Systematic review of endometriosis

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Abstract

Endometriosis, a chronic gynecological disorder characterized by the growth of endometrial-like tissue outside the uterus, affects a significant percentage of reproductive-age women and remains a complex condition with multifaceted clinical, biological, and genetic dimensions. This systematic review critically synthesizes the most highly cited research over the last decade to provide a comprehensive, evidence-based overview of the advances in endometriosis, spanning its epidemiology, pathophysiology, diagnostic approaches, and treatment modalities.

By categorizing studies into key themes, this review highlights emerging insights into the etiology and mechanisms of endometriosis, emphasizing the roles of genetic predisposition, immune dysregulation, and environmental factors. Recent developments in diagnostic techniques, particularly those improving non-invasive diagnostics, are examined, reflecting a shift toward early, accessible detection aimed at mitigating the condition's impact on fertility and quality of life. Furthermore, therapeutic strategies are explored, from pharmacological innovations and hormonal treatments to the evolving scope of surgical interventions, including fertility-preserving options. This work underscores the significant progress made in understanding endometriosis, while also identifying enduring challenges in effective long-term management and individualized care. Limitations in current research, such as the variability in diagnostic criteria and the scarcity of longitudinal data, are discussed to underscore areas for future investigation.

Key words: *Endometriosis; pathogenesis; treatment; fertility impact; psychological impact*

INTRODUCTION

Endometriosis is a chronic, inflammatory, estrogen-dependent disease defined by the presence of endometrial-like tissue outside the uterine cavity, predominantly affecting women of reproductive age. It is associated with a broad spectrum of symptoms, including dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility, significantly impacting patients' physical, emotional, and social well-being [1-5]. The global prevalence is currently estimated at 10–15% among women of reproductive age, although the true incidence may be underestimated due to diagnostic delays and variability in clinical presentation [1,6-8].

The burden of endometriosis extends beyond clinical manifestations. It imposes a significant economic cost due to direct medical expenditures and productivity loss and is now widely recognized as a public health issue [9–15]. The average diagnostic delay, reported between 7 and 10 years, highlights systemic deficiencies in early recognition and accurate diagnosis, often attributed to the normalization of menstrual pain, the lack of non-invasive biomarkers, and inconsistent symptomatology [16-20]. Additionally, disparities in access to healthcare services across different populations exacerbate the diagnostic gap, especially in low-resource settings [21-23].

Over the years, substantial progress has been made in understanding the complex pathophysiology of endometriosis, encompassing genetic, immunologic, and hormonal factors. Despite this, challenges remain in its diagnosis and management. Laparoscopy with histological confirmation remains the diagnostic gold standard

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[24-28]. Less-invasive imaging modalities and biomarker-based approaches are under active investigation [29-36].

Therapeutic options are diverse, ranging from pharmacological treatments—mainly hormonal suppression—to surgical interventions and assisted reproductive techniques in the case of infertility [28,38-45]. However, there is currently no definitive cure, and recurrence after treatment remains common [24,37,38,46,47]. The management of endometriosis should be individualized, taking into account the severity of symptoms, reproductive goals, patient age, and coexisting medical conditions, thereby emphasizing the importance of a patient-centered approach [13,48-50].

This systematic review synthesizes current evidence regarding the epidemiology, pathogenesis, clinical manifestations, diagnostic methods, therapeutic strategies, and socioeconomic implications of endometriosis. Furthermore, it explores emerging research directions and knowledge gaps that could inform future innovation in diagnostics, personalized treatment, and policy-making [51-54].

1. METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework.

A comprehensive electronic search was performed across PubMed, Scopus and the Cochrane Library databases to identify studies published between January 2010 and August 2024.

The following keywords and Boolean operators were applied in various combinations: "endometriosis", "pathogenesis", "diagnosis", "management", "treatment", "fertility", "quality of life", "psychosocial impact" and "economic burden".

Only peer-reviewed original articles, systematic reviews, meta-analyses, and clinical guidelines written in English and involving human subjects were included. Exclusion criteria comprised non-English publications, animal studies, case reports, and non-peer- reviewed materials. Duplicates were removed before screening.

Two independent reviewers performed study selection and data extraction and discrepancies were resolved through consensus. The study selection process is presented in Figure 1.

2. EPIDEMIOLOGY

2.1 Global Prevalence of Endometriosis

The global prevalence of endometriosis is estimated at 10–15% among women of reproductive age, with variations depending on the diagnostic methods and population characteristics [1,6-8]. Underdiagnosis in developing countries may lead to inaccurate global estimates, while higher prevalence is reported in urban areas and is linked to lifestyle factors such as delayed childbearing, stress, and diet [7,55-58].

2.2 High-Risk Populations and Incidence Variability

Incidence rates of endometriosis are higher among women aged 20–40, with ethnic and socioeconomic disparities affecting diagnosis and access to care [14,21-23,59]. Genetic predisposition plays a significant role, with a heritability estimate of around 50% [60-65]. Familial aggregation and twin studies have confirmed this genetic influence, highlighting the importance of early recognition in high-risk populations [63-65].

