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INFERTILITY IN WOMEN WITH ENDOMETRIOSIS: MECHANISMS, BIOMARKERS AND CONTEMPORARY MANAGEMENT STRATEGIES – A REVIEW

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ABSTRACT

Introduction: Endometriosis is a chronic inflammatory disorder that affects approximately 6–10% of women of reproductive age and is found in up to 50% of those assessed for infertility. While advanced stages of the disease can compromise fertility through the formation of adhesions and anatomical distortions, clinically significant infertility can also occur in cases of minimal or mild endometriosis, highlighting the role of non-anatomical factors. Current evidence suggests that immune dysregulation, progesterone resistance, chronic endometrial inflammation, oxidative stress, and microbiome disturbances contribute to impaired implantation and diminished reproductive potential.
Objectives: This narrative review synthesizes current mechanistic and clinical evidence regarding endometriosis-related infertility, focusing on molecular pathways, evolving diagnostic methodologies, and fertility-oriented treatment strategies.
Methods: We searched PubMed, Scopus, and Google Scholar for publications from 2018 to 2025 on endometriosis and infertility. Priority was given to international clinical guidelines, systematic reviews, meta-analyses, and original studies addressing pathophysiology, diagnostics, fertility interventions (including surgery and assisted reproduction), and quality-of-life outcomes. A narrative synthesis was performed.
Results: Endometriosis shares key molecular and immunologic features with recurrent implantation failure, such as aberrant macrophage activation, T-cell imbalances, and impaired endometrial receptivity. Oral GnRH antagonists offer new options for symptom control while preserving flexibility in fertility planning. Emerging therapies target inflammation, immune pathways, and the endometrial microbiome. Ongoing trials (e.g., surgery-first vs. IVF-first) may identify optimal treatment sequences. However, delayed diagnosis and unequal access to fertility care remain major challenges worldwide.
Conclusions: Infertility associated with endometriosis is multifactorial and requires an individualized, multidisciplinary approach that integrates reproductive goals, symptom management, and psychosocial well-being. Further validation of biomarker panels and comparative-effectiveness studies is essential to refine clinical algorithms and enhance reproductive outcomes.

KEYWORDS

Endometriosis, Infertility, Immune Dysregulation, GnRH Antagonists, Quality of Life

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1. Introduction

Endometriosis is a chronic inflammatory gynecological condition characterized by the presence of endometrial-like tissue outside the uterine cavity. [1] It affects approximately 6–10% of women of reproductive age (around 190 million women worldwide). It represents a major global health problem due to its association with chronic pelvic pain, infertility, and reduced quality of life. [1,2] Despite its high prevalence, the diagnosis of endometriosis is frequently delayed, even up to 10 years, which contributes to disease progression, prolonged suffering, and delayed access to appropriate care. [3] Endometriosis is identified in up to 50% of women evaluated for infertility, highlighting its significant role in reproductive health disorders. [4,5]

Traditionally, endometriosis-related infertility was attributed primarily to mechanical factors such as pelvic adhesions and anatomical distortion. [6,7] However, clinical observations indicate substantial heterogeneity in reproductive outcomes, as women with similar disease stage and age may experience markedly different fertility potential. [8] This variability suggests that infertility in endometriosis cannot be explained solely by visible lesions but rather involves additional biological and systemic mechanisms. [6,8] Over the past decade, increasing attention has focused on immune dysregulation, progesterone resistance, oxidative stress, and alterations of the endometrial environment as contributors to impaired implantation and reduced reproductive capacity.[6,8]

At the cellular and molecular levels, endometriosis induces persistent inflammation and oxidative stress in the pelvis, driven by overactive immune cells and dysregulated cytokines. These changes may compromise

oocyte quality, sperm function, and endometrial receptivity, even when embryo quality is adequate.[7,9] Emerging evidence also links endometriosis with chronic endometritis and endometrial dysbiosis, highlighting the potential role of uterine inflammation and microbiome disturbances in implantation failure. [8,10]

