS); similar overall safety, with OCPs increasing risk of weight gain and hand numbness
Yang, 2025, Medicine	To evaluate the efficacy of acupuncture as monotherapy for endometriosis-related pain compared with non-acupuncture interventions	535 participants	Acupuncture significantly reduced pain intensity (MD −1.67, 95% CI −2.85 to −0.49); improved cure rate (OR 2.61, 95% CI 1.38–4.95); no overall effect on CA125 (MD −1.46, 95% CI −20.69 to 17.76); borderline effect on overall effective rate (OR 2.18, P=0.05)
Zhou, 2025, PLOS ONE	To evaluate the efficacy of vitamin D supplementation in reducing pain associated with primary dysmenorrhea and endometriosis based on registered randomized controlled trials	510 participants total (primary dysmenorrhea n=362; endometriosis n=148)	Vitamin D reduced pain severity on VAS overall (MD −1.12, 95% CI −2.16 to −0.07; I^2 81%); significant benefit in primary dysmenorrhea but not endometriosis; reduced pain duration in one study (MD −1.56); no significant effect on pain medication use

Riemma, 2025, International Journal of Gynecology & Obstetrics	To evaluate whether hormone pre-treatment with GnRH agonists or progestins improves reproductive outcomes in women with endometriosis undergoing ART	2,087 women	No significant differences between hormone pre-treatment strategies and no treatment for CPR or LBR; no treatment ranked highest for LBR (SUCRA 50.0%); long and ultralong GnRH agonists showed higher SUCRA for implantation rate without translating into higher CPR or LBR
Vallée, 2025, Scientific Reports	To compare pregnancy rates after colorectal resection versus other surgical techniques (rectal shaving, disc excision, expectant management) in women with deep infiltrating rectal endometriosis	3,248 patients total; pregnancy data available for 2,131 patients	Colorectal resection associated with lower pregnancy rate vs other techniques (OR 0.64, 95% CI 0.52–0.79; I^2=35%); lower vs shaving (OR 0.51, 95% CI 0.36–0.73); no significant difference vs disc excision (OR 0.65, 95% CI 0.37–1.13); no significant difference in spontaneous pregnancy rates
Yang, 2025, Archives of Gynecology and Obstetrics	To compare the effectiveness and safety of different acupuncture-related therapies (alone or combined with pharmacotherapy) for symptomatic endometriosis using a network meta-analysis	1,776 patients	Ear electroacupuncture ranked highest for CER (SUCRA 83.0%); acupuncture-related therapies superior to conventional treatment for CER (OR 2.87, 95% CI 1.90–4.82); VAS significantly reduced vs conventional treatment (MD −0.73, 95% CI −0.93 to −0.54); limited and mostly mild adverse events reported
Darici, 2025, Acta Obstetricia et Gynecologica Scandinavica	To compare gastrointestinal function outcomes following radical (segmental resection) versus conservative colorectal surgery for deep endometriosis	1,846 patients overall; 13 studies pooled for meta-analysis	Conservative surgery associated with lower postoperative constipation (OR 2.02 favoring conservative) and fewer stools >3/day (OR 2.67); higher postoperative GIQLI vs segmental resection (MD −5.76 favoring conservative); no differences in gas/stool incontinence, defecation pain, LARS; no significant differences when comparing pre–post changes in GIQLI, KESS or Wexner scores
Xie, 2025, PLOS ONE	To assess the effectiveness and safety of physical activity and exercise interventions on symptoms and quality of life in women with endometriosis	251 women	Exercise improved QoL domains of pain (WMD −20.22), control and powerlessness (WMD −23.07), and emotional well-being (WMD −14.35) vs controls; narrative evidence suggests benefits for pain, mental health, pelvic floor dysfunction, and bone density, but meta-analysis feasible only for two trials
Huang, 2025, Journal of Ethnopharmacology	To compare the efficacy and safety of ten Chinese patent medicines combined with conventional therapies for endometriosis using a Bayesian network meta-analysis	16,198 participants	All CPMs improved total effective rate and VAS pain vs conventional therapy; SZC ranked highest for total effective rate (RR 5.51 vs hormone therapy); DFP most effective for pain reduction (MD −2.10 vs hormone therapy); XC showed greatest CA125 reduction (MD −16.21); several CPMs associated with lower adverse event risk
Kalra, 2024, Cochrane Database of Systematic Reviews	To evaluate the safety and efficacy of laparoscopic excision (cystectomy) versus laparoscopic drainage and ablation for ovarian endometrioma	578 women	Excision reduced recurrence of dysmenorrhoea (OR 0.25), dyspareunia (OR 0.09), endometrioma recurrence (OR 0.17), and need for further surgery (OR 0.16); no clear difference in spontaneous pregnancy rates (OR 1.27); little or no difference in AMH; AFC lower after excision

Chen, 2024, Archives of Gynecology and Obstetrics	To evaluate the clinical efficacy of acupuncture as monotherapy for relieving endometriosis-related pain	793 patients	Acupuncture significantly reduced pain severity (SMD −1.10, 95% CI −1.45 to −0.75); improved response rate (RR 1.25, 95% CI 1.09–1.44); reduced CA125 (SMD −0.62, 95% CI −1.15 to −0.08); reduced pelvic mass volume and improved QoL; no significant reduction in 1-year recurrence
Veth, 2024, Fertility and Sterility	To determine the anatomical recurrence rate of surgically treated ovarian endometrioma in women not receiving postoperative hormonal treatment	5,254 women included in the systematic review; 1,204 women included in meta-analyses	Weighted mean recurrence rates were 4% at 3 months (n=125), 14% at 6 months (n=229), 17% at 12 months (n=729), and 27% at 24 months (n=313)
Viviano, 2024, Reproductive BioMedicine Online	To assess the efficacy and safety of GnRH antagonists for endometriosis-associated pain, with specific consideration of add-back therapy	Approximately 2,000 participants across included trials	GnRH antagonists significantly reduced dysmenorrhoea (OR −13.12) and non-menstrual pelvic pain (OR −3.08) vs placebo; add-back therapy maintained pain efficacy while reducing hypo-oestrogenic adverse effects; no significant difference between relugolix alone vs with add-back for most pain outcomes
Bandini, 2024, Acta Obstetricia et Gynecologica Scandinavica	To evaluate the natural history of untreated deep endometriosis and the effect of hormonal suppression on lesion progression over time	1,015 patients total (285 untreated; 730 hormonally treated)	Untreated lesions progressed in 21.4% of patients (95% CI 6.8–40.8%; I^2 90.5%); progression during hormonal therapy was 12.4% (95% CI 9.0–16.1%; I^2 0%); hormonal treatment reduced odds of progression vs no treatment (OR 0.52, 95% CI 0.41–0.66); mean lesion volume decreased by 0.87 cm^3 (−28.5%) with hormonal therapy
Bayu, 2024, PLOS ONE	To assess the efficacy of combined vitamin C and vitamin E antioxidant supplementation for reducing endometriosis-associated pain	338 women	Vitamin C+E increased likelihood of pain reduction vs placebo for chronic pelvic pain (RR 7.30, 95% CI 3.27–16.31), dysmenorrhea (RR 1.96, 95% CI 1.25–3.07), and dyspareunia (RR 5.08, 95% CI 2.10–12.26)
Liang, 2024, Frontiers in Endocrinology	To compare fertility outcomes of first-line surgery versus first-line assisted reproductive technology (ART) in women with deep infiltrating endometriosis	899 women	Pregnancy rate per patient (OR 1.47, 95% CI 0.59–3.63), pregnancy rate per cycle (OR 1.16, 95% CI 0.45–2.99), and live birth per patient (OR 1.66, 95% CI 0.56–4.91) were comparable between surgery and ART; when complete and incomplete surgery were pooled, surgery was associated with higher pregnancy rate per patient (OR 1.63, 95% CI 1.11–2.40)
Qing, 2024, BMC Pregnancy and Childbirth	To evaluate whether adjuvant gonadotropin-releasing hormone agonist (GnRH-a) therapy after conservative surgery improves pregnancy outcomes in women with endometriosis	2,485 patients	GnRH-a modestly increased pregnancy rate after surgery (RR 1.20, 95% CI 1.02–1.41) and shortened time to pregnancy (SMD −1.17, 95% CI −1.70 to −0.64); no significant differences in live birth, miscarriage, ectopic pregnancy, multiple pregnancy, recurrence, or adverse reactions
Paffoni, 2024, JAMA Network Open	To evaluate whether a history of endometriosis is associated with live birth rates and other ART outcomes in recipients of oocyte donation IVF cycles	Published studies: 7,212 oocyte donation cycles; registry data: 162,082 cycles (SART 137,182; HFEA 24,900)	Meta-analysis of published studies showed no significant difference in live birth rate (adjusted OR 0.54, 95% CI 0.19–1.57); pooled registry data showed a modest but statistically significant reduction in live birth rate in women with endometriosis (adjusted OR 0.89, 95% CI 0.81–0.97)