2.3 Regional and Socioeconomic Influences on Endometriosis

Endometriosis is often underdiagnosed in low-income countries due to limited healthcare resources, while higher prevalence in developed regions may reflect improved diagnostic capabilities [14,21–23]. Environmental and occupational exposures, particularly to endocrine-disrupting chemicals (EDCs), have emerged as potential contributors to the rising incidence of endometriosis [55,56,58].

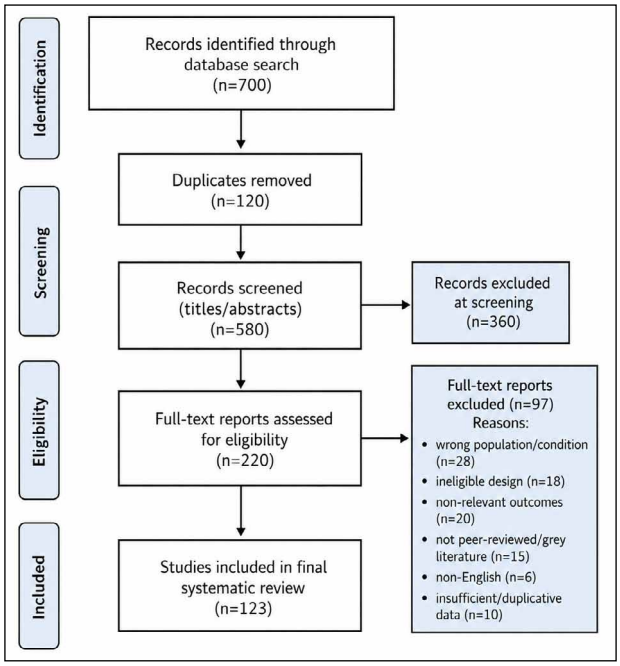

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

Socioeconomic disparities, access to gynecological care, and cultural perceptions of menstrual pain further affect diagnosis and disease management across populations [14,19–23].

Recent epidemiological data indicate that the global burden of endometriosis may be underestimated, especially among underserved groups, emphasizing the need for harmonized diagnostic criteria and the development of international registries [7,66].

3. PATHOGENESIS AND RISK FACTORS

3.1 Retrograde Menstruation and Other Pathophysiological Theories

The theory of retrograde menstruation, originally proposed by Sampson in 1927, remains a central explanation for pathogenesis of endometriosis [67-69]. It posits that menstrual debris containing viable endometrial cells travels backward through the fallopian tubes into the peritoneal cavity, where it adheres and proliferates on ectopic sites. However, this theory alone cannot explain all cases, including such as distant lesions or those occurring in women with obstructed menstrual flow [68,69].

Consequently, alternative mechanisms such as coelomic metaplasia, Müllerian remnant transformation, and stem-cell involvement have been proposed [68,69,70-72]. The coelomic-metaplasia theory suggests that peritoneal cells, under specific stimuli, may transform into endometrial-like cells [68-71]. Müllerianosis and lymphatic or hematogenous dissemination have also been implicated in extrapelvic disease, including thoracic and neural endometriosis [68,69]. More recently, bone-marrow-derived and mesenchymal stem cells have been shown to contribute to lesion initiation and persistence, particularly in deep infiltrating endometriosis and ovarian endometriomas [70-72].

3.2 Genetic and Epigenetic Factors

Familial clustering of endometriosis supports a genetic predisposition [62,63,65]. Twin and genome-wide association studies (GWAS) have identified susceptibility loci on chromosomes 1p36, 7p15.2, 9p21 and 12q22 [60,62,63]. Several single nucleotide polymorphisms (SNPs) near genes involved in estrogen metabolism [estrogen receptor 1 (ESR1)], cell adhesion [cyclin dependent kinase inhibitor 2B antisense RNA 1 (CDKN2BAS)], and immune modulation [wingless-type MMTV integration site family, member 4 (WNT4), vezatin (VEZT)] are consistently linked with increased risk [60,62,63,65,73]. A growing body of evidence supports a unifying genetic-epigenetic model linking heritable susceptibility with acquired molecular alterations in endometriotic tissue [74].

Epigenetic mechanisms — including DNA methylation, histone modifications, and non- coding RNAs — play a pivotal role in aberrant gene expression within endometriotic lesions [69,71,72,75]. Aberrant methylation of genes regulating steroid-hormone signaling, matrix remodeling, and inflammation (e.g. HOXA10, SF-1, CYP19A1) has been demonstrated [69,71,72]. Moreover, dysregulation of microRNAs such as the miR- 200 family and let-7 further contributes to lesion persistence, proliferation, and apoptosis resistance [69,71,72,75].

3.3 Inflammation and Immune Dysfunction

Endometriosis is increasingly recognized as a chronic systemic inflammatory disease [66,69,71]. Peritoneal fluid of affected women contains elevated levels of pro-inflammatory cytokines [interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α)] and growth factors [vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1)], promoting angiogenesis and lesion survival [69,71,72,76].

Macrophages, neutrophils, and activated T cells exhibit impaired phagocytic activity, enabling ectopic endometrial cells to evade immune clearance [69,71,72]. Natural killer cells show reduced cytotoxicity, while regulatory T cells (Tregs) are up-regulated, contributing to immune tolerance [69,71,72]. The detection of autoantibodies further supports a possible autoimmune component [71].