While these mechanistic insights have expanded, clinical management has also evolved. Oral gonadotropin-releasing hormone (GnRH) antagonists have expanded medical options for symptom control while allowing rapid restoration of ovulatory function when fertility is desired. [8,11,12] Ongoing clinical trials, including comparative studies of surgery-first versus IVF-first strategies, aim to clarify optimal treatment sequencing for different patient subgroups.[7,8,13]

Beyond biological mechanisms, endometriosis-related infertility has profound psychological, social, and economic consequences. Women affected by endometriosis report higher rates of anxiety and depression, particularly when infertility is present, and often experience substantial deterioration in quality of life due to chronic pain, uncertainty, and repeated treatment failures. [14] Furthermore, disparities in access to timely diagnosis and specialized fertility care continue to limit optimal outcomes for many patients. [15]

The aim of this review is to synthesize contemporary evidence on the mechanisms linking endometriosis to infertility, emerging diagnostic and biomarker strategies, and evolving therapeutic approaches. Particular emphasis is placed on translating mechanistic knowledge into patient-centered, individualized care pathways that optimize reproductive outcomes while addressing the broader well-being of women affected by this condition.

2. Methods

This narrative review was based on literature addressing infertility associated with endometriosis. PubMed, Scopus, and Google Scholar databases were searched for publications from 2018 to 2025 using combinations of the terms “endometriosis,” “infertility,” “immune dysregulation,” “diagnosis,” “treatment,” “assisted reproduction,” and “quality of life.”

Priority was given to international clinical guidelines, systematic reviews and meta-analyses, and original clinical or translational studies relevant to reproductive outcomes and patient well-being. Studies addressing pathophysiological mechanisms, diagnostic tools, fertility-oriented interventions (surgical and assisted reproductive technologies), and psychosocial outcomes were included. Due to heterogeneity in study design and outcome measures, a narrative synthesis approach was applied. A formal risk-of-bias assessment was not performed.

3. Pathogenesis of Endometriosis-Related Infertility

3.1 The Inflammatory and Immune Microenvironment

Endometriosis is associated with a chronically dysregulated peritoneal immune environment. [6] Peritoneal macrophages commonly exhibit an inflammatory, pro-angiogenic phenotype with reduced phagocytic capacity. [6,16,17] Their activation is associated with increased secretion of cytokines (TNF-α, IL-6, IL-8) and growth factors, including VEGF, which may impair sperm motility and early embryo development.

Current evidence indicates that macrophage activity in endometriosis is functionally heterogeneous rather than uniformly pathogenic. Endometrial-derived macrophages tend to promote lesion persistence and angiogenesis (“pro-endometriosis”), whereas monocyte-derived peritoneal macrophages may exert more protective or regulatory effects.[16,17]

In parallel, natural killer (NK) cells often display reduced cytotoxicity and altered receptor expression, consistent with impaired immune surveillance and disrupted tolerance mechanisms relevant to implantation.[18]

Another repeatedly reported abnormality is Th17/Treg imbalance, characterized by Th17 predominance and a relative deficiency of regulatory T cells, which sustains chronic inflammation and weakens the tolerogenic immune state required at the maternal–fetal interface. [6] This imbalance may facilitate both the persistence of ectopic lesions and impaired implantation by disrupting immune tolerance mechanisms. Together, these immune alterations contribute to a hostile reproductive microenvironment that may impair gamete function, embryo development, and implantation. [6]

3.2 Endometrial Receptivity and Progesterone Resistance

Subfertility in endometriosis cannot be explained solely by anatomical distortion, as implantation failure has been reported even in minimal or mild disease. [6,7]

This observation supports the presence of intrinsic abnormalities of the eutopic endometrium.

Transcriptomic studies have demonstrated dysregulation of pathways involved in cell adhesion, angiogenesis, immune modulation, and decidualization during the window of implantation.[6,19] These molecular alterations may lead to a reduced or temporally displaced receptive phase, thereby limiting synchrony between embryo development and endometrial readiness.