Keukens, 2024, European Journal of Obstetrics & Gynecology and Reproductive Biology	To evaluate the effects of surgery and/or medication on pain and quality of life in women with ovarian endometrioma	7,148 women in the systematic review; 4,556 women in meta-analyses	Both surgery and medication reduced VAS scores and proportions of all pain types over time; surgery plus medication reduced pain more than surgery alone but not more than medication alone; highest VAS reduction observed after medication; QoL improved after medication but was unchanged or worsened after surgery plus medication
Gao, 2024, Alternative Therapies in Health and Medicine	To evaluate the impact of different hemostasis methods used during laparoscopic cystectomy for ovarian endometriomas on ovarian reserve function	1,557 patients	Suture hemostasis associated with higher postoperative AFC compared with electrocoagulation and ultrasonic scalpel (overall MD ~1.60); AMH levels showed no consistent significant differences between methods; electrocoagulation and ultrasonic scalpel had comparable effects
Csirzó, 2024, Surgical Endoscopy	To compare the effectiveness and safety of robot-assisted laparoscopy versus conventional laparoscopy in endometriosis surgery	2,021 patients (1,009 conventional laparoscopy; 1,012 robot-assisted laparoscopy)	No significant differences between approaches for intra- or postoperative complications, conversion rates, hospital stay, or blood loss; robot-assisted laparoscopy associated with longer operative time (MD 28.09 min) and operating room time (MD 51.39 min)
Ronsini, 2023, Medicina	To compare clinical and fertility outcomes of sclerotherapy versus surgery for the management of ovarian endometrioma	1,642 patients overall; 370 patients included in comparative meta-analyses	Surgery showed a non-significant lower recurrence rate vs sclerotherapy (OR 0.87, 95% CI 0.18–4.32); pregnancy rate was non-significantly higher after surgery vs sclerotherapy (OR 0.47, 95% CI 0.21–1.09); sclerotherapy success rates mostly >80% with low complication rates
Zheng, 2023, Reproductive Biology and Endocrinology	To assess the effects of antioxidant vitamin supplementation on endometriosis-related pain and oxidative stress markers, with secondary evaluation of fertility outcomes	589 patients	Antioxidant vitamin supplementation significantly reduced endometriosis-related pain overall (chronic pelvic pain SMD −1.79); vitamin E (±C) showed consistent benefit, whereas vitamin D effects were not statistically significant vs placebo; oxidative stress markers (MDA, inflammatory cytokines) decreased; no clear improvement in pregnancy rates
Shao, 2023, Journal of Ovarian Research	To evaluate the impact of dienogest (DNG) pretreatment versus non-DNG pretreatment on IVF-ET outcomes in women with endometriosis	568 women	Overall, DNG showed no significant difference vs non-DNG for clinical pregnancy (RR 1.26) or live birth (RR 1.23); compared with non-hormonal treatment, DNG significantly increased clinical pregnancy (RR 2.06) and live birth rates (RR 2.14); outcomes were inferior to long GnRH-a but superior to no treatment, particularly in fresh embryo transfers
Zheng, 2023, Medicine	To evaluate the efficacy and safety of different subsequent hormonal therapies after fertility-preserving surgery for endometriosis	4,576 patients	Dienogest and LNG-IUS ranked highest for symptom relief and recurrence prevention; dienogest ranked highest for pregnancy rate; all active treatments reduced recurrence vs placebo but increased adverse reactions vs placebo

Veth, 2023, Cochrane Database of Systematic Reviews	To assess the effectiveness and safety of gonadotropin-releasing hormone analogues (GnRHas) for pain relief and bone mineral density outcomes in women with symptomatic endometriosis	7,355 women	GnRHas probably reduce overall pain compared with placebo and progestogens but are associated with greater bone mineral density loss compared with gestrinone or GnRHas plus calcium-regulating agents; adverse effects (e.g. hot flushes) are more common; evidence certainty mostly low or very low
Muzii, 2023, Reproductive Sciences	To determine whether postoperative dienogest reduces disease and pain recurrence after endometriosis surgery compared with placebo/no therapy or alternative hormonal treatments	1,668 patients	Dienogest significantly reduced cyst recurrence vs placebo/no therapy (OR 0.14, 95% CI 0.07–0.26); no significant difference vs GnRH-a for recurrence (OR 0.81); trend toward pain reduction at 6 months vs placebo; compared with GnRH-a, dienogest increased spotting (OR 17.84) and weight gain (OR 3.37) but reduced hot flushes (OR 0.08)
Xin, 2023, Archives of Gynecology and Obstetrics	To compare the efficacy and safety of different oral non-peptide GnRH antagonists for moderate-to-severe endometriosis-associated pain	2,732 women	Most oral GnRH antagonists significantly reduced pain vs placebo at 12 weeks; elagolix 400 mg ranked highest for pelvic pain and dyspareunia; relugolix 40 mg most reduced analgesic use; safety outcomes were dose-dependent, with higher doses associated with more TEAEs and spinal BMD loss (notably elagolix 250 mg)
Mitchell, 2022, BMC Women's Health	To evaluate the effectiveness and safety of progestins for symptomatic pain management in women with endometriosis	≈5,400 women (range across studies 25–3,356; exact pooled n not explicitly stated)	Progestins significantly reduced pelvic pain vs placebo (SMD −0.61); single-arm analyses showed substantial pain reduction (MD −2.60); no clear differences between progestin types; adverse effects were generally mild with low discontinuation rates
Zhang, 2022, Fertility and Sterility	To compare the impact of cystectomy versus ablation for ovarian endometrioma on ovarian reserve assessed by antral follicle count (AFC) and anti-Müllerian hormone (AMH)	294 patients	Both procedures significantly reduced AMH; cystectomy caused a greater postoperative reduction in AFC than ablation (postoperative AFC MD −1.33, 95% CI −2.15 to −0.51); at 6 months, AFC significantly declined after cystectomy but not after ablation
Yan, 2022, Fertility and Sterility	To assess and compare the efficacy and safety of different doses and types of oral GnRH antagonists for endometriosis-associated pain	2,796 women	All oral GnRH antagonists significantly reduced pain vs placebo with clear dose–response effects; highest efficacy observed with elagolix 400 mg and linzagolix 75–200 mg; higher doses were associated with increased adverse events and bone mineral density loss
Ma, 2022, Computational Intelligence and Neuroscience	To compare the efficacy of uterine artery embolization (UAE) with traditional treatments for endometriosis	524 patients	UAE significantly reduced serum CA125 levels (SMD −0.85, 95% CI −1.12 to −0.59) and dysmenorrhea VAS scores (SMD −1.86, 95% CI −2.21 to −1.50) compared with controls; no significant differences in total effective rate or sex hormone levels
Fraga, 2022, Revista Brasileira de Ginecologia e Obstetrícia	To evaluate the impact of surgical treatment for deep infiltrating endometriosis on pelvic floor disorders and sexual function	346 women	Surgery was associated with improvement in dyspareunia (MD −0.82, 95% CI −1.05 to −0.59) and fecal incontinence/constipation scores (KESS MD −1.63; Wexner MD −0.25); gastrointestinal quality of life improved (GIQLI MD +26.56); no comparative data available for urinary incontinence or pelvic organ prolapse

Dong, 2021, Annals of Palliative Medicine	To evaluate the efficacy and safety of traditional Chinese medicine (TCM) compound therapy for infertility caused by endometriosis	1,071 women	TCM compound significantly improved pregnancy rate (OR 1.94, 95% CI 1.50–2.50) and effective rate (OR 1.26, 95% CI 1.00–1.60), and reduced abortion rate (OR 0.16, 95% CI 0.06–0.48); no significant differences in adverse reactions or LH/E2 levels
Gibbons, 2021, Cochrane Database of Systematic Reviews	To determine the effectiveness and safety of postoperative levonorgestrel-releasing intrauterine device (LNG-IUD) for pain relief and quality-of-life outcomes in women with symptomatic endometriosis	157 women	Meta-analysis was largely not possible; individual trials suggested possible improvement in dysmenorrhea, quality of life, and satisfaction with LNG-IUD vs expectant management, but no clear benefit vs GnRH-a; evidence certainty very low
Moreno-Sepulveda, 2022, JBRA Assisted Reproduction	To assess the effect of laparoscopic surgery for ovarian endometrioma on ovarian reserve measured by anti-Müllerian hormone (AMH) levels at different postoperative time points	4,374 women	Endometrioma surgery significantly reduced AMH in the short, medium, and long term vs baseline (MD −1.31 to −1.62); no significant recovery from short to long term; greater AMH decline with bilateral disease and cysts >7 cm; bipolar energy and cystectomy caused larger AMH reductions than laser/ablation or non-thermal hemostasis
Grammatis, 2021, Cochrane Database of Systematic Reviews	To determine the effectiveness and safety of pentoxifylline for the management of endometriosis-associated pain and infertility	415 women	No studies reported live birth or overall pain; effect on clinical pregnancy rate vs placebo uncertain (RR 1.38, 95% CI 0.91–2.10; very low certainty); uncertain effects on miscarriage and recurrence; no data on adverse events
van Hoesel, 2021, Cochrane Database of Systematic Reviews	To evaluate the effectiveness and safety of selective oestrogen receptor modulators (SERMs) for the management of endometriosis	93 women	The single RCT did not report pain relief directly; raloxifene was associated with earlier return of pelvic pain vs placebo (P=0.03); no clear differences in adverse events; mental health QoL favored placebo at 12 months; effects on recurrence uncertain
Casals, 2021, Journal of Minimally Invasive Gynecology	To assess whether surgery for deep infiltrating endometriosis (DIE) before IVF improves reproductive outcomes compared with IVF without prior surgery	≈493 women included in meta-analyses (total across all included studies larger but variably reported)	Surgery before IVF significantly increased pregnancy rate per patient (OR 1.84, 95% CI 1.28–2.64), pregnancy rate per cycle (OR 1.84, 95% CI 1.26–2.70), and live birth rate per patient (OR 2.22, 95% CI 1.42–3.46); benefit observed in DIE with and without bowel involvement
Chen, 2020, Cochrane Database of Systematic Reviews	To evaluate the effectiveness of medical hormonal suppression given before and/or after conservative surgery for endometriosis in reducing pain and disease recurrence and improving pregnancy rates	3,378 women	Postsurgical hormonal therapy may reduce pain recurrence (RR 0.70) and disease recurrence (RR 0.30–0.88) and probably increases pregnancy rates (RR 1.19); evidence for presurgical therapy is very uncertain; no clear benefit for presurgical vs postsurgical timing
Bafort, 2020, Cochrane Database of Systematic Reviews	To assess the effectiveness and safety of laparoscopic surgery for pain and infertility associated with endometriosis	1,563 women	Laparoscopic surgery probably increases viable intrauterine pregnancy rates compared with diagnostic laparoscopy (OR 1.89, 95% CI 1.25–2.86); effects on overall pain and quality of life are uncertain; no data on live birth; adverse events insufficiently reported
Zakhari, 2021, Human Reproduction Update	To evaluate whether postoperative hormonal suppression reduces endometriosis recurrence and pain after conservative surgery	2,137 women	Postoperative hormonal suppression significantly reduced recurrence risk (RR 0.41, 95% CI 0.26–0.65) and improved pain scores (SMD −0.49); consistent benefit for CHC and LNG-IUS; effects for progestins and GnRH agonists trended toward benefit but were less certain