3.4 Hormonal Dysregulation

Endometriosis is an estrogen-dependent and progesterone-resistant disorder [69,72,77]. Ectopic lesions display increased aromatase expression and local estrogen production even without ovarian activity [69,72]. Progesterone-receptor isoform B (PR-B) is down- regulated in ectopic tissue, resulting in impaired responsiveness, persistent inflammation, and unopposed estrogen-driven proliferation [72,77]. Estrogen promotes cellular proliferation, angiogenesis, and neuroinflammation, enhancing lesion persistence [69,71,72]. The imbalance between estradiol and progesterone contributes to apoptosis resistance and chronic disease progression [69,72].

3.5 Environmental and Anatomical Factors

Exposure to endocrine-disrupting chemicals (EDCs) — including dioxins, polychlorinated biphenyls (PCBs) and phthalates — has been linked to increased endometriosis risk in both animal and epidemiologic

studies [55,56,58]. Although mechanisms are not fully elucidated, these agents likely disrupt hormonal signaling and immune surveillance [55,56,58]. Anatomical abnormalities such as Müllerian anomalies enhance retrograde menstruation and are associated with early-onset and severe disease [68,69,71]. Menstrual characteristics — early menarche, short cycles, prolonged bleeding — further modify individual risk [59,78,79].

4. CLINICAL PRESENTATION AND DIAGNOSIS

4.1 Symptomatology

Endometriosis exhibits a broad spectrum of clinical manifestations, ranging from asymptomatic cases to severe, debilitating symptoms. The most commonly reported include dysmenorrhea, non-cyclic pelvic pain, deep dyspareunia, dyschezia, dysuria, and infertility [81-83].

Symptoms are typically chronic and progressive, profoundly affecting quality of life [81,82]. Pain intensity often shows poor correlation with disease extent — women with minimal lesions may experience severe pain, while others with extensive disease can remain asymptomatic [81,82,84].

Infertility affects approximately 30–50% of women with endometriosis and may result from distorted pelvic anatomy, chronic inflammation, altered immune responses [69], or impaired folliculogenesis and endometrial receptivity [41,42,85-87]. Gastrointestinal and urinary manifestations are more common in deep infiltrating endometriosis (DIE), particularly when lesions involve the rectovaginal septum, bowel, or bladder [29,30,31,88].

Psychological distress — notably anxiety, depression, and sexual dysfunction — is highly prevalent, underscoring the need for a holistic, multidisciplinary management approach [89-92].

4.2 Classification and Staging

Multiple systems have been proposed to assess the extent and severity of endometriosis. The revised American Society for Reproductive Medicine (rASRM) classification remains the most widely applied, staging disease from I (minimal) to IV (severe) based on lesion location, depth, and adhesions. However, it correlates poorly with symptom burden and fertility outcomes [26,28,84].

To address these limitations, the #ENZIAN classification was introduced, enabling detailed topographic mapping of DIE and extraperitoneal disease compartments [93]. Comparative analyses suggest that #ENZIAN offers improved prognostic accuracy for fertility outcomes relative to rASRM and the Endometriosis Fertility Index (EFI) [94]. The EFI, in turn, is validated as a predictive tool for spontaneous conception following surgery and is increasingly adopted in reproductive practice [95]. Recent consensus guidelines emphasize the integration of these complementary systems into individualized clinical decision-making [96].

4.3 Diagnostic Modalities

The diagnostic gold standard remains laparoscopy with histological confirmation of endometrial glands and/or stroma in ectopic sites [24,26,28,97,98]. Its invasive nature and variable surgical expertise have, however, prompted a major shift toward non- invasive diagnostic approaches [24,28,30,34-36,99].

Transvaginal ultrasound (TVUS) is considered the first-line imaging tool for suspected endometriomas or DIE when performed by trained sonographers [29,31,100].

Magnetic resonance imaging (MRI) offers superior delineation and pre-surgical mapping, especially in complex or multifocal disease [28-31].

Serum biomarkers, notably CA-125, demonstrate limited sensitivity in early disease; novel candidates such as miRNAs, cytokine panels, and immune-modulatory molecules show promise but remain non-validated for clinical routine [32-35].

Artificial intelligence (AI)–based diagnostic tools are an emerging field, enhancing lesion detection on TVUS and MRI while reducing inter-observer variability. Early trials show high sensitivity but require large-scale validation before clinical adoption [100-103].

Given the absence of a reliable non-invasive test, timely recognition of characteristic symptoms, clinical expertise, and prompt referral remain essential for accurate diagnosis [16-20,24,25,28]. Future diagnostic strategies will increasingly rely on the integration of imaging, molecular, and AI-driven tools within specialized multidisciplinary centers [36,102]. The main diagnostic modalities are summarized in Table 1.

5. TREATMENT OPTIONS

5.1 Pharmacological Management

Medical therapy for endometriosis aims to suppress ovarian function, reduce estrogen- driven inflammation, and relieve pain.

