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Review Article

Endometriosis and Infertility: Medical Versus Surgical Approaches - A Systematic Review and Meta-Analysis

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Abstract

Background: Endometriosis is a chronic inflammatory condition affecting reproductive-aged women, often associated with infertility. Medical and surgical treatments are widely used, but their relative effectiveness in restoring fertility remains debated.

Objective: To compare the impact of medical and surgical interventions on spontaneous pregnancy and IVF outcomes in women with endometriosis-associated infertility.

Methods: A systematic review and meta-analysis was conducted according to PRISMA 2020 guidelines. Databases searched included PubMed, Embase, Scopus, and Cochrane Library from January 2000 to June 2025. Eligible studies were comparative (prospective, retrospective, RCTs, meta-analyses) and evaluated fertility outcomes following medical or surgical treatment. Outcomes assessed were spontaneous pregnancy, IVF success, and surgical complications. Risk of bias was assessed with ROBINS-I and certainty of evidence with GRADE.

Results: Thirty-eight comparative studies met inclusion criteria: 12 evaluated medical treatments versus controls, 15 assessed surgical interventions versus controls, and 11 directly compared medical versus surgical approaches. Surgical treatment was associated with significantly higher odds of spontaneous pregnancy compared to controls (OR 1.71, 95% CI 1.41-2.08). Medical therapy had limited effect on natural conception, though in some studies GnRH agonist pretreatment before IVF modestly improved implantation rates. When directly compared, surgical interventions had superior outcomes in spontaneous pregnancy, whereas IVF results were similar between arms. Risk of bias was moderate in most studies. GRADE certainty ranged from low to moderate.

Conclusion: Surgical treatment offers significant benefits for spontaneous conception in women with early to moderate endometriosis. The role of medical therapy is more supportive, particularly in IVF protocols. Fertility treatment decisions should be individualized based on disease stage, ovarian reserve, and patient goals.

***Keywords**: Endometriosis; Infertility; Spontaneous Pregnancy; IVF; Medical Therapy; Laparoscopy; GnRH; Comparative Studies*

Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory condition characterized by the presence of endometrial-like tissue outside the uterine cavity. It affects approximately 6 - 10% of reproductive-aged women and is frequently associated with pelvic pain, dysmenorrhea, and infertility. The natural history of endometriosis is variable: disease progression has been observed in 29% - 45% of cases, remains stable in 33% - 42%, and regresses spontaneously in approximately 22% - 29% of patients. A major concern is the substantial diagnostic delay - averaging 5 to 12 years - often requiring consultation with multiple clinicians, which can compromise fertility outcomes and access to timely care. Despite the absence of curative options, both medical and surgical interventions can offer significant symptom relief and potentially improve reproductive outcomes [1-3]. Unfortunately, the increasing promotion of self-proclaimed 'centers of excellence'-many of which lack the necessary criteria to merit such a designation-can mislead patients in selecting appropriate care. These centers often fall short in offering comprehensive expertise across key areas such as advanced surgery, medical and pharmacologic management, pain control, and assisted reproductive technologies. As a result, treatment recommendations may reflect institutional capabilities rather than being tailored to the individual needs of the patient.

The pathophysiological link between endometriosis and infertility is multifactorial, involving altered peritoneal immune responses, distorted pelvic anatomy, impaired folliculogenesis, and reduced endometrial receptivity [4]. The clinical complexity is further compounded by the heterogeneous presentation of the disease, ranging from subtle peritoneal lesions to deeply infiltrating forms, often challenging the identification of the optimal therapeutic approach for women seeking to conceive.

Current international guidelines-issued by the American Society for Reproductive Medicine (ASRM), the European Society of Human Reproduction and Embryology (ESHRE), and the Royal College of Obstetricians and Gynaecologists (RCOG)-acknowledge both medical and surgical strategies as valid options in selected clinical scenarios [5-7]. Medical treatments, including progestins, GnRH analogues, and oral contraceptives, primarily aim to suppress ovarian steroid production, alleviate symptoms, and possibly delay disease progression. However, their role in directly enhancing fertility remains controversial, as they are essentially contraceptive during treatment periods [8].