Nankali, 2020, Health and Quality of Life Outcomes	To evaluate the effect of unilateral versus bilateral laparoscopic surgery for endometriosis on ovarian reserve measured by AMH at 3 and 6 months	≈1,300 women (exact pooled n not explicitly reported; varies by unilateral/bilateral subgroup)	Both unilateral and bilateral laparoscopic surgery significantly reduced AMH at 3 and 6 months; AMH decline was greater after bilateral surgery and increased further at 6 months compared with 3 months
Bendifallah, 2020, Journal of Minimally Invasive Gynecology	To compare postoperative complications and surgical outcomes of different colorectal surgical techniques for deep infiltrating endometriosis	17,495 patients	Rectal shaving was associated with significantly lower risk of rectovaginal fistula (OR 0.19 vs disc excision; OR 0.26 vs segmental resection) and leakage (OR 0.22 vs disc excision); disc excision had lower risk of anastomotic stenosis than segmental resection (OR 0.15); no significant difference between disc excision and segmental resection for fistula or leakage
Wattanayingcharoenchai, 2021, BJOG	To compare and rank postoperative hormonal regimens for preventing endometrioma recurrence after ovarian cystectomy	3,764 women (RCTs n=675; cohorts n=3,089)	Long-term hormonal therapy reduced recurrence vs expectant management; in cohort NMA LNG-IUS ranked highest, followed by dienogest and continuous OC; RCT NMA showed no statistically significant differences between regimens, though GnRHa+LNG-IUS ranked highest
Miller, 2020, Scientific Reports	To compare the efficacy and safety of conservative endometriosis surgery with versus without adjunctive presacral neurectomy (PN) for chronic endometriosis-related midline pelvic pain	503 women (250 PN; 253 control)	Adjunctive PN significantly reduced treatment failure compared with surgery alone (RR 0.43, 95% CI 0.30–0.60); benefit persisted in RCT-only analyses; PN increased postoperative constipation risk (12.5% vs 0%) but not operative complications or reoperation
Hodgson, 2020, Fertility and Sterility	To compare the effectiveness of different interventions for endometriosis-related infertility	2,245 women in network meta-analysis (36 trials identified overall)	Compared with placebo, surgical laparoscopy alone (OR 1.63, 95% CI 1.13–2.35) and GnRH agonist alone (OR 1.68, 95% CI 1.07–2.46) increased odds of clinical pregnancy; lipiodol and surgery plus pentoxifylline ranked highest but based on single small trials; evidence for live birth and adverse events insufficient
Georgiou, 2019, Cochrane Database of Systematic Reviews	To determine the effectiveness and safety of long-term GnRH agonist therapy (≥3 months) before IVF/ICSI compared with no pretreatment or other pretreatments in women with endometriosis	640 women	Compared with no pretreatment, GnRH agonist pretreatment showed very uncertain effects on live birth (RR 0.48, 95% CI 0.26–0.87; 1 RCT), complications, and clinical pregnancy (RR 1.13, 95% CI 0.91–1.41); no consistent benefit across secondary outcomes; evidence very low certainty

3.3 Methodological Quality (AMSTAR 2)

The methodological quality of the included systematic reviews with meta-analyses was assessed using the AMSTAR 2 tool. Overall, confidence in the results of the included reviews was heterogeneous but predominantly moderate to high, with a substantial proportion of reviews meeting key methodological standards (Table 3).

Based on AMSTAR 2 ratings, 15 reviews (31%) were classified as high confidence, 19 (38%) as moderate confidence, 10 (19%) as low confidence, and 5 (12%) as critically low confidence. Thus, nearly two thirds of the included reviews achieved high or moderate methodological quality (Fig.2).

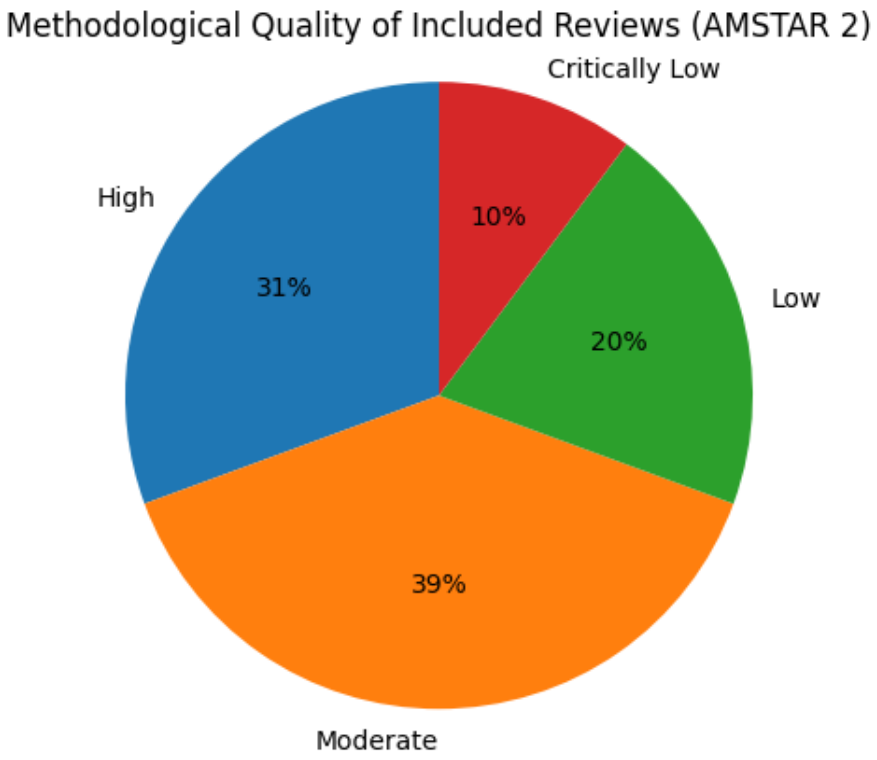


Fig. 2. *AMSTAR 2 Quality Distribution*

Reviews rated as high or moderate confidence generally demonstrated clearly defined research questions, comprehensive and systematic literature searches, explicit eligibility criteria, and appropriate application of meta-analytic methods for quantitative synthesis. Most of these reviews provided adequate descriptions of included primary studies and transparently reported effect estimates.

Nevertheless, several recurring methodological limitations were identified across the evidence base. A considerable proportion of reviews did not report a registered or published protocol, or failed to justify deviations from an a priori design. Assessment of risk of bias in primary studies was frequently incomplete or insufficiently integrated into the interpretation of pooled estimates, limiting confidence in the robustness of some findings.

Additionally, publication bias was not systematically assessed in many reviews, particularly when the number of included primary studies was small. Reporting of funding sources for included primary studies was uncommon, precluding a structured evaluation of potential conflicts of interest at the study level. Statistical heterogeneity was often substantial, and although measures such as I^2 were usually reported, exploration of heterogeneity through subgroup or sensitivity analyses was inconsistently performed.

Reviews rated as low or critically low confidence most commonly failed to address multiple critical AMSTAR 2 domains simultaneously, particularly protocol registration, risk-of-bias consideration, and assessment of publication bias. In contrast, higher methodological quality was more frequently observed among Cochrane reviews and recent network meta-analyses, although even these were constrained by limitations inherent to the underlying primary evidence.