First-line options include nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and combined oral contraceptives (COCs), which suppress ovulation and

Table 1. *Diagnostic Modalities for Endometriosis.*

Diagnostic Modality	Description / Mechanism	Accuracy (Sensitivity/ Specificity)	Key Advantages	Limitations	Reference s
TVUS (transvagin al ultrasound)	First-line imaging for ovarian endometrioma s and DIE; detects lesions in ovaries, rectovaginal septum, bladder.	DIE sensitivity > 90%, specificity > 85% (expert hands).	Widely available, non-invasive, low cost, dynamic.	Operator-dependent; limited for small superficial lesions.	[29,31,100]
MRI (magnetic resonance imaging)	Multiplanar mapping; valuable for complex or pre-surgical cases.	DIE sensitivity > 90%, specificity ≈ 88%.	Excellent soft-tissue contrast, detects extrapelvic disease.	High cost; limited access; specialized interpretation.	[28-31]
Serum biomarkers (CA-125, miRNAs)	Reflect inflammatory/ ectopic activity.	CA-125 sens. 50–70%; miRNAs promising but heterogeneous.	Simple, minimally invasive; adjunct to imaging.	Non-diagnostic alone; no validated biomarker for routine use.	[32-35]
AI-assisted imaging	Algorithm- aided TVUS/MRI for lesion detection/ class ification.	Early studies → high sensitivity (pilot data).	Reduces operator bias; speeds interpretation.	Still experimental; external validation needed.	[100-103]
Diagnostic laparoscopy (gold standard)	Direct visualization ± biopsy confirmation.	Specificity ≈ 100%.	Enables simultaneous diagnosis & treatment.	Invasive; anesthesia/surgical risk; cost.	[24,26,28,97]

induce a pseudo- pregnancy state to reduce menstrual bleeding [24,28,77,96].

Progestins such as dienogest and norethisterone acetate are widely used for their anti- estrogenic and anti-inflammatory effects. Dienogest, in particular, effectively reduces lesion volume and pain with excellent long-term tolerability [37,77].

Gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide, triptorelin) create a reversible hypoestrogenic state akin to medical menopause, reducing pain but often causing vasomotor symptoms, bone loss, and mood changes. Add-back therapy with low- dose estrogen–progestin is recommended for extended use [24,28,96].

GnRH antagonists (e.g., elagolix, relugolix) act directly at the pituitary level, providing dose-dependent estrogen suppression and faster reversibility. Recent phase-3 trials confirm significant improvements in pain and quality of life with manageable side effects [38].

Aromatase inhibitors (e.g., letrozole, anastrozole) can be used as adjuncts in refractory or postmenopausal cases, though their off-label status and bone demineralization risk limit long-term use [105].

Despite symptomatic relief, medical therapies do not eliminate lesions or prevent recurrence after discontinuation, emphasizing the importance of individualized, stepwise management [24,28,53,86]. The principal hormonal treatment options are summarized in Table 2.

5.2 Surgical Approaches

Laparoscopic surgery remains the cornerstone of definitive diagnosis and treatment, especially for cases resistant to medical therapy or associated with endometriomas and DIE [26,46,104,106,107,108].

The surgical goal is complete excision or ablation of visible lesions, adhesiolysis, and restoration of pelvic anatomy [46,104,106,107].

Excision is generally favored over ablation for deep lesions, as it offers lower recurrence and greater pain relief [46,104,106,107].

For ovarian endometriomas, cystectomy is preferred to drainage/coagulation, yielding improved symptom control and lower recurrence - though with possible impact on ovarian reserve [24,41,43,46,108].

Recurrence rates remain 30–50% within five years, depending on disease severity, surgeon experience,

Table 2. *Hormonal Therapies for Endometriosis: Mechanism, Efficacy, and Limitations*

Therapy	Mechanism of Action	Main Benefits	Limitations / Side Effects	Reference s
NSAIDs	Inhibit prostaglandin synthesis	Analgesia, menstrual pain relief	GI irritation, minimal lesion effect	[28,77,80,88,96]
COCs	Suppress ovulation, reduce menstrual flow	Cycle control, pain reduction	Breakthrough bleeding, contraindicated in vascular disease	[28,77,80,88,96]
Progestins (e.g., dienogest)	Endometrial atrophy, anti-inflammatory	Pain reduction, long-term safety	Irregular bleeding, mood changes	[77,37]
GnRH agonists	Pituitary downregulation → hypoestrogenism	Effective for severe pain	Bone loss, hot flushes → add-back therapy	[24, 28,96]
GnRH antagonists	Immediate, reversible suppression	Dose flexibility, rapid effect	Mild hypoestrogenic effects long-term	[38]
Aromatase inhibitors	Inhibit peripheral/local estrogen synthesis	Useful for refractory disease	Bone loss, arthralgia	[105]
SPRMs / SERMs	Modulate progesterone/ estroge n receptors	Promising targeted therapy	Limited clinical data	[28,50,77]

and postoperative hormonal suppression [37,44,46,77, 85,104,106,107]. The main surgical approaches and outcomes are summarized in Table 3.

5.3 Assisted Reproductive Technologies (ART)

For women with endometriosis-associated infertility, assisted reproductive technologies provide an effective route to conception [42,45,85,109].

In mild to moderate disease, intrauterine insemination (IUI) with ovulation induction may be attempted [42,85,109].