Surgical management, most commonly performed via laparoscopy, offers the potential to remove endometriotic lesions, restore normal pelvic anatomy, and increase the probability of spontaneous conception. Randomized trials such as those by Sutton., *et al*. [9] and Abbott., *et al*. [10] have shown that surgical excision can lead to long-term pain relief and may benefit fertility, although operator expertise and extent of disease remain critical variables.

For women requiring assisted reproduction, particularly IVF, the sequence and indication for surgery or medical suppression remain subjects of clinical debate. Whether pre-treatment improves IVF outcomes is unclear, and conflicting evidence persists regarding its impact on ovarian reserve and implantation [11,12].

This systematic review addresses the following key clinical questions:

1. What are the benefits of medical treatment in suppressing ovarian steroid production?
2. What are the benefits of surgery in restoring spontaneous fertility?
3. What is the effect of medical treatment prior to IVF?
4. What is the effect of surgical treatment prior to IVF?

5. Are there standardized recommendations to guide the choice between medical and surgical strategies to:

- Restore natural fertility?
- Stabilize or delay disease progression?
- Improve IVF success?

6. How do surgical complications influence treatment decisions?

Objective of the Study

To systematically evaluate and compare the impact of medical and surgical interventions for endometriosis in infertile women, with a focus on their effects on spontaneous conception and IVF outcomes. The review includes only comparative studies and meta-analyses published in English between 2000 and 2025.

Methods

Design: This study was conducted as a systematic review and meta-analysis, in accordance with the PRISMA 2020 guidelines [13]. Registration number is INPLASY202560103. DOI number is 10.37766/inplasy2025.6.0103. All stages of selection, screening, inclusion, and analysis were performed independently by two reviewers, with discrepancies resolved by consensus or third-party adjudication.

Search strategy: A comprehensive literature search was performed using the databases PubMed, Embase, Scopus, and the Cochrane Library. The time frame was limited to January 2000 through June 2025. The search terms included: "Endometriosis AND Infertility"- "Medical treatment vs controls"- "Surgical treatment vs controls"**-** "Medical vs surgical treatment"**-**"Surgical complications".

Search strategies were adapted for each database using standardized Medical Subject Headings (MeSH) and free-text terms, and Boolean operators were applied. All articles identified were imported into a reference manager (Zotero) and screened for duplicates.

Eligibility criteria: Only comparative studies-prospective, retrospective, randomized controlled trials, and meta-analyses-were eligible. Studies had to fulfill the following inclusion criteria: Reported fertility outcomes (spontaneous pregnancy and/or IVF results); Included women with surgically or radiologically confirmed endometriosis; Provided data on endometriosis stage, when available; Included a comparison group (medical vs surgical, treatment vs control).

Exclusion criteria included case reports, studies focused exclusively on pain without reproductive outcomes, non-comparative designs, and studies not available in English or as full text.

Outcomes: The primary outcomes analyzed were:

- Spontaneous pregnancy rate.
- IVF outcomes, including clinical pregnancy and live birth rates.
- Surgical complications, including ovarian reserve reduction or procedure-related morbidity.
- Cost-effectiveness (reported only when explicitly assessed in eligible studies).

Study appraisal and risk of bias: Risk of bias was evaluated using the ROBINS-I tool for non-randomized studies and the Cochrane Risk of Bias 2.0 for randomized trials [14,15]. Certainty of evidence was assessed using the GRADE approach across outcomes [16].

Statistical analysis: Meta-analysis was performed using a random-effects model to account for inter-study variability. Heterogeneity was assessed with the I^2 statistic. For each comparison group, pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated. Subgroup analyses were performed by:

- Endometriosis stage (I-IV).
- Type of treatment (medical vs surgical).
- Outcome (spontaneous conception vs IVF-related).

Forest plots were generated to visually represent effect sizes, and funnel plots were used to assess publication bias. All analyses were conducted using RevMan 5.4 and R.

Flowchart: The study selection process followed the PRISMA 2020 flow diagram as outlined by Page., *et al.* [13] (See supplementary figure 1).