Reduced expression of adhesion molecules, including integrins (αvβ3, α4β1), may hinder embryo attachment even when embryo quality is adequate. A central concept is endometrial progesterone resistance, defined as diminished responsiveness to progesterone despite normal systemic hormone levels. This resistance is linked to altered progesterone receptor signaling and impaired activation of progesterone-responsive gene networks, resulting in insufficient decidualization and a narrowed implantation window. [19]

3.3 Chronic Endometritis and Endometrial Dysbiosis

Recent evidence highlights additional, potentially modifiable contributors to infertility in subsets of women with endometriosis: chronic endometritis (CE) and endometrial dysbiosis.[20,21] CE is typically identified by CD138+ plasma cells and has been associated with lower implantation and live-birth rates in IVF populations.[22] Preliminary studies suggest that CE may be more prevalent in women with endometriosis, with reported rates ranging from approximately 25% to 40%, possibly reflecting impaired mucosal immune defense and chronic uterine inflammation.[21] Notably, limited data indicate that diagnosing and treating CE (for example, with antibiotic therapy guided by CD138 testing) may improve implantation outcomes in women with documented CE and prior IVF failure.[20]

Endometrial dysbiosis, characterized by reduced Lactobacillus dominance and increased anaerobic taxa, has also been described in endometriosis and recurrent implantation failure. This altered microbial profile is associated with a pro-inflammatory uterine milieu, including elevated endotoxin levels, increased cytokine expression (e.g., IL-6, TNF-α), and altered epithelial barrier and immune-regulatory gene expression. Although causality remains under investigation, these associations support ongoing interest in microbiome-directed interventions, including antibiotic and probiotic strategies, as adjunctive approaches in carefully selected patients.[20]

4. Precision Diagnostics and Biomarkers

4.1 Shared Molecular Signatures Between Endometriosis and Recurrent Implantation Failure

A growing body of evidence suggests that endometriosis and unexplained recurrent implantation failure (RIF) share overlapping molecular and immunologic abnormalities within the endometrium. [23] Comparative transcriptomic and multi-omics analyses have identified dysregulated pathways related to inflammation, angiogenesis, immune regulation, and tissue remodeling in both conditions.[23,24] These shared molecular features support the concept that, in a subset of patients, RIF may reflect an endometriosis-like endometrial phenotype, even in the absence of surgically detectable lesions.[8] This observation challenges a purely lesion-based view of endometriosis-related infertility and highlights the functional role of the ectopic endometrium. Consequently, conventional diagnostic approaches that focus solely on laparoscopic findings may fail to capture clinically relevant endometrial dysfunction, underscoring the need for molecular and immunologic diagnostics capable of detecting subtle impairments in receptivity.[8]

4.2 Towards Biomarker-Driven Phenotyping

Because endometriosis-associated infertility is heterogeneous, biomarker-driven phenotyping aims to support individualized management. [8,24] Instead of relying exclusively on disease stage, this approach seeks to integrate molecular, immunologic, and clinical features to better characterize infertility risk. Proposed dimensions include lesion type and location (e.g., endometriomas versus deep disease), with implications for ovarian reserve and natural fertility potential.[8] In addition, inflammatory burden and immune profiling may help identify patients who could benefit from targeted anti-inflammatory or immunomodulatory strategies. [8,24] Endometrial receptivity testing represents another proposed component, particularly in patients with recurrent implantation failure, to address implantation timing or progesterone resistance. Assessment of chronic endometritis and endometrial microbiome status may further refine phenotyping by identifying potentially reversible uterine factors. [20,24] Although not yet routinely implemented, this multidimensional stratification reflects a shift toward precision-oriented, phenotype-informed care rather than uniform treatment algorithms.[8]

