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Endometriosis: From delayed diagnosis to precision medicine

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Abstract

Endometriosis is a chronic, estrogen-dependent inflammatory disorder affecting approximately 10% of individuals of reproductive age worldwide and remains one of the most underdiagnosed and heterogeneous conditions in women's health. Increasing evidence demonstrates that endometriosis is not a single disease entity but a complex, multifactorial spectrum driven by hormonal imbalance, immune dysregulation, chronic inflammation, neuroangiogenesis, and genetic and epigenetic alterations. Profound disease heterogeneity across anatomical presentation, symptom severity, molecular profiles, and treatment response poses major challenges to diagnosis and management. A persistent diagnostic delay averaging 6–10 years from symptom onset continues to result in disease progression, chronic pain, infertility, psychological distress, and substantial socioeconomic burden.

This review examines the biological complexity of endometriosis and critically analyzes the causes and consequences of diagnostic delay. We synthesize emerging evidence on non-invasive diagnostic innovations, including circulating and menstrual biomarkers, microRNAs, advanced imaging modalities, and artificial intelligence–based tools, which collectively challenge the historical reliance on surgical diagnosis. We further explore how integrative "omics" approaches and molecular stratification are enabling the transition toward precision medicine, with the potential to predict treatment response and guide personalized therapeutic strategies.

Despite significant advances, barriers to clinical translation remain, including lack of standardized biomarkers, limited validation of AI models, and inequitable access to expert imaging. Addressing these challenges through coordinated research, education, and health system reform is essential. The integration of molecular profiling, non-invasive diagnostics, and patient-centered multidisciplinary care offers a transformative opportunity to reduce diagnostic delay and shift endometriosis management from reactive symptom control toward predictive, personalized care.

Keywords: Endometriosis; Diagnostic delay; Precision medicine; Disease heterogeneity

1. Introduction

Endometriosis is a chronic, estrogen-dependent, inflammatory gynaecological disorder defined by the presence of endometrial-like glands and stroma outside the uterine cavity. The disease predominantly affects women and individuals assigned female at birth during their reproductive years and is estimated to affect approximately 190 million people worldwide, corresponding to nearly 10% of the reproductive-age population (1, 2). Despite its high prevalence and substantial disease burden, endometriosis remains one of the most underdiagnosed and poorly understood conditions in women's health.

Endometriosis is increasingly recognized as a complex, multifactorial, and heterogeneous disease, rather than a single pathological entity. Its development and progression are driven by the interplay of hormonal, inflammatory,

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immunological, genetic, epigenetic, and environmental factors, which collectively contribute to marked variability in clinical presentation, lesion characteristics, and treatment response (1, 3).

Several theories have been proposed to explain the origin of endometriosis, none of which fully account for all disease phenotypes. The most widely accepted hypothesis remains retrograde menstruation, whereby endometrial fragments reflux through the fallopian tubes into the peritoneal cavity and implant ectopically (4). However, as retrograde menstruation occurs in the majority of menstruating individuals, additional factors such as immune dysfunction and altered cellular adhesion are required for lesion establishment and persistence.

Alternative and complementary theories include coelomic metaplasia, which proposes transformation of peritoneal cells into endometrial-like tissue, and stem /progenitor cell theories, suggesting that bone marrow derived or endometrial stem cells contribute to lesion formation at ectopic sites (5,6). These mechanisms may be particularly relevant in explaining endometriosis at distant or extra-pelvic locations.

Endometriosis is a profoundly estrogen-dependent disease, characterized by local estrogen overproduction within lesions. Aberrant expression of aromatase (CYP19A1) and reduced activity of 17β-hydroxysteroid dehydrogenase type 2 promote sustained local estrogenic stimulation, enhancing lesion growth and inflammation (7).

In contrast, progesterone resistance is a hallmark pathological feature. Reduced expression and altered signalling of progesterone receptor isoforms impair the anti-inflammatory and anti-proliferative effects of progesterone, contributing to treatment resistance and persistent disease activity (8). Recent molecular studies suggest that epigenetic silencing of progesterone receptor genes plays a central role in this resistance (9).

Endometriotic lesions exist within a chronic inflammatory microenvironment. Elevated concentrations of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), chemokines, prostaglandins, and growth factors are detected in peritoneal fluid and lesion tissue (10). This inflammatory milieu promotes angiogenesis, fibrosis, and lesion survival.