Table 3. AMSTAR2 Assessment

Authors (Year)	Overall Confidence	Critical Flaws
Xie et al. (2025)	High	No
Gu et al. (2025)	High	No
Yang et al. (2025)	Moderate	Yes – protocol not registered
Zhou et al. (2025)	High	No
Riemma et al. (2025)	High	No
Vallee et al. (2025)	Moderate	Yes – lack of formal risk of bias assessment for included non-randomized studies
Yang et al. (2025)	Moderate	Yes – no PROSPERO registration and no formal certainty of evidence assessment
Darici et al. (2025)	Moderate	Yes – risk of bias not adequately accounted for in interpretation of results
Xie et al. (2025)	Moderate	Yes – risk of bias not adequately incorporated into interpretation
Huang et al. (2025)	Moderate	Yes - no list of excluded studies; publication bias not formally assessed; funding of included RCTs not reported
Kalra et al. (2024)	High	No
Chen et al. (2024)	Moderate	Yes – no list of excluded studies and inadequate consideration of risk of bias in interpretation
Veth et al. (2024)	High	No
Viviano et al. (2024)	High	No
Bandini et al. (2024)	High	No
Bayu & Wibisono (2024)	Moderate	Yes – no list of excluded studies with reasons
Liang et al. (2024)	Moderate	Yes – risk of bias not adequately incorporated into interpretation and no list of excluded studies
Qing et al. (2024)	Moderate	Yes – no complete list of excluded studies with reasons
Paffoni et al. (2024)	Moderate	Yes – no complete list of excluded studies and only partial formal certainty of evidence assessment
Keukens et al. (2024)	Moderate	Yes – no complete list of excluded studies with reasons
Gao et al. (2024)	Moderate	Yes – no protocol registration and no list of excluded studies with reasons
Csirzó et al. (2024)	Moderate	Yes – no complete list of excluded studies with reasons
Ronsini et al. (2023)	Low	Yes – one critical domain not met (Q13)
Zheng et al. (2023)	Moderate	Yes – one critical domain not met (Q13)
Shao et al. (2023)	Low	Yes – one critical domain not met (Q13)
Zheng et al. (2023)	Low	Yes – one critical domain not met (Q13)
Veth et al. (2023)	High	No

Muzii et al. (2023)	Low	Yes – multiple critical domains not met (Q13, Q15)
Xin et al. (2023)	Low	Yes – multiple critical domains not met (Q2, Q13, Q15)
Mitchell et al. (2022)	Low	Yes – multiple critical domains not met (Q13, Q15)
Zhang et al. (2022)	Low	Yes – multiple critical domains not met (Q13, Q15)
Yan et al. (2022)	Low	Yes – multiple critical domains not met (Q13, Q15)
Ma et al. (2022)	Critically Low	Yes – multiple critical domains not met (Q2, Q4, Q7, Q13, Q15)
Fraga et al. (2022)	Low	Yes – one critical domain not met (Q13)
Dong et al. (2021)	Critically Low	Yes – multiple critical domains not met (Q2, Q4, Q7, Q13, Q15)
Gibbons et al. (2021)	High	No
Moreno-Sepulveda et al. (2022)	Critically Low	Yes – multiple critical domains not met (Q2, Q4, Q7, Q13, Q15)
Grammatis et al. (2021)	High	No
van Hoesel et al. (2021)	High	No
Casals et al. (2021)	Low	Yes – one critical domain not met (Q13)
Chen et al. (2020)	High	No
Bafort et al. (2020)	High	No
Zakhari et al. (2021)	Moderate	Yes – one critical domain not met (Q13)
Nankali et al. (2020)	Critically Low	Yes – multiple critical domains not met (Q2, Q4, Q7, Q9, Q13)
Bendifallah et al. (2020)	Critically Low	Yes – multiple critical domains not met (Q2, Q4, Q7, Q9, Q13, Q15)
Wattanayingcharoenchai et al. (2021)	Moderate	Yes – one critical domain not met (Q13)
Miller et al. (2020)	Moderate	Yes – one critical domain not met (Q13)
Hodgson et al. (2020)	Moderate	Yes – one critical domain not met (Q13)
Georgiou et al. (2019)	High	No

3.4 Assessment of Overlap of Primary Studies

Overlap of primary studies across included evidence syntheses was quantified using the Corrected Covered Area (CCA), CCA is derived from the citation matrix of primary studies across reviews and is computed as:

$$CCA = (N - r) / (r \times c - r)$$

where N denotes the total number of included primary study occurrences across reviews, r is the number of unique primary studies, and c is the number of reviews. In line with common practice, CCA values were interpreted using descriptive categories, with emphasis placed on clusters expected to share primary evidence. Heatmaps and citation matrices were generated to support the interpretation of overlap patterns.

Pharmacological management

In the pharmacological domain, overlap was generally low (Table 4). For the GnRH analogues/antagonists cluster, the overlap was slight (CCA = 0.0262, c = 5; r = 86; N = 95), indicating that the evidence base was largely complementary despite shared pharmacological targets and partially overlapping clinical trial programs. When the broad GnRH cluster was recalculated excluding one review, overlap

increased markedly to a very high level (CCA = 0.2143, c = 4; r = 14; N = 23), consistent with a tighter grouping of reviews centered on a smaller, highly reused set of pivotal antagonist trials. By contrast, overlap within progestin-based therapies and other non-standard pharmacological agents was negligible (both clusters yielded CCA values consistent with no meaningful overlap), reflecting either highly review-specific study selection or limited cross-reuse of the same primary trials across syntheses.

Table 4. Pharmacological management Heatmap

Ref Num	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]
[10]		0	0	0	0	0	0	0	0
[11]	0		0	0	0	0	0	0	0
[12]	0	0		0	0	0	0	0	0
[13]	0	0	0		2	4	0	0	0
[14]	0	0	0	2		3	1	0	0
[15]	0	0	0	4	3		1	0	0
[16]	0	0	0	0	1	1		0	0
[17]	0	0	0	0	0	0	0		0
[18]	0	0	0	0	0	0	0	0	

Surgical management

Within surgical management, overlap varied by subtopic and was overall low (Table 5). For the ovarian endometrioma cluster, overlap was slight (CCA = 0.0265, c = 6; r = 98; N = 111), suggesting broadly independent primary study sets across reviews despite thematic relatedness (differences in populations, endpoints such as AMH vs fertility outcomes, and operative approaches). For deep infiltrating endometriosis (DIE) and colorectal surgery outcomes, overlap was low-to-moderate (CCA = 0.0507, c = 4; r = 46; N = 53), consistent with a shared core of cohorts and surgical series across outcome-focused syntheses. Finally, overlap in adjunct/technological approaches (including presacral neurectomy and robotic surgery–related syntheses) remained very low (CCA = 0.0147, c = 3; r = 34; N = 35), indicating minimal redundancy and limited reuse of identical primary studies across these technically distinct questions.

Table 5. Surgical management Heatmap

Ref Num	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]
[19]		3	2	0	0	0	0	0	0	0	0	0	0
[20]	3		2	0	0	0	0	0	0	0	0	0	0
[21]	2	2		8	0	0	0	0	0	0	0	0	0
[22]	0	0	8		0	0	0	0	0	0	0	0	0
[23]	0	0	0	0		0	0	0	0	0	0	0	0
[24]	0	0	0	0	0		0	0	0	0	0	0	0
[25]	0	0	0	0	0	0		3	3	0	0	0	0
[26]	0	0	0	0	0	0	3		2	0	0	0	0
[27]	0	0	0	0	0	0	3	2		0	0	0	0
[28]	0	0	0	0	0	0	0	0	0		1	0	0
[29]	0	0	0	0	0	0	0	0	0	1		1	0
[30]	0	0	0	0	0	0	0	0	0	0	1		0
[31]	0	0	0	0	0	0	0	0	0	0	0	0	

Perioperative and expectant management

In the perioperative/expectant management domain, overlap remained low to moderate (Table 6). Among reviews addressing postoperative hormonal suppression, the corrected covered area was 0.0658 (c = 6; r = 79; N = 105). This indicates a limited degree of redundancy, with partial reuse of postoperative comparative studies across reviews, while the majority of primary evidence remained review-specific.

Table 6. Perioperative and expectant management Heatmap

Ref Num	[32]	[33]	[34]	[35]	[36]	[37]	[38]
[32]		0	0	1	0	2	0
[33]	0		0	2	0	1	0
[34]	0	0		10	4	5	1
[35]	1	2	10		4	2	1
[36]	0	0	4	4		0	0
[37]	2	1	5	2	0		0
[38]	0	0	1	1	0	0	

Endometriosis-associated infertility and ART

In the infertility/ART domain, overlap depended strongly on the clinical question (Table 7). For medical pretreatment before ART, overlap was high (CCA = 0.1235, c = 4; r = 27; N = 37), reflecting repeated inclusion of a common core of trials evaluating GnRH agonist strategies and related pretreatment regimens prior to IVF/ART. In contrast, overlap for surgery-first versus ART-first strategies was very high (CCA = 0.6667, c = 2; r = 6; N = 10), indicating that both reviews relied on an almost identical set of comparative studies. Finally, the group focusing on ART outcomes in special populations demonstrated no measurable overlap (CCA = 0.0000, c = 2; r = 14; N = 14), consistent with distinct evidence bases.

Table 7. Endometriosis-associated infertility and ART Heatmap

Ref Num	[39]	[40]	[41]	[42]	[43]	[44]	[45]	[46]
[39]		3	2	5	0	0	0	1
[40]	3		0	3	0	0	0	1
[41]	2	0		0	0	0	0	0
[42]	5	3	0		0	0	0	1
[43]	0	0	0	0		4	0	0
[44]	0	0	0	0	4		0	0
[45]	0	0	0	0	0	0		0
[46]	1	1	0	1	0	0	0	

Non-pharmacological and complementary therapies

For non-pharmacological/complementary interventions, overlap showed a clear separation between acupuncture-focused syntheses and broader nutritional/traditional medicine approaches (Table 8). Within acupuncture-based interventions, overlap was moderate (CCA = 0.0897, c = 3; r = 39; N = 46), consistent with re-use of several core RCTs across acupuncture meta-analyses and network meta-analyses. For the combined cluster of nutritional supplementation and traditional medicine approaches, overlap was slight (CCA = 0.0226, c = 5; r = 133; N = 145), indicating a large and heterogeneous set of primary studies with limited redundancy across syntheses. Importantly, when recalculated excluding one review, overlap increased to moderate (CCA = 0.0952, c = 4; r = 28; N = 36), demonstrating that the review contributed substantial breadth (many unique primary studies) that diluted the apparent overlap within the remaining supplementation/TCM subset.