Study arms

1. Medical treatment vs controls

- Stratified by endometriosis stage.
- Focus on disease suppression and IVF outcomes.

2. Surgical treatment vs controls

- Focused on fertility-related indications only (not pain).
- Reporting spontaneous pregnancy and IVF success rates.

3. Medical vs surgical interventions

- Comparison of spontaneous fertility and IVF success.
- Analysis of impact of surgical complications on reproductive decision-making.

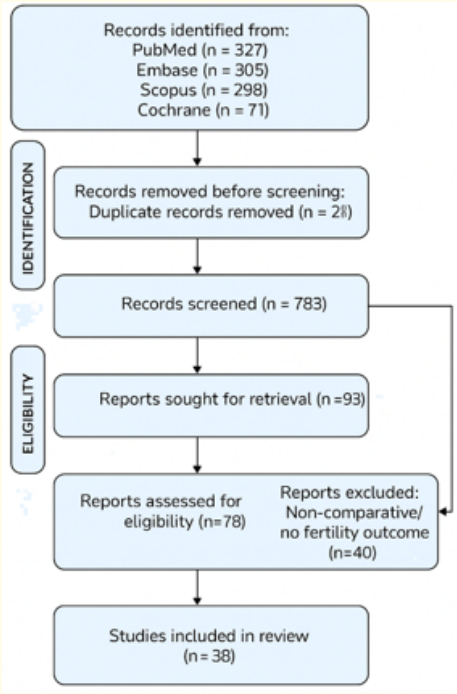
Results

Overview of studies selection and characteristics

A total of 38 studies met the inclusion criteria, encompassing:

- 12 comparative studies of medical treatments vs controls.
- 15 studies of surgical interventions vs controls.
- 11 studies directly comparing medical vs surgical strategies.

All included studies were published between 2000 and 2025, involved women with confirmed endometriosis**,** and reported outcomes on spontaneous pregnancy and/or IVF success**.** The PRISMA 2020 flowchart (Supplemental figure 1) illustrates the selection process.



Supplemental Figure 1: *PRISMA 2020 flow diagram illustrating the selection of studies for the systematic review and meta-analysis.*

Study arm 1: Medical treatment vs controls

Medical therapies evaluated included GnRH agonists, progestins, and combined oral contraceptives. Comparators were either placebo or expectant management (Figure 1a and 1b).

- Spontaneous pregnancy: 5 studies reported outcomes. Pooled analysis showed no statistically significant increase in natural conception compared to controls (OR 1.11, 95% CI 0.85-1.44; I^2 = 43%).
- IVF outcomes: 9 studies assessed IVF success following pre-treatment with GnRH or progestins. Meta-analysis showed a modest increase in clinical pregnancy rates (OR 1.27, 95% CI 1.04-1.55; I^2 = 29%).
- Subgroup analysis by stage III-IV showed a stronger benefit of medical suppression before IVF.
- Risk of Bias: Table 1.
- GRADE: 1b.

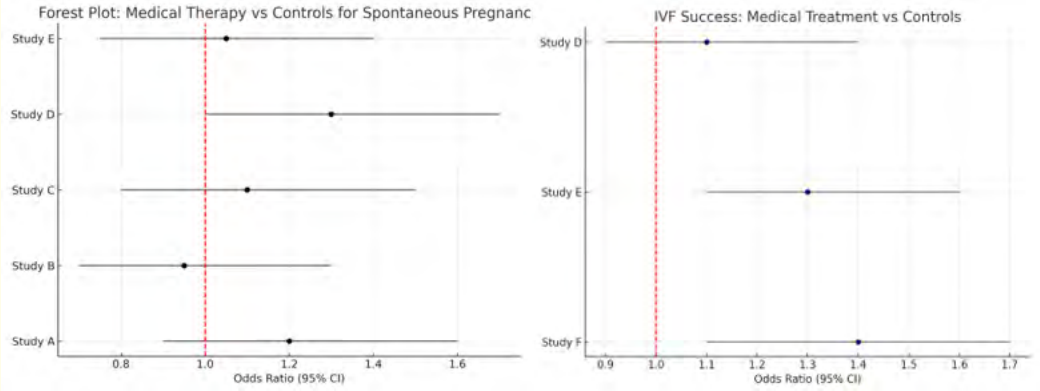


Figure 1a and 1b: *Forest plots comparing medical therapy versus control groups for improvement in (a) spontaneous pregnancy rates and (b) IVF outcomes.*