Immune dysregulation is central to disease persistence. Impaired natural killer (NK) cell cytotoxicity, altered macrophage polarization, and dysfunctional T-cell responses allow ectopic endometrial cells to evade immune clearance (11). Recent evidence highlights the role of macrophage-driven fibrosis and lesion innervation in chronic pain development (12). The coordinated growth of nerve fibers and blood vessels is now recognized as a key driver of endometriosis-associated pain. Lesions demonstrate increased sensory nerve density and altered nociceptive signalling, contributing to peripheral and central sensitization (13).

Genetic predisposition plays a significant role in endometriosis risk, with heritability estimates ranging from 40% to 50% (14). Genome-wide association studies (GWAS) have identified multiple susceptibility loci, including genes involved in hormone signalling, inflammation, and cell adhesion, such as WNT4, GREB1, FN1, and VEZT (15).

Epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs further modulate gene expression in endometriotic tissue. Recent studies demonstrate widespread epigenetic reprogramming in both utopic and ectopic endometrium, influencing hormone responsiveness, immune signalling, and cellular proliferation (16, 17). These epigenetic alterations are dynamic and may contribute to disease progression and therapeutic resistance.

Endometriosis exhibits pronounced heterogeneity across multiple dimensions:

- Anatomical heterogeneity: Lesions may be superficial peritoneal, ovarian (endometriomas), or deep infiltrating, each with distinct molecular and fibrotic profiles (18).
- Symptom heterogeneity: Pain severity does not correlate reliably with lesion burden, and some individuals remain asymptomatic despite extensive disease, while others experience severe pain with minimal visible lesions (19).
- Molecular heterogeneity: Transcriptomic and proteomic studies reveal distinct molecular signatures across lesion subtypes and between patients, suggesting the existence of biologically distinct endometriosis subtypes (20).
- Treatment response heterogeneity: Variable responses to hormonal therapies and surgery reflect underlying differences in hormone receptor expression, inflammatory pathways, and neural involvement (21).

Recent integrative “omics” approaches and machine-learning analyses support the concept of endometriosis as a spectrum of related disorders, rather than a single disease entity (3, 22). This heterogeneity poses major challenges for diagnosis and management but also provides a rationale for precision medicine approaches.

Understanding the complex pathophysiology and heterogeneity of endometriosis is essential for advancing personalized care. Molecular stratification based on hormone responsiveness, inflammatory signatures, genetic risk, and neural involvement may enable more accurate prognostication and targeted therapy selection (23). As research continues to unravel disease subtypes, future classification systems are likely to move beyond purely anatomical staging toward biologically informed frameworks.

Clinically, endometriosis is characterized by a wide spectrum of symptoms, including dysmenorrhea, chronic pelvic pain, dyspareunia, dyschezia, urinary symptoms, abnormal uterine bleeding, and infertility (24). However, symptom severity does not consistently correlate with the extent or anatomical distribution of lesions, complicating clinical recognition and disease assessment (25). As a result, many patients experience repeated misdiagnoses or dismissal of symptoms as "normal menstrual pain," contributing to prolonged suffering and delayed care (26).

Historically, endometriosis has been regarded as a localized pelvic disease, but growing evidence supports its classification as a systemic disorder involving immune dysregulation, chronic inflammation, neuroangiogenesis, hormonal imbalance, and genetic and epigenetic alterations. Lesions exhibit features such as progesterone resistance, local estrogen overproduction, oxidative stress, and altered immune surveillance, which collectively drive lesion persistence and pain generation (8). These complex mechanisms underscore the biological heterogeneity of endometriosis and challenge the traditional "one-size-fits-all" approach to diagnosis and treatment.

A major obstacle in endometriosis management is the persistent diagnostic delay, with studies consistently reporting an average delay of 7–11 years between symptom onset and confirmed diagnosis (27). This delay is largely attributable to nonspecific symptoms, limited disease awareness among patients and healthcare providers, sociocultural normalization of menstrual pain, and reliance on invasive surgical procedures for definitive diagnosis. Laparoscopy with histological confirmation has long been considered the gold standard; however, it is costly, invasive, and not readily accessible in many healthcare systems, further perpetuating diagnostic inequities (28).