Table 8. Non-pharmacological and complementary therapies Heatmap

Ref Num	[47]	[48]	[49]	[50]	[51]	[52]	[53]	[54]	[55]
[47]		6	1	0	0	0	0	1	0
[48]	6		0	0	0	0	0	1	0
[49]	1	0		0	0	0	0	3	0
[50]	0	0	0		0	0	0	0	0
[51]	0	0	0	0		3	0	0	0
[52]	0	0	0	0	3		4	2	1
[53]	0	0	0	0	0	4		0	0
[54]	1	1	3	0	0	2	0		3
[55]	0	0	0	0	0	1	0	3	

3.5. Evidence Synthesis

3.5.1 Pharmacological Management of Endometriosis

Progestins and Progestin-Based Therapies

Evidence indicates that progestin-based therapies are associated with a clinically meaningful reduction in endometriosis-related pain [10]. Pooled analyses demonstrate a significant analgesic effect compared with placebo, with no consistent evidence of superiority among individual progestin agents, supporting a class-level effect rather than drug-specific advantages. Treatment discontinuation due to adverse events is generally low, although irregular bleeding and weight gain are commonly reported. Substantial heterogeneity in study design, dosing regimens, formulations, and outcome measures limits the precision of effect estimates for individual agents [10].

Comparative evidence between progestins and combined oral contraceptives suggests differential effects across pain domains. Oral contraceptives may provide greater short-term improvement in pelvic pain and dyspareunia, whereas progestins—particularly dienogest—appear to confer advantages in selected pain outcomes and endometriosis-specific quality-of-life domains [11]. Physical components of quality of life tend to favor progestin therapy, while mental health–related outcomes do not consistently differ between treatment strategies. Overall safety profiles are broadly comparable, although adverse event patterns vary by treatment type [11].

Gonadotropin-Releasing Hormone (GnRH) Analogues and Antagonists

Evidence from systematic reviews indicates that GnRH agonists provide greater short-term relief of endometriosis-associated pain compared with placebo, including improvements in dysmenorrhea, dyspareunia, and pelvic pain [12]. However, the certainty of evidence is low to very low for most outcomes, and comparative analyses do not demonstrate consistent superiority over other hormonal agents. GnRH agonist therapy is consistently associated with hypoestrogenic adverse effects, particularly vasomotor symptoms and reductions in bone mineral density, which limit long-term tolerability [12].

More recent evidence focuses on oral GnRH antagonists, which demonstrate significant reductions in pelvic pain, dysmenorrhea, and dyspareunia compared with placebo, with clear dose–response relationships [13,14]. Higher doses are associated with greater analgesic efficacy but also increased rates of adverse events, including hot flushes and bone mineral density loss. Network meta-analyses consistently rank elagolix and linzagolix among the most effective agents for overall pain reduction, while relugolix shows a particularly strong effect on dysmenorrhea [13,14]. Although the included trials are generally assessed as low risk of bias, follow-up durations are limited.

The addition of add-back therapy modifies the benefit–risk profile of GnRH antagonists. Combined regimens preserve analgesic efficacy while attenuating hypoestrogenic adverse effects, particularly bone mineral density loss, supporting their potential use in longer-term treatment strategies, although available data remain restricted to short- and medium-term follow-up [15].

Patient-reported outcome measures further support the efficacy of GnRH antagonists. Treatment with relugolix is associated with significant improvements in disease-specific quality-of-life domains, including pain, emotional well-being, and self-image, compared with placebo, though efficacy appears lower in direct comparisons with GnRH agonists and heterogeneity across studies is substantial [16].

Other Hormonal and Non-Standard Pharmacological Agents

Evidence for non-standard pharmacological agents in endometriosis is sparse and characterized by very low certainty.

Evidence for pentoxifylline does not demonstrate consistent benefit for endometriosis-associated pain, fertility outcomes, or disease recurrence. Available randomized trials are few, underpowered, and affected by methodological limitations, resulting in very low-certainty evidence and no support for clinical effectiveness [17].

Evidence for selective estrogen receptor modulators (SERMs) is even more limited. Data are restricted to a single randomized trial conducted in a postoperative setting, which showed no benefit for pain, recurrence, or quality-of-life outcomes and suggested a shorter time to pain recurrence compared with placebo. The certainty of evidence is very low, and current data do not support the use of SERMs in endometriosis management [18].

Section Summary

Pharmacological management of endometriosis is supported by consistent evidence for progestins and GnRH modulators, which are associated with clinically meaningful reductions in pain but differ in tolerability and adverse effect profiles. Oral GnRH antagonists demonstrate dose-dependent efficacy, with an improved short-term benefit–risk profile when combined with add-back therapy. In contrast, evidence for other non-standard pharmacological agents, including immunomodulatory therapies and selective estrogen receptor modulators, is sparse, heterogeneous, and of very low certainty, limiting their role to selected or experimental settings.

3.5.2 Surgical Management of Endometriosis

Ovarian endometrioma: excision, ablation, and sclerotherapy

Evidence on the surgical management of ovarian endometrioma highlights a trade-off between recurrence prevention, pain control, and preservation of ovarian reserve. Excisional surgery is associated with lower recurrence of dysmenorrhea, dyspareunia, and endometrioma compared with ablative techniques, while no clear differences are observed in short-term spontaneous pregnancy rates. However, the certainty of evidence supporting these findings is low, and reporting of surgical complications is limited [19].

Across multiple systematic reviews and meta-analyses, excisional techniques are consistently associated with greater postoperative impairment of ovarian reserve than ablative approaches. Larger declines in serum anti-Müllerian hormone and antral follicle count are observed after cystectomy, particularly in women with bilateral disease or larger cysts [20,21,22]. The choice of hemostatic technique further modifies this risk, with

bipolar electrocoagulation resulting in greater ovarian reserve loss compared with suturing or alternative methods [23].

Evidence for sclerotherapy as an alternative to surgical cystectomy is derived primarily from comparative observational studies. Meta-analytic data suggest no statistically significant differences in recurrence rates between sclerotherapy and surgery, while pregnancy rates tend to favor surgical management without reaching statistical significance. Sclerotherapy is associated with fewer postoperative complications; however, the overall certainty of evidence is limited by non-randomized study designs, clinical heterogeneity, and variability in treatment protocols [24].

Deep infiltrating endometriosis

Surgical management of deep infiltrating endometriosis (DIE), particularly with colorectal involvement, involves trade-offs between reproductive outcomes, postoperative function, and surgical morbidity. Comparative evidence suggests that more radical approaches, such as colorectal resection, are associated with lower overall pregnancy rates compared with conservative techniques, especially rectal shaving, while spontaneous pregnancy rates do not differ consistently between approaches [25].

Postoperative functional outcomes tend to favor conservative surgery in cross-sectional comparisons, with lower rates of constipation and higher gastrointestinal quality-of-life scores compared with segmental resection. However, analyses focusing on within-patient changes from pre- to postoperative status do not demonstrate consistent differences between surgical techniques, limiting causal interpretation [26].

Complication profiles vary by technique. Rectal shaving is associated with lower rates of rectovaginal fistula and anastomotic leakage compared with discoid excision and segmental resection, whereas discoid excision is associated with higher rates of early postoperative voiding dysfunction. Evidence regarding pelvic floor outcomes indicates potential improvements in dyspareunia and fecal incontinence following DIE surgery, but substantial heterogeneity and limited comparative data preclude attribution of benefit to specific techniques. Overall, the certainty of evidence across outcomes is limited, reflecting the predominance of non-randomized study designs [27,28].

Adjunct and technological approaches

Adjunctive and technology-focused surgical strategies have been explored as approaches to improve pain control or perioperative outcomes. Adjunctive presacral neurectomy is associated with a reduced risk of treatment failure for midline pelvic pain, particularly dysmenorrhea, but this benefit is offset by a higher incidence of postoperative constipation, while other complication rates do not differ significantly [29].

With respect to surgical approach and technology, laparoscopic surgery is associated with higher rates of viable intrauterine pregnancy compared with diagnostic laparoscopy alone; however, evidence for pain relief and quality-of-life outcomes remains very uncertain. Comparative analyses do not demonstrate clear superiority of laparoscopic excision over ablation or of specific laparoscopic energy modalities. Robot-assisted laparoscopy does not confer advantages over conventional laparoscopy in terms of perioperative safety or recovery outcomes and is associated with longer operative times [30,31].

Section summary

Surgical management of endometriosis involves complex trade-offs between symptom control, recurrence prevention, and preservation of reproductive function. For ovarian endometrioma, excisional surgery is associated with lower recurrence rates but greater impairment of ovarian reserve compared with ablative techniques, underscoring the need to balance disease control against potential impacts on fertility. In deep infiltrating endometriosis, conservative colorectal approaches tend to be associated with more favorable reproductive and functional outcomes and lower rates of severe complications than radical resection, although the available evidence is predominantly observational. Adjunctive procedures and advanced surgical technologies have specific, limited roles and do not consistently confer additional benefit across clinical outcomes.

3.5.3 Perioperative and Expectant Management

Postoperative hormonal suppression

Evidence consistently indicates that postoperative hormonal therapy reduces the risk of disease recurrence after conservative surgery for endometriosis, while effects on pain recurrence and fertility outcomes are more variable.