In advanced stages or after failed conservative management, in vitro fertilization (IVF) remains the preferred option [42,45,85,110].

Pre-IVF surgical treatment may improve outcomes in selected patients, but unnecessary surgery should be avoided to preserve ovarian reserve [41-44,85,95].

Meta-analyses confirm that fertility outcomes depend heavily on disease stage and prior surgery, underscoring the need for individualized reproductive planning [42,45,85,94,109,110].

5.4 Emerging and Complementary Therapies

Recent studies explore targeted molecular and immunologic therapies, including anti- TNF-α agents, angiogenesis inhibitors, and neuroinflammatory pathway modulators [47,50,102].

Cochrane evidence suggests anti-TNF-α may reduce

Table 3. *Surgical Approaches and Outcomes in Endometriosis.*

Surgical Technique	Indication / Lesion Type	Main Advantages	Risks / Limitations	References
Ablation (thermal/laser)	Superficial disease	Minimally invasive	Incomplete removal → recurrence	[46,106,107]
Excision (laparoscopic/ robotic)	DIE, endometriomas	Lower recurrence, QoL improvement	Technical complexity, potential complications	[46,106,107]
Cystectomy	Ovarian endometriomas >3–4 cm	Pain relief, improved IVF access	Reduced ovarian reserve	[43,46,108]
Bowel shaving/resection	DIE with bowel infiltration	Improved pain and bowel function	Surgical morbidity	[46,104,107]
Multidisciplinary surgery	Urinary + GI involvement	Complete anatomical restoration	Prolonged OR time, ↑ complications	[46,97,104,107]

pelvic pain but requires further validation [47].

The endocannabinoid system and microbiota modulation are new research frontiers, with cannabinoid-based interventions showing potential benefits for pain and inflammation control [111].

Complementary approaches — dietary modification, acupuncture, and pelvic-floor physiotherapy — may improve pain and quality of life, though evidence remains limited and heterogeneous [39,48,49].

5.5 Personalized and Multidisciplinary Management

A multidisciplinary, patient-centered model is essential for long-term disease control. Collaboration between gynecologists, fertility specialists, pain physicians, psychologists, and pelvic physiotherapists ensures comprehensive care [25,28,48,49].

Therapeutic decisions should consider symptom profile, fertility goals, patient age, comorbidities, and personal preferences, promoting optimal quality of life and functional outcomes [25,48,49,88].

6. FERTILITY AND PREGNANCY OUTCOMES

6.1 Impact on Fertility

Endometriosis is a major cause of infertility, affecting up to 50% of women seeking conception [85,112].

The underlying mechanisms are multifactorial. In advanced disease, pelvic adhesions and anatomical distortion compromise oocyte release, tubal patency, and fertilization [42,44,85]. However, even in minimal or mild endometriosis, infertility can result from subclinical inflammation, oxidative stress, immune dysregulation, and defective endometrial receptivity [71,86,87,113].

Endometrial receptivity is reduced due to altered expression of implantation markers such as integrins, Homeobox A10 (HOXA10), and leukemia inhibitory factor (LIF), all critical for embryo implantation [86,87]. Elevated concentrations of cytokines, prostaglandins, and reactive oxygen species (ROS) in the peritoneal and follicular fluid further impair gamete function and embryo development [71,76,114].

Ovarian endometriomas may adversely affect the follicular microenvironment, lower antral follicle count, and diminish ovarian reserve, particularly after repeated surgery or when bilateral [71,85,113].

6.2 Role of Surgery and ART

Laparoscopic excision of endometriotic lesions can improve spontaneous conception rates, especially in stage I–II disease [42,44,85]. However, its benefit in advanced disease is less consistent, as irreversible anatomic damage often limits natural fertility [42,44,85].

Assisted reproductive technologies (ART) — particularly in vitro fertilization (IVF) — remain the cornerstone of fertility management for moderate-to-severe endometriosis [42,44,45,110]. IVF outcomes are generally favorable, though some studies report reduced oocyte yield and implantation rates compared with those associated with other infertility etiologies [42, 45, 85, 109].

Surgical removal of endometriomas prior to IVF remains controversial. While it may enhance follicle accessibility and reduce local inflammation, it can also compromise ovarian reserve. Thus, intervention should be individualized and guided by endometrioma size, ovarian function, and previous surgical history [41-44,85].

The Endometriosis Fertility Index (EFI) is a validated tool integrating surgical and reproductive data to predict natural conception probability and guide the timing of ART [95]. The main fertility and pregnancy outcomes associated with endometriosis are summarized in Table 4.

6.3 Pregnancy Outcomes

Although endometriosis does not preclude pregnancy, affected women exhibit higher obstetric risk profiles. Meta-analyses have demonstrated increased rates of preterm birth, placenta previa, preeclampsia, small-for-gestational-age infants, and cesarean delivery [85,113,115].

In DIE, abnormal placentation and defective decidualization likely contribute to these complications through chronic inflammation and fibrosis at the implantation site [85,113,114].

Additionally, women with endometriosis have higher rates of first-trimester bleeding and spontaneous miscarriage, particularly those with severe pelvic disease or those with extensive adhesions [85,113,115].