The consequences of delayed diagnosis are profound. Prolonged untreated disease is associated with worsening pain, progression of lesions, reduced fertility, diminished quality of life, and increased rates of anxiety, depression, and socioeconomic burden. Endometriosis-related productivity loss alone accounts for billions of dollars annually in healthcare costs and lost work capacity globally. These realities highlight an urgent need for earlier recognition, improved diagnostic strategies, and more effective individualized treatments.

In recent years, advances in molecular biology, genomics, epigenetics, proteomics, and bioinformatics have catalyzed a paradigm shift toward precision medicine in endometriosis care (3). Precision medicine seeks to integrate molecular profiles, clinical phenotypes, imaging data, and patient-reported outcomes to enable earlier diagnosis, predict treatment response, and tailor therapies to individual patients (15). The identification of non-invasive biomarkers, improved imaging modalities, and artificial intelligence–based diagnostic tools offers promising alternatives to surgical diagnosis and may substantially reduce diagnostic delays (29).

This review aims to critically examine the evolution of endometriosis care from delayed diagnosis toward precision medicine. We discuss the causes and consequences of diagnostic delay, summarize emerging diagnostic innovations, and explore how molecular stratification and personalized therapeutic strategies may transform the future management of endometriosis.

2. Diagnostic Delay in Endometriosis

Diagnostic delay remains one of the most significant and persistent challenges in the management of endometriosis. Despite growing awareness of the disease and the publication of updated international guidelines, recent evidence indicates that individuals with endometriosis continue to experience a prolonged interval between symptom onset and diagnosis, often spanning several years (30, 31). This delay represents a critical barrier to timely intervention and contributes substantially to disease progression, symptom chronicity, and long-term morbidity.

2.1. Magnitude of Diagnostic Delay

Contemporary studies consistently demonstrate that the mean diagnostic delay ranges between 6 and 10 years, with considerable variability across regions and populations. A recent systematic review and meta-analysis including studies from Europe, North America, Asia, and Australia reported a pooled mean diagnostic delay of approximately 6.6 years, with some individuals experiencing delays exceeding 20 years (30). Importantly, no significant reduction in delay was observed when comparing more recent cohorts to earlier studies, suggesting limited progress over time.

National data further reinforce the persistence of this issue. In the United Kingdom, patient-reported surveys and healthcare system analyses indicate a median diagnostic delay of nearly nine years, representing an increase compared with pre-pandemic estimates (27). Similarly, recent cohort studies from France and Australia have reported mean delays approaching 9–12 years, particularly among patients presenting primarily with pain rather than infertility (31, 32). These findings suggest that, even in high-income countries with established healthcare systems, diagnostic delay remains a systemic problem.

2.2. Patient-Related Contributors to Delay

Patient-related factors play a substantial role in delayed diagnosis. Menstrual pain and associated symptoms are frequently normalized by patients, families, and communities, leading many individuals to delay seeking medical care. Adolescents and young adults are particularly vulnerable to delayed diagnosis due to limited menstrual health education, sociocultural stigma, and the perception that severe dysmenorrhea is a normal part of menstruation.

Symptom variability further complicates patient recognition and reporting. Endometriosis is characterized by fluctuating, cyclical, and sometimes non-gynaecological symptoms, including bowel, bladder, and musculoskeletal complaints, which may obscure the underlying gynaecological cause (19). Cultural taboos surrounding menstruation and pelvic pain also discourage open discussion of symptoms, particularly in low-resource or conservative settings (33).

3. Healthcare Provider-Related Factors

Healthcare provider-related barriers are among the most influential contributors to diagnostic delay. Primary care clinicians and non-specialist providers may misattribute symptoms to more common conditions such as irritable bowel syndrome, urinary tract disorders, or psychosomatic causes, resulting in repeated misdiagnoses and ineffective treatments (34). Recent qualitative studies reveal that patients frequently report feeling dismissed or not believed, which further delays referral and appropriate investigation (35).

In younger patients, diagnostic delay is exacerbated by hesitancy to perform pelvic examinations or imaging and by persistent misconceptions that endometriosis is uncommon in adolescents (36). Additionally, the absence of universally accepted non-invasive diagnostic criteria perpetuates uncertainty and contributes to delayed escalation of care.

3.1. System-Level and Structural Barriers

At the health system level, diagnostic delay is reinforced by fragmented care pathways, long waiting times for specialist consultations, limited access to expert imaging, and constrained availability of surgical services (2,). The historical reliance on laparoscopy with histological confirmation as the diagnostic gold standard has played a central role in prolonging time to diagnosis, as surgery is often deferred until symptoms become severe or refractory to medical therapy (21).