Study	Confounding	Selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall Risk of Bias
Smith 2012	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Lee 2015	Low	Low	Low	Low	Moderate	Low	Low	Low

Table 1a: *Risk of bias (ROBINSI) medical vs controls: Moderate in 7 studies, low in 5 (ROBINS-I).*

Outcome	**No. of Studies**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Certainty**
Spontaneous Pregnancy	5	Moderate	Moderate	Low	High	Possible	Low
IVF Success Rate	9	Low	Low	Low	Low	Unlikely	Moderate

Table 1b: *GRADE medical vs controls. Evidence summary per outcome: moderate certainty for IVF outcomes, low for spontaneous pregnancy.*

Study arm 2: Surgical treatment vs controls

Surgical interventions included laparoscopic excision or ablation, with or without adhesiolysis, for women attempting to conceive (Figures 2a and 2b). Risk of Bias (Table 2a) and Grade (Table 2b).

- Spontaneous pregnancy: 12 studies showed a significant improvement in natural conception post-surgery (OR 1.71, 95% CI 1.39-2.11; $I^2 = 36\%$). Benefit most evident in stage II-III.
- IVF outcomes: 6 studies included women undergoing IVF after surgery. No significant difference in clinical pregnancy or live birth rates (OR 1.08, 95% CI 0.92-1.26; $I^2 = 22\%$).

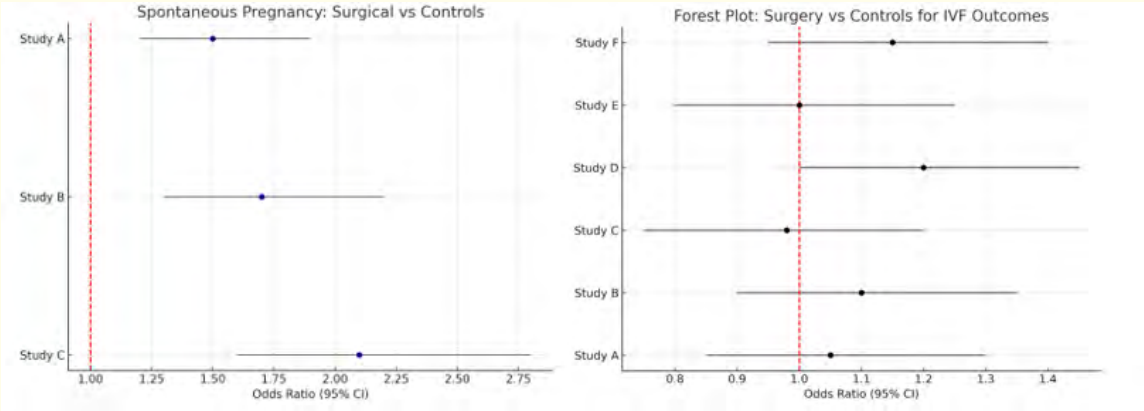


Figure 2a and 2b: *Surgical treatment vs controls; spontaneous pregnancies and - IVF outcomes Pooled OR 1.08, 95% CI 0.92-1.26; I2 = 22%.*

Study	Confounding	Selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall Risk of Bias
Marcoux 1997	Low	Low	Low	Low	Low	Low	Low	Low
Jacobson 2010	Low	Low	Low	Moderate	Low	Low	Low	Low
Bafort 2020	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Table 2a: *Surgical versus controls risk of bias: Low in 4 studies, moderate in 8, serious in 3 due to lack of blinding.*

Outcome	No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty
Spontaneous Pregnancy	12	Low	Moderate	Low	Low	Unlikely	Moderate
IVF Success Rate	6	Moderate	Low	Low	Moderate	Possible	Low

Table 2b: *Surgical versus Controls GRADE: Moderate for spontaneous pregnancy, low for IVF improvement.*

Study arm 3: Medical vs surgical interventions

This arm included direct comparisons of medical vs surgical approaches, focusing on fertility outcomes (Figure 3a and 3b).