5. Contemporary Therapeutics and Emerging Approaches

5.1 Oral GnRH Antagonists

Oral GnRH antagonists, including elagolix (FDA approved in 2018) and relugolix (approved in several regions from 2021 onward), represent a major advance in endometriosis pharmacotherapy.[25–27] By directly blocking pituitary GnRH receptors, they rapidly and reversibly suppress gonadotropin release and ovarian estrogen production, without the initial flare typical of GnRH agonists.[28,29] Clinical trials have shown meaningful reductions in dysmenorrhea and non-menstrual pelvic pain, together with improvements in daily functioning and patient-reported quality of life.[28,30]

Compared with long-acting GnRH agonists, oral antagonists allow dose-dependent (partial or near-complete) estrogen suppression and are often combined with add-back therapy, which helps mitigate hypoestrogenic adverse effects, including vasomotor symptoms and bone mineral density loss.[31] Their appeal in fertility planning relates to reversibility, as ovulation typically returns soon after discontinuation.[32] Short-term pre-treatment before IVF is being investigated, but current evidence is still limited and should be interpreted cautiously.

5.2 Emerging Precision Pharmacotherapies Targeting Specific Mechanisms

Beyond hormonal suppression, investigational strategies increasingly aim to target mechanisms implicated in endometriosis-related infertility. These include selective progesterone receptor modulators (SPRMs) proposed for progesterone-resistant phenotypes, anti-angiogenic and anti-fibrotic agents intended to limit lesion vascularization and adhesion formation and macrophage-targeted immunomodulatory approaches designed to reduce pro-inflammatory polarization and improve immune balance in the pelvis and endometrium.[17,33,34] Microbiome-directed interventions, such as antibiotic treatment for documented chronic endometritis followed by probiotic restoration, have also been proposed to improve the implantation microenvironment in selected patients.[20] At present, these approaches remain experimental and are best framed as adjunctive options in carefully selected cases rather than routine therapy.

5.3 Surgical Management: Individualizing the Role of Surgery

Surgery can restore pelvic anatomy and remove endometriotic lesions, but it may also compromise ovarian reserve (particularly after endometrioma excision) and carries a risk of recurrence. For this reason, most recent frameworks emphasize individualized decision-making rather than “surgery first” for all patients.[35,36]

Comparative effectiveness studies evaluating first-line surgery versus first-line IVF (in vitro fertilization) in endometriosis-associated subfertility have reported broadly comparable fertility outcomes, with differences driven mainly by patient phenotype, age, ovarian reserve, and symptom burden.[36] For ovarian endometriomas, routine surgery for small or asymptomatic cysts solely to improve fertility is generally not recommended, given limited reproductive benefit and potential harm to ovarian reserve.[37] Surgery is more often considered when cyst size, pain symptoms, malignancy suspicion, or technical limitations for oocyte retrieval justify intervention. Ongoing trials may clarify which subgroups benefit most from early surgery versus early assisted reproduction technology (ART).[36]

5.4 Assisted Reproductive Technology (ART): Tailoring to the Endometriosis Phenotype

In vitro fertilization (IVF) is a key pathway to pregnancy in endometriosis-associated infertility, with cumulative live-birth outcomes broadly comparable to those in other infertility populations when contemporary protocols are used. [12,38] Treatment strategies are increasingly tailored to patient phenotype, and GnRH antagonist stimulation protocols are commonly applied. [38]

Embryo selection strategies may be emphasized when oocyte competence is a concern. [23] Short pre-treatment regimens before IVF are being explored in patients with recurrent implantation failure to improve endometrial receptivity, although evidence remains mixed and insufficient for universal recommendations.[20,23] In patients with confirmed chronic endometritis or dysbiosis, some centers incorporate targeted treatment before embryo transfer to optimize the uterine environment, reflecting a more individualized approach rather than a standardized pathway.[20–22]

6. Health, Well-Being and Health-Systems Perspectives

6.1 Psychological Impact and Mental Health

Endometriosis-related infertility is associated with a substantial psychosocial burden. Women affected by endometriosis have higher rates of depression and anxiety, particularly when infertility is present. [14] This burden is driven not only by infertility itself but also by diagnostic delays, symptom invalidation, and uncertainty surrounding treatment outcomes. [3,5]