Postoperative administration of dienogest significantly reduced cyst recurrence compared with placebo or no postoperative treatment, with no significant differences observed when compared with GnRH agonists. Effects on pain recurrence were less certain, showing a non-significant trend toward benefit at six months and

substantial heterogeneity. Adverse effect profiles differed between treatments, with dienogest associated with higher rates of spotting and weight gain but fewer vasomotor symptoms than GnRH agonists [32].

Evidence for intrauterine progestin delivery remains limited. Trials evaluating levonorgestrel-releasing intrauterine systems did not assess overall pain as a primary outcome, but individual studies suggested possible improvements in dysmenorrhea, quality of life, and patient satisfaction compared with expectant management. Comparisons with GnRH agonists were inconclusive due to small sample sizes and imprecision [33].

Broader perioperative strategies indicate a clearer benefit for postoperative rather than preoperative hormonal therapy. Presurgical hormonal suppression did not demonstrate consistent reductions in pain recurrence, disease recurrence, or improvements in pregnancy outcomes. In contrast, postsurgical hormonal therapy reduced pain recurrence within 12 months and disease recurrence compared with surgery alone and was probably associated with higher pregnancy rates, although certainty varied across outcomes [34].

These findings were supported by pooled analyses demonstrating a significant reduction in recurrence risk with postoperative hormonal suppression compared with placebo or expectant management, with benefits observed across combined oral contraceptives, progestins, and levonorgestrel-releasing intrauterine systems. Reduced pain scores were also reported, although heterogeneity was substantial. Importantly, sustained hormonal suppression was required to maintain benefit, as recurrence increased following treatment discontinuation [35].

However, discordance exists between randomized and observational evidence. While cohort studies suggested reduced endometrioma recurrence with long-term use of levonorgestrel-releasing intrauterine systems, dienogest, and continuous oral contraceptives, randomized evidence did not demonstrate statistically significant benefits over expectant management. These discrepancies highlight ongoing uncertainty and the need for adequately powered randomized trials [36,37].

Natural history and expectant management

The natural course of untreated deep endometriosis has been evaluated in a systematic review and meta-analysis including 29 studies in qualitative synthesis and 19 studies (1,015 women) in quantitative analyses [38].

Among women managed without hormonal treatment, lesion progression occurred in approximately one in five patients, although estimates varied widely across studies. Lesion stability was more common than progression, while spontaneous regression was uncommon. Progression rates differed substantially depending on symptom burden, lesion location, and duration of follow-up, contributing to marked heterogeneity [38].

In contrast, hormonal suppression was associated with a lower pooled progression rate and a significantly reduced risk of lesion progression compared with expectant management (OR 0.52). Hormonal therapy was also associated with reductions in lesion volume, corresponding to an average decrease of approximately 28% from baseline. However, progression was not completely prevented, and lesion regression was not universal despite treatment [38].

Notably, lesion progression was not consistently associated with symptom worsening, and no cases of bowel obstruction or obstructive uropathy were reported among untreated patients in pooled analyses. These findings suggest that expectant management may be appropriate in selected asymptomatic or mildly symptomatic patients, provided that regular clinical and imaging surveillance is maintained to detect potential silent disease progression [38].

Section summary

Postoperative hormonal suppression consistently reduces the risk of endometriosis recurrence and may improve pain and fertility outcomes, with evidence favoring postsurgical rather than presurgical initiation. The magnitude and durability of benefit appear to depend on treatment duration and diminish after discontinuation. In untreated disease, deep endometriosis remains stable in most patients; however, clinically relevant progression occurs in a substantial minority, supporting individualized decision-making and careful longitudinal follow-up when expectant management is selected.

3.5.4 Endometriosis-Associated Infertility and Reproductive Outcomes

Medical pretreatment before ART

Systematic reviews and meta-analyses consistently indicate limited or no benefit of hormonal pretreatment before ART for key reproductive outcomes in women with endometriosis. Across randomized controlled trials comparing GnRH agonist protocols, progestins, and no pretreatment prior to IVF/ICSI, no strategy significantly improved clinical pregnancy or live birth rates compared with no pretreatment. Although long and ultralong GnRH agonist protocols were associated with higher implantation rankings, these effects did not translate into improved pregnancy or live birth outcomes, providing no support for routine pretreatment before ART [39].

These findings are consistent with evidence synthesized in a Cochrane review, which reported very low-certainty evidence and substantial uncertainty regarding the effects of long-term GnRH agonist pretreatment on live birth, clinical pregnancy, miscarriage, or multiple pregnancy rates. Evidence quality was limited by imprecision, heterogeneity, and methodological shortcomings across included trials [40].

More heterogeneous results have been reported for dienogest pretreatment. Overall, dienogest demonstrated similar ART outcomes to no hormonal pretreatment and appeared superior to non-hormonal management in pooled analyses. However, when directly compared with long GnRH agonist protocols, dienogest was associated with lower clinical pregnancy and live birth rates. Subgroup analyses suggested a potential benefit in fresh embryo transfer cycles, but conclusions were constrained by small sample sizes and mixed study designs [41].

Finally, adjuvant GnRH agonist therapy administered after conservative surgery and before conception was associated with a modest increase in pregnancy rate and a shorter time to pregnancy, without significant effects on live birth or miscarriage rates. Substantial heterogeneity and predominantly observational evidence limit the certainty of these findings [42].

Surgery-first versus ART-first strategies

Comparative evidence evaluating initial surgical management versus immediate ART is derived exclusively from observational studies and is therefore subject to substantial methodological limitations. Across comparative analyses, fertility outcomes were broadly similar between surgery-first and ART-first strategies, with wide confidence intervals and marked heterogeneity, indicating limited precision and stability of pooled estimates. Sensitivity analyses demonstrated that results were highly dependent on individual studies, although analyses incorporating both complete and incomplete excision of deep infiltrating endometriosis suggested higher pregnancy rates with a surgery-first approach. Overall, the evidence was characterized by a high risk of selection bias and residual confounding [43].

More favorable reproductive outcomes associated with surgery before ART have been reported in additional observational syntheses, which demonstrated higher pregnancy and live birth rates among women undergoing surgical treatment of deep infiltrating endometriosis prior to IVF/ICSI. Benefits were observed across multiple reproductive endpoints and persisted when incomplete surgical excision was included in analyses. However, the absence of randomized data, limited adjustment for confounders, and sparse reporting of surgical morbidity and ART-related complications substantially constrain the certainty and generalizability of these findings [44].

ART outcomes and special populations

ART outcomes in specific clinical contexts have been evaluated in a limited number of systematic reviews, with overall low certainty of evidence. Analyses of oocyte donation IVF cycles, designed to isolate uterine factors, showed no statistically significant difference in live birth rates between recipients with and without endometriosis in published observational studies. In contrast, pooled data from large ART registries demonstrated a modest but statistically significant reduction in live birth rates among women with endometriosis. These discrepant findings likely reflect differences in study design, adjustment for confounders, and population characteristics, with overall certainty limited by observational evidence and residual confounding [45].

Broader interventions for endometriosis-associated infertility were assessed using randomized controlled trials. Although ART-related studies were identified, they could not be incorporated into network meta-analyses due to lack of common comparators. Within the modeled network, surgical laparoscopy and GnRH agonist therapy were associated with higher odds of clinical pregnancy compared with placebo or no treatment, while evidence for live birth outcomes remained insufficient. Overall, the available evidence highlights the scarcity of robust randomized data directly evaluating ART strategies and special populations in endometriosis-associated infertility [46].

Section summary

Current evidence does not support routine hormonal pretreatment before ART in women with endometriosis, as no consistent improvement in live birth or clinical pregnancy rates has been demonstrated. Observational data suggest that surgery prior to ART may improve reproductive outcomes in selected women with deep infiltrating endometriosis; however, these findings are subject to substantial bias and lack confirmation from randomized trials. ART outcomes in special populations, including oocyte donation recipients, indicate at most a modest reduction in live birth rates associated with endometriosis, highlighting the need for individualized treatment strategies and well-designed comparative studies.

3.5.5 Non-Pharmacological and Complementary Therapies

Acupuncture-based interventions

Evidence from systematic reviews suggests that acupuncture-based therapies may reduce endometriosis-associated pain, although effect estimates are heterogeneous and the overall certainty of evidence is generally moderate to low. Acupuncture interventions were associated with statistically significant reductions in pain intensity and higher clinical response rates compared with non-acupuncture or sham controls [47,48]. However, heterogeneity across trials was substantial, reflecting variability in acupuncture modalities, treatment protocols, and comparator groups. Effects on biochemical markers such as serum CA125 were inconsistent and, when observed, modest [47,48].

Comparative evidence across different acupuncture-related approaches—including electroacupuncture, auricular acupuncture, and moxibustion-based techniques—demonstrated lower pain scores compared with conventional medical treatment in pairwise analyses [49]. Network meta-analytic rankings suggested differential effectiveness across modalities, although these rankings should be interpreted cautiously due to methodological limitations and indirect comparisons. Adverse events were infrequently reported and were generally mild when described, with no consistent signal of serious harms [49].

Overall, acupuncture-based interventions appear to be associated with pain reduction in women with endometriosis, but interpretation is limited by substantial heterogeneity in intervention types, outcome definitions, control conditions, and trial quality, precluding firm conclusions regarding comparative effectiveness or optimal modality.