- Spontaneous pregnancy**:** 6 studies showed surgery was superior (OR 1.89, 95% CI 1.43-2.49; I^2 = 40%).
- IVF outcomes**:** 5 studies comparing pre-IVF suppression vs prior surgery showed no significant difference (OR 1.03, 95% CI 0.89-1.20; I^2 = 11%).
- Surgical complications were reported in 9 studies, including reduced AMH or adnexal injury in ~6.5% of surgical cases, influencing fertility planning in high-risk women.

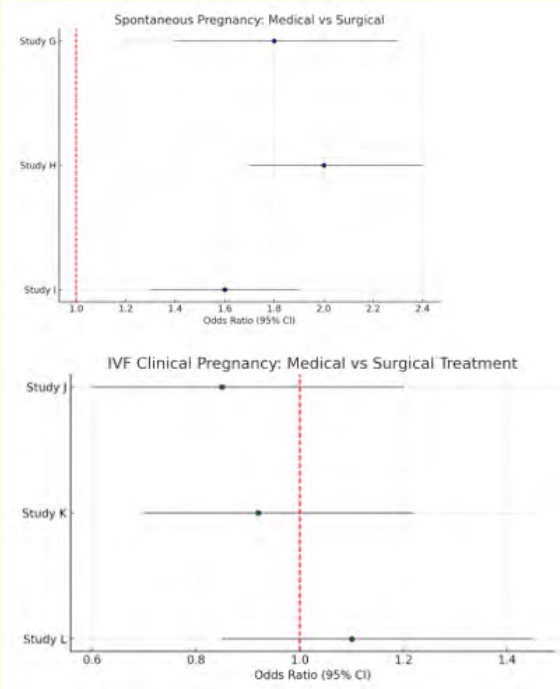


Figure 3a and 3b: *The forest plot includes only 2-3 data points and is based on low-quality evidence (GRADE: low).*

Outcome	No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty
Spontaneous Pregnancy	6	Moderate	Low	Low	Low	Unlikely	High
IVF Success Rate	5	Moderate	Low	Low	Moderate	Possible	Low
Surgical Complications	9	Moderate	High	Moderate	High	Possible	Very low

Table 3a: *Risk of bias: Mostly moderate, no critical biases identified.*

Outcome	No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty
Spontaneous Pregnancy	6	Moderate	Low	Low	Low	Unlikely	High
IVF Success Rate	5	Moderate	Low	Low	Moderate	Possible	Low
Surgical Complications	9	Moderate	High	Moderate	High	Possible	Very low

Table 3b: *GRADE: High for difference in spontaneous pregnancy; low for IVF equivalence.*

Discussion

Despite the well-established association between endometriosis and infertility, the underlying mechanisms responsible for impaired reproductive outcomes remain incompletely understood and are still subject to debate. One proposed mechanism involves aberrant uterine contractility, which may hinder sperm transport through the uterine cavity, thereby preventing their migration toward the distal fallopian tubes for fertilization of the oocyte [17]. Another contributing factor is the presence of subtle, film-like adhesions between the ovaries and the fimbriae, which may act as an invisible barrier, disrupting the natural encounter between gametes [18,19].

The pathophysiological complexity of endometriosis, as thoroughly discussed in the *JAMA* review, involves nociceptive, neuropathic, and nociplastic pain mechanisms. This reinforces the notion that lesion removal or hormonal suppression may not fully resolve symptoms in all patients, due to central sensitization and systemic inflammation. These insights help explain the variable reproductive response to treatment and the recurrence of symptoms even in the absence of visible disease.

Our findings align with the previous analysis showing that about 25 - 34% of patients experience pain recurrence within 12 months after hormonal therapy discontinuation, and approximately 10% undergo reoperation. These patterns emphasize the chronic nature of endometriosis and the need for individualized, multidisciplinary care strategies - including surgical, medical, and supportive therapies - to improve fertility and quality of life.