Despite these risks, most pregnancies progress favorably with appropriate prenatal surveillance and multidisciplinary obstetric management [85,113,115].

Symptoms of endometriosis often improve during pregnancy due to hormonal suppression, but recurrence is common postpartum, necessitating counseling and long- term follow-up [113].

7. QUALITY OF LIFE AND PSYCHOSOCIAL IMPACT

7.1 Physical and Functional Impairment

Endometriosis profoundly affects physical functioning and daily life, mainly through chronic pelvic pain, fatigue, dysmenorrhea, and dyspareunia [4,90,116].

Table 4. *Fertility and Pregnancy Outcomes in Women with Endometriosis.*

Aspect	Findings / Mechanisms	Clinical Implications	References
Spontaneous fertility	Reduced fecundity even in minimal disease due to inflammation and altered receptivity	Early fertility assessment and individualized strategy	[71,85-87,113,114]
Surgical benefit	Excision improves conception in stage I–II; limited benefit in stage III– IV	Consider surgery before ART only if anatomic correction feasible	[42, 44, 85]
IVF / ART outcomes	Slightly lower oocyte yield and live-birth rate (~10– 15% lower vs. tubal factor infertility)	ART remains primary treatment; optimize stimulation protocol	[42,45,85,107,108]
EFI score	Combines surgical and reproductive factors	Predicts fertility potential; EFI ≥7 → high probability of conception	[95]
Endometriomas	Bilateral/recurrent cysts reduce reserve; surgery may worsen	Avoid repeated cystectomy unless symptomatic	[41-43, 85]

Many women experience reduced occupational productivity, including both presenteeism and absenteeism as well as restrictions in physical or social activities [117].

Pain, often cyclic, may evolve into a chronic state, severely impairing mobility, sleep, and overall well-being [90,116].

Beyond pain, persistent fatigue, gastrointestinal discomfort, and low physical stamina undermine quality of life [90,116].

Endometriosis-associated fatigue is increasingly recognized as a distinct clinical symptom, independent of lesion extent and is associated with inflammatory cytokines and endocrine dysregulation [90,114].

7.2 Psychological Distress and Mental Health

A substantial proportion of patients report anxiety, depression, and emotional distress. Chronic pain, dyspareunia, and infertility contribute to feelings of helplessness, frustration, and social isolation [89,90,118].

Elevated rates of major depressive and generalized anxiety disorders—and even suicidal ideation—have been documented among women with moderate-to-severe disease [51,90,108].

Sleep disturbance and emotional dysregulation frequently persist during asymptomatic phases, underscoring the chronic psychological dimension of endometriosis [51,90]. Dyspareunia further aggravates relationship strain and body-image dissatisfaction, fueling low self-esteem and sexual dysfunction [81,119].

Such psychological sequelae often remain unresolved despite medical or surgical therapy, emphasizing the need for integrated mental-health support within standard care [51,114].

7.3 Social and Relational Challenges

The social consequences of endometriosis extend to intimacy, relationships, and social participation. Fear of pain during intercourse may lead to avoidance, communication breakdown, and emotional withdrawal [81,119].

Among younger women, symptom unpredictability can interfere with education, dating, and career planning [83].

Persistent stigma and under ecognition contribute to delayed diagnosis and psychological suffering.

Many patients describe feeling dismissed or disbelieved by clinicians, relatives, or employers, thereby intensifying distress [19,20,119,120].

This invisibility often drives social isolation and loss of workplace belonging, reinforcing the importance of public awareness and advocacy [13].

7.4 Economic and Occupational Impact

The economic burden of endometriosis is substantial [11,13,15,117].

It includes direct healthcare costs (consultations, imaging, surgeries and medication) and indirect costs from reduced work capacity, disability leave, and productivity loss [11,15,117].

Women with endometriosis miss more workdays and are more likely to change jobs, or reduce working hours [13,117].

On average, 10–12 hours of productivity are lost

weekly per patient, with measurable national economic implications [11,117].

Combined with out-of-pocket medical expenses and limited insurance coverage, these factors highlights the need for earlier diagnosis, effective pain management, and supportive employment policies [13,15,117].

7.5 Importance of Holistic and Multidisciplinary Care

Optimizing quality of life requires a holistic, patient-centered model that extends beyond pharmacologic symptom control.

Comprehensive care should include psychological counseling, sexual therapy, physiotherapy, and social-support services tailored to individual needs [28,49,52]. Multidisciplinary teams—comprising gynecologists, psychologists, pain specialists, and physiotherapists—address the full biopsychosocial burden [28,49,52].

Education, empowerment, and self-management programs improve treatment adherence, coping skills, and emotional resilience, reinforcing their role in long-term management [49,52].

8. FUTURE DIRECTIONS AND RESEARCH PERSPECTIVES

Despite major progress in understanding endometriosis, significant challenges persist in diagnosis, treatment, and long-term management.

The future of research lies in interdisciplinary collaboration, emerging molecular technologies, and personalized medicine, all aiming for earlier detection, targeted therapies, and improved quality of life.

This section outlines the most promising directions shaping the next era of endometriosis research.

8.1 Refining Pathophysiological Models

Traditionally viewed as a gynecologic disorder caused by retrograde menstruation, endometriosis is now recognized as a complex, systemic disease driven by endocrine, immune, genetic, and epigenetic mechanisms [71,114,121].