Lifestyle and exercise

Evidence for lifestyle and physical interventions remains limited but suggests potential benefits for quality of life and selected pain-related outcomes in women with endometriosis. Meta-analytic evidence from randomized controlled trials evaluating diverse exercise modalities—including aerobic and resistance training, yoga, relaxation-based programs, and digitally delivered interventions—demonstrated significant improvements across multiple Endometriosis Health Profile-30 domains, particularly pain, emotional well-being, and control/powerlessness [50].

Pain outcomes assessed using VAS were heterogeneous. Some trials reported significant reductions in pelvic pain or dysmenorrhea, while others showed non-significant trends toward improvement. Interventions incorporating mind–body components were more consistently associated with improvements in mental health outcomes, and limited evidence suggested potential benefits for pelvic floor–related symptoms. Exercise interventions were generally well tolerated, with no serious adverse events reported. In women receiving GnRH agonist therapy, one trial suggested that structured physical activity may attenuate treatment-related bone mineral density loss [50].

Nutritional and traditional medicine approaches

Evidence for nutritional supplementation suggests differential effects depending on the type of intervention. Systematic reviews evaluating vitamin D supplementation reported inconsistent findings, with observed pain reductions largely driven by studies in primary dysmenorrhea rather than endometriosis-specific populations. In analyses restricted to endometriosis-related pain, vitamin D did not demonstrate a statistically significant benefit over placebo, and overall certainty of evidence was low [51,52].

In contrast, antioxidant vitamin supplementation—particularly vitamin E alone or in combination with vitamin C—was more consistently associated with reductions in chronic pelvic pain, dysmenorrhea, and dyspareunia. Meta-analyses reported significant effect sizes for these outcomes, although substantial heterogeneity and concerns regarding risk of bias were noted across included trials [52,53].

Traditional Chinese Medicine interventions, primarily evaluated as adjuncts to conventional therapies, were associated with improvements in pain, composite clinical response measures, and reductions in serum CA125 levels. In women with endometriosis-associated infertility, combined TCM and Western medical treatment was associated with higher pregnancy rates and lower abortion rates compared with Western medicine alone. However, certainty of evidence ranged from low to moderate due to methodological limitations, including inadequate blinding, variable outcome definitions, and restriction of most trials to single-country settings [54,55].

Section summary

Complementary and lifestyle interventions may provide adjunctive benefits for pain relief and quality of life in women with endometriosis. Acupuncture-based therapies and antioxidant vitamin supplementation show the most consistent signals of benefit, whereas evidence for exercise-based interventions primarily supports improvements in quality of life rather than robust or uniform pain reduction. Traditional Chinese

Medicine demonstrates favorable outcomes in large evidence syntheses; however, methodological limitations and restricted generalizability temper the strength of conclusions. Overall, these approaches should be considered adjunctive to established treatments, with individualized application and cautious interpretation of the underlying evidence quality.

3.5.6 Cross-Cutting Outcomes and Recurrence

This section synthesizes outcomes that cut across treatment modalities, focusing on pain trajectories, quality of life, and disease recurrence.

Evidence derived from longitudinal analyses of women with ovarian endometrioma indicates that pain severity decreases over time following surgery, medical therapy (predominantly hormonal), or combined treatment approaches [56]. Direct comparative evidence between surgery and medical therapy is lacking, and no included trials evaluated analgesics as standalone interventions. Baseline pain severity differed across treatment groups, with higher initial pain levels observed in medically treated cohorts.

Across pain domains—including dysmenorrhea, dyspareunia, chronic pelvic pain, and non-specified pelvic pain—downward trends were observed over follow-up, although not all changes reached statistical significance. The only consistent between-group difference was noted for non-specified pelvic pain, where combined surgery and medical therapy was associated with a more favorable pain trajectory compared with surgery alone. Quality-of-life outcomes were infrequently reported and could not be robustly synthesized; limited narrative evidence suggested short-term improvement after medical therapy, with uncertain or inconsistent effects following combined treatment [56].

Anatomical recurrence following surgical treatment in the absence of postoperative hormonal suppression has been quantified in pooled analyses [57]. Recurrence rates increased progressively over time, reaching approximately 27% at 24 months postoperatively. These estimates represent baseline recurrence risk under expectant postoperative management and provide important context for interpreting the benefits of postoperative hormonal suppression strategies reported elsewhere in this review.

Section summary

Across treatment modalities, pain associated with endometriosis tends to improve over time following surgical, medical, or combined interventions, although direct comparative evidence between strategies is lacking. Combined surgical and medical approaches may offer more favorable pain trajectories for selected outcomes, but quality-of-life data remain sparse and inconclusive. In the absence of postoperative hormonal suppression, anatomical recurrence after endometrioma surgery increases substantially over time, highlighting recurrence as a central cross-cutting outcome that informs long-term management decisions across therapeutic strategies.

3.5.7 Non-standard interventional approaches

Uterine artery embolization has been explored as a minimally invasive, non-standard interventional option for the management of endometriosis. A systematic review and meta-analysis evaluating this approach reported reductions in pain-related outcomes following embolization; however, the available evidence was derived from a limited number of heterogeneous studies, frequently including mixed populations with endometriosis and adenomyosis, variable embolization techniques, and short follow-up durations. Data on fertility outcomes were sparse or absent, and no robust comparisons with standard surgical management were available. As a result, despite signals of potential symptomatic benefit, the certainty of evidence remains low, and uterine artery embolization cannot be considered an established therapeutic option for endometriosis management outside selected or experimental contexts [58].

4. Discussion

4.1 Principal Findings

This umbrella review synthesized evidence from recent systematic reviews and meta-analyses evaluating the full spectrum of medical, surgical, reproductive, and complementary interventions for endometriosis. By integrating findings across heterogeneous therapeutic domains and explicitly accounting for methodological quality and overlap of primary studies, this review aimed to clarify which conclusions are supported by robust evidence and where apparent consistency may reflect limitations of the underlying evidence base rather than true treatment effects.

Across pharmacological interventions, the most consistent and methodologically supported evidence relates to progestins and gonadotropin-releasing hormone (GnRH) modulators. Both classes are associated

with clinically meaningful reductions in endometriosis-related pain, although their benefit–risk profiles differ substantially. Oral GnRH antagonists demonstrate dose-dependent efficacy and represent an effective short-term option, particularly when combined with add-back therapy; however, the strength of inference is constrained by short follow-up durations and a high degree of overlap among pivotal randomized trials, which may inflate perceived consistency across reviews.

Surgical management is characterized by clear trade-offs rather than unequivocal superiority of any single approach. For ovarian endometrioma, excisional techniques consistently reduce recurrence compared with ablative approaches but are associated with greater impairment of ovarian reserve, an effect that is magnified in bilateral disease and influenced by surgical technique. In deep infiltrating endometriosis, conservative colorectal approaches tend to show more favorable reproductive and functional profiles than radical resection, yet this evidence is derived predominantly from observational studies and is therefore vulnerable to selection bias and residual confounding. Overall, surgical effectiveness must be interpreted in light of competing risks, patient priorities, and the limited availability of randomized comparative data.

In the context of endometriosis-associated infertility, current evidence does not support routine hormonal pretreatment before assisted reproductive technology (ART), as no consistent improvements in live birth or clinical pregnancy rates have been demonstrated. Observational data suggest a possible benefit of surgery prior to ART in selected populations, particularly women with deep infiltrating disease, but these findings remain uncertain due to non-randomized designs and overlapping cohorts across reviews. ART outcomes in special populations, including oocyte donation recipients, indicate at most a modest reduction in live birth rates associated with endometriosis, underscoring the need for individualized treatment strategies rather than generalized algorithms.

Complementary and lifestyle interventions, including acupuncture-based therapies, exercise, nutritional supplementation, and traditional medicine approaches, show signals of benefit for pain and quality-of-life outcomes. However, these findings are supported by evidence of low to moderate methodological quality, substantial heterogeneity, and frequent reliance on small or geographically restricted primary studies. While such interventions may serve as adjuncts in selected patients, their role cannot be clearly defined without higher-quality comparative trials and standardized outcome assessment.

Across all therapeutic domains, cross-cutting analyses revealed a lack of direct head-to-head comparisons between major treatment strategies and considerable heterogeneity in outcome definitions, follow-up duration, and patient populations. Importantly, the degree of overlap of primary studies varied substantially between domains and was particularly high in pharmacological and ART-related reviews, raising the risk of double counting and overestimation of evidentiary concordance. These findings highlight that apparent agreement across reviews does not necessarily equate to independent confirmation and should be interpreted cautiously.

In addition to standard medical and surgical strategies, limited evidence suggests that non-standard interventional approaches, such as uterine artery embolization, may be associated with short-term reductions in pain-related outcomes; however, the evidence base is small, heterogeneous, and of low certainty, precluding firm conclusions regarding effectiveness or clinical role.

4.2 Methodological Considerations and Quality of the Included Systematic Reviews

The methodological quality of the included systematic reviews was heterogeneous, with important implications for the strength and interpretability of the synthesized evidence. Using the AMSTAR 2 tool, 15 reviews (31%) were rated as high confidence, 19 (38%) as moderate, 10 (19%) as low, and 5 (12%) as critically low. This distribution indicates that although a substantial proportion of the evidence base is methodologically sound, a non-negligible fraction of conclusions rests on reviews with significant limitations.

Reviews rated as high or moderate confidence generally shared several methodological strengths, including clearly formulated research questions, comprehensive and systematic search strategies, explicit eligibility criteria, and appropriate use of quantitative synthesis methods. These reviews were more likely to provide transparent descriptions of included studies and to apply meta-analytic techniques in a manner consistent with their stated objectives. Higher-quality reviews were most frequently observed among Cochrane reviews and recent network meta-analyses, although even these were often constrained by limitations inherent to the underlying primary evidence, such as small sample sizes and short follow-up durations.