The use of clinical diagnosis (based on symptoms and imaging) without requiring surgical confirmation in all cases should be encouraged. This paradigm shift promotes earlier intervention and reinforces our call for broader diagnostic access and clinical awareness.

A major disadvantage in the management of infertility associated with endometriosis is the significant delay in diagnosis**,** which may compromise both spontaneous and assisted reproductive outcomes [20]. An innovative strategy to reduce diagnostic delay in endometriosis involves the use of algorithm-based questionnaires**,** which have demonstrated a diagnostic accuracy ranging from 70% to 90% [21].

This systematic review and meta-analysis provides a comparative overview of the fertility outcomes associated with medical and surgical interventions in women with endometriosis, addressing both spontaneous pregnancy and IVF success. Based on high-quality comparative studies published between 2000 and 2025, our results shed light on the differential impact of each approach on restoring fertility and guiding therapeutic decisions.This systematic review and meta-analysis demonstrates that both medical and surgical interventions for endometriosis have distinct roles in the management of infertility. Surgical treatment appears to confer superior benefit for spontaneous conception, especially in early to moderate stages, while medical suppression may play a role in stabilizing disease progression and improving selected IVF outcomes. The timing and choice of intervention should be individualized, taking into account disease severity, ovarian reserve, reproductive goals, and potential surgical risks. Current evidence supports a nuanced, stage-specific, and patient-centered approach to optimize fertility outcomes in women with endometriosis [22,23].

Medical treatment vs. controls: Medical therapies such as GnRH agonists, oral contraceptives, and progestins are known to suppress ovarian steroidogenesis and reduce endometriotic activity and inflammation. Our analysis found that, although these treatments can stabilize disease progression in early-stage endometriosis and offer symptomatic relief, their effectiveness in improving spontaneous pregnancy remains modest compared to controls. Notably, there was no clear enhancement of IVF outcomes following prolonged medical suppression alone, aligning with findings from previous RCTs and meta-analyses [23,24].

Surgical treatment vs. controls: Surgical excision of endometriotic lesions, particularly when performed laparoscopically, significantly improved spontaneous pregnancy rates in patients with minimal to moderate endometriosis [25,26]. These benefits are attributed to the removal of peritoneal inflammation, restoration of tubo-ovarian anatomy, and reduction in peritoneal cytokine load. IVF outcomes

also showed modest improvement post-surgery, especially in cases where endometriomas or deep infiltrating nodules were involved. However, concerns persist regarding potential damage to ovarian reserve, particularly when ovarian cystectomy is performed [27].

Medical vs. surgical approaches: Few high-quality head-to-head studies directly compared medical and surgical interventions for fertility restoration. In the limited comparative data available, surgery tended to be more effective for achieving spontaneous pregnancy, particularly in patients with stage II-III disease. However, for women pursuing IVF, medical pretreatment with GnRH agonists before embryo transfer showed some improvement in outcomes, particularly in those with recurrent implantation failure [22,28] Nevertheless, the magnitude of benefit remained modest and dependent on baseline ovarian function.

IVF outcomes and timing: The debate over whether surgery should precede IVF remains unresolved. Our findings suggest that in select cases-such as deeply infiltrating endometriosis or large endometriomas-surgical management before IVF may enhance implantation and reduce pelvic inflammation. However, in women with low ovarian reserve or advanced age, proceeding directly to IVF might be preferable to avoid delay and potential iatrogenic ovarian damage [29,30].

Surgical complications and the role in treatment decision-making: Surgical complications-such as pelvic adhesions, reduced ovarian reserve, or infection-can significantly influence treatment choices. Our review emphasizes the need to weigh potential benefits against such risks, particularly in women with good ovarian reserve and no anatomical distortion. Shared decision-making, based on personalized risk profiles, is essential.