Contemporary models suggest a multi-hit pathogenesis involving peritoneal inflammation, immune escape, altered stem-cell behavior, and epigenetic reprogramming [40,71,114,121].

Emerging evidence links aberrant Müllerian development and disruption of the endometrial–myometrial interface to DIE, particularly among adolescents and early-onset cases [71,104,123].

Such findings could lead to the identification of molecular subtypes ("phenotypes"), improving diagnostic accuracy, prognostic evaluation, and individualized therapy [27,62,104].

8.2 Biomarkers and Non-Invasive Diagnosis

A key unmet need remains the development of non-invasive diagnostic tools. While laparoscopy is the diagnostic gold standard, its invasive nature, cost, and contribution to diagnostic delay drive the search for reliable biomarkers.

Candidate markers include microRNAs, inflammatory cytokines (IL-6, TNF-α), CA-125, and vascular endothelial growth factor (VEGF); however their sensitivity and specificity remain inconsistent. Recent advances in transcriptomics, metabolomics, and proteomics from blood, urine, or menstrual effluent are promising avenues [96, 102].

Integrating these multi-omic signatures through machine learning and AI may enable high-accuracy diagnostic panels capable of complementing or replacing surgical confirmation [74,96,100,102,103].

AI-assisted imaging—especially MRI and high-resolution transvaginal ultrasound (TVUS)—is evolving toward automated lesion mapping, potentially revolutionizing early and non-invasive diagnosis [29,31,100,103].

8.3 Innovation in Therapeutics

The next generation of endometriosis treatment moves beyond hormonal suppression, targeting molecular pathways that drive inflammation, neuroangiogenesis, and fibrosis [40,72,121].

Current research directions include:

- Anti-angiogenic agents (e.g., bevacizumab, sunitinib) to suppress neovascularization and lesion growth [50,121].
- Immunomodulators (e.g., TNF-α and IL-1β inhibitors) to restore immune homeostasis and improve lesion clearance [122].
- Selective estrogen and progesterone receptor modulators (SERMs, SPRMs) offering tissue-selective hormonal control [28,50,77].
- GnRH antagonists (such as elagolix and relugolix) that allow dose-dependent suppression with fewer hypoestrogenic effects [28,38].
- Cannabinoids and neuromodulators for pain modulation through central and peripheral pathways [51,111].

Experimental frontiers include gene therapy, mesenchymal stem-cell repair, and anti- fibrotic molecules such as pirfenidone or transforming growth factor-β

(TGF-β) inhibitors, though these remain in preclinical stages [50,53].

8.4 Personalized Medicine and Disease Stratification

Endometriosis is a heterogeneous disorder—clinically, histologically, and molecularly. The rise of precision medicine—fueled by genomic and proteomic profiling—promises a transformative approach.

AI-based algorithms integrating clinical, imaging, and molecular data are being developed to predict disease progression, recurrence, and treatment response [96,100,102,103].

Patient stratification by molecular phenotype, hormone-receptor profile, or neurovascular characteristics could enable tailored therapies while minimizing overtreatment [27,62,96,104].

Ongoing and future clinical trials are adopting subgroup-specific designs, enhancing real- world applicability and moving toward truly individualized care [38,53,95].

8.5 Addressing Health Equity and Inclusion in Research

Historically, endometriosis research has underrepresented non-majority populations, creating critical knowledge gaps.

Future efforts must prioritize inclusivity across demographics and gender identities, encompassing:

- Adolescents, in whom disease may be underdiagnosed or misattributed to primary dysmenorrhea [123].
- Transgender and non-binary individuals, who face distinct diagnostic and therapeutic barriers.
- Ethnic and socioeconomic minorities, who disproportionately experience delayed diagnosis and limited care access [13,21-23].

Integrating patient-centered qualitative research and real-world registries from diverse populations is essential to develop equitable global guidelines and ensure that advances reach all affected individuals [14,23,59-61].

8.6 Policy Advocacy and Funding Priorities

Despite its high prevalence and economic burden, endometriosis remains underfunded relative to comparable chronic diseases.

Key policy priorities include:

- Expanding public awareness and menstrual health education to shorten diagnostic delay.
- Increasing investment in basic and translational research.
- Establishing national registries and longitudinal databases to monitor disease course and treatment outcomes.
- Embedding endometriosis management within broader reproductive health and chronic pain frameworks.

Sustained governmental and institutional support is vital to translate scientific progress into accessible, evidence-based care, ensuring measurable improvement in women's health worldwide [11-15,21,114]. Emerging therapeutic strategies are summarized in Table 5.