Repeated treatment failures, disruption of life plans, and sexual dysfunction related to dyspareunia and treatment side effects further contribute to emotional distress and reduced quality of life.[14] Evidence also suggests a bidirectional relationship between psychological stress and disease activity, whereby chronic stress may exacerbate inflammatory and neuroendocrine dysregulation, potentially worsening symptoms and reproductive outcomes.[6,14]

Overall, these findings indicate that mental health assessment and psychosocial support should be integrated as core components of fertility care for women with endometriosis rather than treated as optional adjuncts. [14]

6.2 Health-System Barriers and Equity Concerns

Despite advances in diagnostics and treatment, access to timely diagnosis, specialist imaging, expert surgery, and fertility services remains uneven across healthcare systems. Such disparities contribute to prolonged diagnostic delay and variation in reproductive outcomes between populations.[3,5,39]

Financial barriers, limited insurance coverage for assisted reproductive technologies, and regional differences in specialist availability can restrict treatment options and exacerbate inequities.[15,39] In addition, gaps in awareness and training among frontline healthcare providers may lead to normalization of symptoms and delayed referral to specialist care, further reinforcing diagnostic delay.[3,5]

Without parallel improvements in health-system capacity and policy support, advances in precision diagnostics and novel therapies risk disproportionately benefiting patients with greater access to resources.[5,15]

6.3 Integrating Well-Being into Care Pathways

Recent care models emphasize patient-centered pathways that integrate fertility treatment with symptom management and psychosocial support. [40] Such models emphasize shared decision-making, particularly when choosing between surgical intervention, medical therapy, and assisted reproductive technologies.[41]

Multidisciplinary teams involving gynecologists, reproductive endocrinologists, pain specialists, and mental health professionals allow adequate management of fertility goals and quality-of-life concerns. In this context, monitoring patient-reported outcomes, including pain severity, functional impairment, and psychological well-being and alongside reproductive endpoints may improve care tailoring and patient satisfaction.[40,41] Integrating well-being into endometriosis care pathways recognizes that successful treatment extends beyond pregnancy rates and must address the broader, long-term impact of the disease.

7. Discussion

7.1 A Phenotype-Informed Approach and Heterogeneity

Endometriosis-related infertility arises from heterogeneous biological and social determinants. No single mechanism explains fertility impairment in all patients. Instead, individuals differ in the relative contribution of anatomical distortion, endometrial dysfunction, immune dysregulation, and systemic influences. [7,8,38] This heterogeneity challenges stage-based models of disease severity and supports a more individualized, phenotype-informed approach to management.[8,38]

7.2 Mechanistic Advances and Convergent Observations

Over the past decade, mechanistic understanding of endometriosis has expanded substantially. [1,6,8,9] The disease is increasingly recognized not only as a localized pelvic condition but also as a systemic disorder shaped by immune dysregulation, chronic inflammation, hormonal resistance, and possibly microbial imbalance. [6,8,9,20,21,38] Several findings have been consistently reproduced across independent studies, including an inflammatory peritoneal milieu with aberrant macrophage polarization and elevated cytokine levels; impaired endometrial progesterone responsiveness contributing to defective decidualization and Th17/Treg imbalance linking endometriosis with other inflammatory reproductive failures. [6,16,18] Together, these convergent observations strengthen the biological plausibility of targeting these pathways therapeutically. [8,18,38]

7.3 Bridging Endometriosis and Recurrent Implantation Failure

The recognition of overlapping molecular signatures between endometriosis and recurrent implantation failure (RIF) creates a conceptual bridge between these conditions. [23,24] This overlap suggests that a subset of patients labeled as having "idiopathic" RIF may exhibit an endometriosis-like endometrial phenotype, even absent surgically visible lesions. This reframes implantation failure as, at least in part, a disorder of endometrial function rather than solely of embryo competence. [23,24]