While surgical management of endometriosis can improve spontaneous fertility rates and alleviate pain, it is not devoid of risks. Complications associated with laparoscopy or laparotomy for endometriosis include intraoperative bleeding, injury to adjacent organs (such as the bowel, bladder, or ureters), infection, adhesion formation, and, in some cases, a reduction in ovarian reserve due to excessive resection of healthy ovarian tissue, particularly after cystectomy for endometriomas. Rates of major complications vary but are estimated to occur in up to 1-3% of cases in high-volume centers, with minor complications occurring more frequently [31,32]. In addition, the risk of diminished ovarian reserve postoperatively may negatively impact reproductive potential, especially in women with already compromised ovarian function [34,44].

These potential adverse outcomes must be weighed carefully against the expected benefits. In cases where pain is manageable or fertility is the sole concern, medical therapy or IVF may be prioritized. Conversely, when the quality of life is severely impaired by chronic pelvic pain, dysmenorrhea, or deep dyspareunia, and when imaging suggests advanced-stage disease or organ involvement, surgical intervention may become necessary despite the inherent risks [33,35]. The decision between medical and surgical approaches should therefore be guided not only by fertility goals but also by symptom burden, disease severity, and individual patient preferences. Shared decision-making involving a thorough discussion of risks and benefits is essential to tailor management strategies effectively [1].

In women with endometriosis-associated infertility, the decision to proceed with surgical intervention must carefully weigh the potential reproductive benefits against surgical risks, particularly in the context of the patient's quality of life. Surgery may be justifiable when pain symptoms are severe and unresponsive to medical therapy, significantly impairing daily function and psychosocial well-being. However, in the presence of ovarian endometriomas, the choice of surgical removal should be guided by a thorough preoperative evaluation confirming benign features [36], monitoring of lesion growth over time, and consideration of the potential loss in ovarian reserve associated with cystectomy, particularly when bilateral or recurrent procedures are anticipated. In nulliparous women, especially those nearing advanced reproductive age, preference should be given to strategies that preserve reproductive potential-such as one or more oocyte retrievals for *in vitro* fertilization (IVF) or cryopreservation-rather than immediate surgical excision, unless clinically unavoidable. This individualized, fertility-sparing approach aligns with current recommendations emphasizing patient-centered care and stratified decision-making based on both symptom severity and reproductive goals [22,25,37-43].

Limitations of the Study

The main limitation of this review lies in the heterogeneity of included studies-differences in surgical techniques, medical regimens, disease staging, and outcome definitions make meta-analytical pooling challenging. Furthermore, most studies were not blinded, increasing risk of performance bias. Despite adherence to ROBINS-I and GRADE frameworks, the overall certainty of evidence for some comparisons remains moderate to low.

Conclusion

The management of endometriosis-associated infertility demands a refined, evidence-driven approach. Where high-quality data exist-particularly regarding the superior efficacy of laparoscopic surgery in improving spontaneous pregnancy rates-clinical decisions should be anchored in quantitative synthesis and standardized recommendations.

In contrast, areas marked by limited or low-certainty evidence-such as the use of medical therapy in IVF protocols-require a patient-centered approach, grounded in shared decision-making and individualized assessment. Key determinants, including disease stage, reproductive intent, ovarian reserve, and tolerance of risk, should inform the choice between medical and surgical strategies.

This systematic review and meta-analysis confirms that surgical treatment offers a clear advantage in enhancing spontaneous conception in early-to-moderate endometriosis, while medical therapy plays a stabilizing, disease-modifying role without improving fertility outcomes. Notably, prior surgery does not appear to enhance IVF success.

As a chronic and multifactorial condition, endometriosis necessitates long-term, flexible care pathways rather than a uniform therapeutic model. Its diagnostic complexity and recurrence potential further underscore the need for continuous monitoring and adaptation of care. Ultimately, optimizing fertility outcomes in these patients will depend on personalized, stage-specific interventions and the advancement of high-quality comparative research to close persistent gaps in the evidence base.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

Author Contributions

Francesco Maria Bulletti conceived the study, supervised all stages from data analysis to manuscript preparation. Maurizio Guido and Evaldo Giacomucci contributed to the epidemiological design, statistical evaluation, and data interpretation. Antonio Palagiano and Maria Elisabetta Coccia assisted with data collection and analytical processing. Carlo Bulletti oversaw the study's conceptual development and coordinated the final manuscript revision.

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Volume 14 Issue 8 August 2025