Table 5. *Emerging and Investigational Therapies in Endometriosis.*

Therapeutic Category	Example Agents / Targets	Proposed Mechanism	Development Stage	References
Anti-angiogenic	Bevacizumab, sunitinib	Inhibit neovascularization and lesion growth	Phase II	[50,121]
Immunomodulator y	TNF-α, IL-1β blockers	Restore immune clearance, reduce inflammation	Preclinical / Early clinical	[123]
Anti-fibrotic	Pirfenidone, anti-TGF-β	Reduce fibrosis and adhesion formation	Preclinical	[50,121]
Hormone receptor modulators	SERMs, SPRMs	Tissue-selective hormonal modulation	Phase II–III	[28,50,77]
Neuro-modulators	Cannabinoids, gabapentinoi ds	Central and peripheral pain modulation	Pilot studies	[51,111]
Regenerative / Gene-based	Mesenchyma l stem cells, CRISPR	Tissue repair and genetic correction	Experimental	[50,53]

9. ECONOMIC BURDEN OF DISEASE

Endometriosis imposes a substantial economic burden on individuals, healthcare systems, and society. Total costs include both direct medical expenses and indirect losses related to productivity, disability, and diminished quality of life [11-15,21,117].

9.1 Direct Costs

Direct healthcare costs encompass physician visits, diagnostic imaging, laboratory testing, medical therapy, and surgical interventions.

Among these, laparoscopy and repeat surgeries, particularly for deep infiltrating endometriosis (DIE), account for the largest proportion [12,117].

Prolonged diagnostic delay—often exceeding 7–10 years—further inflates costs due to repeated consultations, misdiagnoses, and ineffective treatments before definitive management [13,19,20,119].

A 2020 European cost-analysis reported an annual per-patient direct cost between €3,000 and €9,000, depending on disease severity, comorbidities, and treatment modality [12,15,21].

Recent health-economic comparisons indicate that endometriosis-related expenditures rival or surpass those of other chronic disorders such as diabetes or Crohn's disease, underscoring its underappreciated financial impact [11,12,14,15].

9.2 Indirect Costs

Indirect costs often exceed direct medical expenses, primarily through absenteeism, presenteeism, disability leave, and early workforce exit [12,15,117].

Women with endometriosis lose on average 10–12 hours of work productivity weekly, particularly during menses or symptomatic exacerbations [11,15,117].

Younger women may experience career delays or educational interruptions, while others face unreimbursed expenses for complementary therapies, fertility procedures, or travel to specialized centers [13,15,21].

A 2023 systematic review confirmed that productivity loss constitutes nearly two-thirds of the total economic cost in high-income countries [12,15,117].

9.3 Broader Societal Impact

At the population level, endometriosis translates into billions of euros in annual healthcare and productivity losses [11,12,21].

A global estimate (2012) placed the yearly economic cost at approximately $69.4 billion in the United States and €30 billion in Europe, with comparable trends in Asia and Latin America [12,15,117].

Despite this scale, endometriosis remains severely underfunded and insufficiently prioritized in public health frameworks.

Strategic investments in earlier diagnosis, streamlined treatment pathways, and multidisciplinary models of care could markedly reduce long-term costs and improve both clinical and economic outcomes [11,13-15,21,117].

10. CONCLUSIONS

Endometriosis is a multifaceted, chronic, and often progressive disease affecting a significant proportion of women of reproductive age, with wide-ranging repercussions for physical health, fertility, psychological well-being, and socioeconomic stability.

Although described over a century ago, it remains a diagnostic and therapeutic challenge due to its heterogeneity, elusive pathogenesis, and variable treatment response.

This review consolidates current evidence on the clinical, psychosocial, and economic burden of endometriosis.

Diagnostic delay remains a major barrier, leading to years of untreated symptoms and preventable suffering.

The absence of a pathognomonic marker and reliance on surgical confirmation perpetuate this gap, while ongoing advances in imaging and biomarker discovery hold promise for the future.

Pathophysiologically, endometriosis represents a systemic inflammatory and hormonal disorder, shaped by retrograde menstruation, immune dysregulation, genetic susceptibility, and epigenetic reprogramming.

The conventional classification into superficial peritoneal, ovarian, and deep infiltrating forms offers clinical guidance but does not fully capture its biological diversity.

Management must be individualized.

Pharmacologic therapies—COCs, progestins, and GnRH analogs—remain first-line for symptom relief, yet they are palliative rather than curative.

Surgical excision, though effective for diagnosis and pain relief, carries recurrence risk and may impact fertility, underscoring the need for judicious selection.

Assisted reproductive technologies (ART) continue to offer reproductive hope, but success rates vary by disease stage and prior surgery.

An interdisciplinary model, integrating fertility, pain,

and mental-health specialists, yields the most favorable long-term outcomes.

Beyond the physical domain, endometriosis exerts a profound psychosocial toll. Depression, anxiety, sexual dysfunction, and relationship strain are common and demand holistic, empathetic care.

Its economic cost, compounded by healthcare spending and lost productivity, further underscores the urgency for policy attention and resource allocation.

The future of endometriosis management will hinge on precision medicine, molecular phenotyping, artificial intelligence, and multi-omic integration, enabling earlier diagnosis and targeted therapy.

Investment in inclusive research, public education, and policy reform is essential to reduce diagnostic delay and improve equity in care access.

In conclusion, endometriosis must be recognized as a systemic, biopsychosocial condition requiring multidisciplinary collaboration, patient-centered strategies, and sustained scientific innovation.

By uniting research, clinical expertise, and advocacy, the global health community can move toward earlier diagnosis, improved quality of life, and true empowerment for the millions of women affected by this disease worldwide.

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