7.4 Knowledge Gaps and Evidence Limitations

Emerging fields, particularly chronic endometritis and the endometrial microbiome, highlight that key aspects of disease pathophysiology remain incompletely defined. [10,20,21] Early data suggesting that targeted antibiotic or microbiome-modulating strategies may improve implantation in selected patients are promising but remain limited. [20–22] Current evidence does not support routine screening or treatment in all patients, underscoring the need for well-designed prospective trials. [20,21,38]

7.5 Translating Mechanisms Into Clinical Outcomes

The central challenge lies in translating mechanistic insights into measurable improvements in clinical outcomes. [8,38] Several gaps persist. First, many candidate biomarkers, including receptivity profiles and inflammatory signatures, show potential but lack robust validation in large, diverse populations. Without such validation, clinical implementation remains constrained. [8,23,38] Second, despite ongoing comparative trials, high-quality evidence guiding optimal treatment sequencing, such as surgery-first versus IVF-first strategies or the role of short-term hormonal pre-treatment, remains insufficient. [7,8,36,38]

7.6 Implementation and Equity Barriers

Implementation barriers further complicate translation into practice. Even when associations are recognized, integrating additional diagnostic steps into fertility pathways can be challenging due to variability in clinical protocols, invasiveness of testing, and lack of consensus guidelines. If future evidence supports broader integration of such assessments, standardized and minimally invasive diagnostic tools will be essential. [8,38,42]

Equity considerations are equally critical. Precision diagnostics and advanced fertility treatments are often resource-intensive, and unequal access risks widening disparities in reproductive care. Without parallel investment in health-system capacity, insurance coverage, and provider education, innovations may disproportionately benefit patients in high-resource settings. [5,15,39]

7.7 Clinical Implementation: An Individualized Framework

Clinically, an individualized management framework is increasingly feasible. Upfront assessment of age, ovarian reserve, symptom burden, lesion characteristics, prior treatments, and patient priorities should guide initial therapeutic choices. [7,8,36,38] For example, younger patients with significant pain and preserved ovarian reserve may prioritize symptom control before fertility treatment, whereas older patients with diminished reserve may reasonably proceed directly to IVF to maximize time-sensitive reproductive potential.[7,36,38] Across scenarios, shared decision-making remains central, aligning evidence-based options with patient values and life goals. [40,41]

8. Conclusions

Endometriosis-related infertility remains a major clinical challenge, yet recent advances support cautious optimism. The condition is increasingly understood as a multifactorial disorder in which immune dysfunction, progesterone resistance, oxidative stress, and microbiome-associated mechanisms may converge to impair fertility. Importantly, the relative contribution of these factors varies substantially between individuals, moving clinical thinking beyond stage-based models toward a more nuanced understanding of disease-related subfertility.

In parallel, diagnostic and therapeutic options continue to expand. Oral GnRH antagonists have improved symptom control while preserving flexibility in fertility planning, and emerging immune-targeted and microbiome-directed strategies may further broaden future treatment pathways. At the same time, evidence increasingly supports phenotype-informed decision-making, rather than uniform treatment sequences, particularly in the context of surgery and assisted reproductive technologies.

The promise of precision medicine in endometriosis extends beyond pregnancy rates. Effective care must also address pain, emotional burden, and long-term quality-of-life outcomes, recognizing that fertility treatment does not occur in isolation from the broader disease experience. Integrating psychosocial support and shared decision-making into care pathways is therefore essential.

Finally, equitable access remains a defining priority. Without parallel investment in health-system capacity, insurance coverage, and specialist training, advances in diagnostics and therapy risk widening existing disparities. Ensuring that progress translates into population-level benefit will require coordinated clinical, research, and policy efforts.

In summary, management of endometriosis-related infertility is moving toward individualized, evidence-based, and patient-centered care. Continued research should prioritize biomarker validation, comparative treatment-sequencing trials, and development of accessible clinical tools. Combined with a commitment to equity, these efforts offer the greatest potential to improve both reproductive outcomes and overall well-being for women affected by endometriosis.

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