In contrast, several recurrent methodological weaknesses were identified across reviews rated as low or critically low confidence. The absence of a registered or published protocol was common, limiting assurance that review methods were defined a priori and increasing the risk of selective outcome reporting. Assessment

of risk of bias in primary studies was frequently incomplete or inconsistently incorporated into the interpretation of pooled effect estimates. In many cases, potential biases at the study level were described but not formally explored in sensitivity analyses or reflected in the strength of conclusions.

Additional limitations included inconsistent assessment of publication bias, particularly in reviews with a limited number of primary studies, and inadequate reporting of funding sources for included trials, precluding evaluation of potential conflicts of interest. Statistical heterogeneity was often substantial across pooled analyses; although heterogeneity metrics such as I^2 were typically reported, systematic exploration of its sources through subgroup or sensitivity analyses was inconsistent.

Beyond methodological quality, overlap of primary studies across reviews represented a critical cross-cutting issue. The degree of overlap varied by therapeutic domain, ranging from low to moderate in some areas of pharmacological management to higher levels in reviews of GnRH modulators and ART-related interventions. In these domains, multiple reviews relied on the same pivotal randomized controlled trials, resulting in clustered evidence bases. Such overlap increases the risk of double counting and may create an impression of concordant findings that reflects repeated analysis of the same datasets rather than independent replication. Heatmap visualizations of overlap patterns highlighted particularly dense clustering around a small number of landmark trials, underscoring the need for cautious interpretation of apparent consistency across reviews.

Taken together, these methodological considerations emphasize that the strength of evidence in this umbrella review is shaped not only by effect estimates but also by the quality and independence of the contributing reviews. Explicit appraisal of methodological rigor and overlap is therefore essential to avoid overconfidence in conclusions and to ensure that clinical and research implications are grounded in the true evidentiary landscape.

4.3 Clinical and Research Implications Implications for Clinical Practice

The findings of this umbrella review support a stratified and individualized approach to the management of endometriosis, informed by both the magnitude of observed effects and the quality of the underlying evidence. Among pharmacological options, progestins and GnRH modulators emerge as the most consistently supported therapies for pain reduction across multiple domains. While both classes demonstrate clinically meaningful analgesic effects, differences in tolerability and adverse effect profiles are critical determinants of treatment selection. In this context, the availability of oral GnRH antagonists, particularly when combined with add-back therapy, offers a potentially favorable short-term benefit–risk balance for women with moderate-to-severe symptoms, although long-term safety and durability of effect remain incompletely characterized.

Surgical management requires careful consideration of trade-offs between symptom control, recurrence prevention, and preservation of reproductive function. Evidence supports excisional approaches for reducing recurrence in ovarian endometrioma, but consistently demonstrates a greater negative impact on ovarian reserve compared with ablative techniques. These findings are particularly relevant for women with current or future fertility plans, in whom conservative surgical strategies and meticulous hemostatic techniques should be prioritized. The absence of robust head-to-head comparisons across surgical modalities and between surgical and medical strategies limits the ability to define optimal treatment algorithms, reinforcing the need for shared decision-making that integrates patient preferences and reproductive goals.

In the context of assisted reproductive technologies, current evidence does not support routine hormonal pretreatment for all women with endometriosis, as no consistent improvements in live birth or clinical pregnancy rates have been demonstrated. Surgical intervention prior to ART may be considered in selected patients, particularly those with deep infiltrating disease or significant symptom burden, but such decisions should be individualized given the predominance of observational evidence and the potential for selection bias.

Complementary and lifestyle interventions, including exercise-based programs, nutritional supplementation, and acupuncture-related therapies, may offer adjunctive benefits for quality of life and selected pain outcomes. However, the certainty of evidence supporting these approaches is generally low, and they should not be viewed as substitutes for established medical or surgical treatments. Instead, their role is best conceptualized as supportive, particularly for patients seeking non-pharmacological options or multimodal symptom management.

Implications for Future Research

The synthesis highlights several priorities for future research aimed at strengthening the evidence base for endometriosis management. First, there is a clear need for well-designed head-to-head randomized trials directly comparing medical, surgical, and combined treatment strategies, particularly for outcomes of greatest

clinical relevance such as long-term pain control, quality of life, fertility, and recurrence. Second, greater standardization of outcome measures—including pain domains, quality-of-life instruments, and definitions of recurrence—would improve comparability across studies and enhance the interpretability of pooled analyses.

Longer follow-up durations are also essential, as many included reviews relied on primary studies with follow-up limited to 6–24 months, restricting insight into the durability of treatment effects and late adverse outcomes. This limitation is especially relevant for chronic disease management and for therapies associated with potential long-term risks, such as hypoestrogenism or diminished ovarian reserve.

Finally, future systematic reviews and meta-analyses should explicitly address overlap of primary studies through formal quantitative methods and transparent reporting. Active management of overlap, including sensitivity analyses and clear mapping of shared evidence bases, is crucial to reduce the risk of double counting and to avoid overestimating the robustness of apparent consensus. Strengthening both primary research and evidence synthesis methodologies will be essential to support more confident, patient-centered decision-making in endometriosis care.

4.4 Strengths and Limitations Strengths

This umbrella review has several important strengths that enhance the robustness and transparency of its findings. First, it provides a comprehensive synthesis of evidence across the full spectrum of endometriosis management, encompassing pharmacological, surgical, perioperative, reproductive, and complementary interventions. By integrating data from 49 systematic reviews, it offers a high-level overview that is directly relevant to both clinical decision-making and research prioritization.

Second, inclusion was restricted primarily to systematic reviews with quantitative meta-analyses, thereby prioritizing evidence derived from formal statistical synthesis rather than narrative interpretation alone. This approach reduces subjectivity and facilitates comparison of effect estimates across intervention categories. The inclusion of a single high-quality Cochrane review without meta-analysis was justified transparently and did not materially affect the overall evidence framework.

Third, methodological quality was systematically assessed using the AMSTAR 2 tool, allowing structured differentiation between high-, moderate-, low-, and critically low-confidence reviews. This enabled interpretation of findings in light of review quality rather than treating all pooled estimates as equally reliable.

A further strength is the formal assessment of overlap of primary studies using corrected covered area (CCA) metrics. Explicit evaluation of overlap—supported by citation matrices and heatmaps—allowed identification of areas where apparent consistency of findings may reflect shared underlying trials rather than independent replication. This approach enhances methodological rigor and guards against overinterpretation of convergent results.

Finally, the evidence synthesis was clinically structured and outcome-focused, emphasizing pain, quality of life, fertility, and recurrence—outcomes of greatest relevance to patients and clinicians—while maintaining a critical appraisal of the certainty and limitations of the evidence base.

Limitations

Several limitations should be acknowledged. Most importantly, the conclusions of this umbrella review are inherently constrained by the quality, design, and reporting of the underlying primary studies. Many included systematic reviews relied on small, heterogeneous trials with variable risk of bias, limiting the precision and generalizability of pooled effect estimates.

Substantial heterogeneity was observed across reviews in terms of patient populations, disease phenotypes, intervention protocols, outcome definitions, and follow-up durations. Pain outcomes were measured using multiple non-standardized instruments, and quality-of-life assessments were inconsistently reported, complicating cross-study comparisons and synthesis.

Follow-up durations in many primary studies were relatively short, particularly for chronic outcomes such as recurrence, long-term pain control, and fertility. As a result, the durability of treatment effects and long-term safety profiles—especially for hormonal therapies and newer GnRH antagonists—remain insufficiently characterized.

The use of a predefined time window for review inclusion, while intended to ensure clinical relevance and contemporary evidence, may have led to the exclusion of older studies that could provide additional longitudinal insight. However, this trade-off was considered acceptable to prioritize methodological quality and relevance to current practice.

Finally, as an umbrella review, this study did not perform new meta-analyses or reanalyze individual patient-level data. Consequently, it was not possible to resolve inconsistencies between reviews, adjust for

overlapping evidence beyond quantitative CCA assessment, or explore subgroup effects in greater depth than reported in the original syntheses.

5. Conclusions

This umbrella review demonstrates that the evidence base for endometriosis management is heterogeneous, uneven in quality, and highly dependent on a limited set of primary studies. Among available interventions, pharmacological therapies—particularly progestins and gonadotropin-releasing hormone modulators—are supported by the most consistent evidence for pain reduction, although differences in tolerability and long-term safety remain clinically relevant. Surgical strategies offer potential benefits for symptom control and selected reproductive outcomes but involve important trade-offs, especially with respect to ovarian reserve and procedural risk, underscoring the need for individualized decision-making.

Across reproductive settings, current evidence does not support routine hormonal pretreatment before assisted reproductive technologies, and the role of surgery prior to ART remains uncertain due to reliance on observational data and limited randomized comparisons. Complementary and lifestyle interventions show signals of benefit for pain and quality of life, but the certainty of evidence is low and these approaches should be considered adjunctive rather than definitive therapies.

Importantly, this review highlights substantial overlap of primary studies across systematic reviews, particularly in pharmacological domains, which may inflate perceived consistency of findings and reinforces the need for cautious interpretation. Future research should prioritize well-designed head-to-head randomized trials, standardized outcome measures, longer follow-up, and systematic management of evidence overlap to strengthen the foundations of evidence-based care in endometriosis.

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