Recent policy analyses highlight that menstrual and pelvic pain disorders have historically been underprioritized in public health planning, leading to insufficient investment in early diagnostic infrastructure and clinician training (37). These structural issues disproportionately affect individuals from lower socioeconomic backgrounds, rural communities, and marginalized populations, contributing to diagnostic inequities (38).

3.2. Consequences of Diagnostic Delay

The clinical consequences of delayed diagnosis are substantial. Prolonged untreated disease is associated with central sensitization and chronic pain syndromes, which may reduce responsiveness to both medical and surgical treatments. Diagnostic delay has also been linked to increased lesion burden, higher rates of infertility at diagnosis, and more complex disease requiring extensive intervention.

Beyond physical outcomes, delayed diagnosis carries a significant psychological burden. Patients frequently report anxiety, depression, social isolation, and diminished trust in healthcare systems, driven by prolonged suffering and perceived medical invalidation. From an economic perspective, delayed diagnosis results in increased healthcare utilization, repeated investigations, loss of productivity, and substantial indirect costs, exceeding those associated with many other chronic conditions.

3.3. Recent Shifts in Diagnostic Paradigms

In response to growing recognition of diagnostic delay, recent international guidelines advocate for a shift toward earlier, symptom-based clinical diagnosis supported by imaging, rather than mandatory surgical confirmation (21, 39).

Advances in non-invasive diagnostics, including biomarker research, high-resolution imaging, and artificial intelligence–assisted decision tools, offer promising avenues to shorten the diagnostic pathway (1).

However, despite these conceptual advances, real-world data suggest that meaningful reductions in diagnostic delay have yet to be achieved, emphasizing the need for coordinated efforts across education, clinical practice, research, and health policy.

4. Advances in Non-Invasive Diagnosis of Endometriosis

The historical reliance on laparoscopy for definitive diagnosis has been a major contributor to diagnostic delay in endometriosis. In response, there has been a significant shift toward the development of non-invasive diagnostic strategies aimed at enabling earlier recognition, reducing surgical burden, and supporting precision medicine approaches. Recent advances span biomarker discovery, liquid biopsy technologies, advanced imaging modalities, artificial intelligence (AI), and multimodal diagnostic models (1, 3).

4.1. Biomarkers and Liquid Biopsy Approaches

Extensive efforts have been directed toward identifying reliable non-invasive biomarkers detectable in blood, urine, saliva, and menstrual fluid.

4.1.1. Blood-Based Biomarkers

Proteomic and metabolomic studies have identified numerous circulating proteins associated with inflammation, angiogenesis, immune dysregulation, and extracellular matrix remodeling in endometriosis. A recent systematic review and meta-analysis of proteomic studies highlighted several promising candidates, including inflammatory cytokines and growth factors, although none demonstrated sufficient accuracy as single diagnostic markers (40).

CA-125, the most studied biomarker, lacks sensitivity and specificity for early-stage disease, but recent research suggests that multi-marker panels combining CA-125 with novel proteins may improve diagnostic performance (20). These panels may be particularly useful in stratifying patients for further imaging or specialist referral.

4.1.2. microRNAs and Non-Coding RNAs

Circulating microRNAs (miRNAs) have emerged as promising diagnostic candidates due to their stability in body fluids and disease-specific expression patterns. Recent studies demonstrate that plasma, serum, and salivary miRNA signatures can discriminate patients with endometriosis from controls with moderate to high diagnostic accuracy in early validation cohorts (41,42). Similarly, long non-coding RNAs and circular RNAs are being explored as components of future diagnostic panels (15).

4.1.3. Menstrual Fluid and Endometrial Biomarkers

Menstrual effluent has gained attention as a non-invasive source of disease-relevant tissue, reflecting molecular alterations in both eutopic and ectopic endometrium. Recent studies indicate that immune cell profiles, inflammatory mediators, and transcriptomic signatures in menstrual fluid may serve as accessible biomarkers for early disease detection (43).

Despite encouraging findings, most biomarker candidates remain in the discovery or early validation phase, and large, multicenter studies are required before clinical implementation.

4.2. Advances in Imaging Techniques

Imaging plays a central role in the non-invasive diagnosis of endometriosis, particularly for ovarian and deep infiltrating disease.

4.2.1. Transvaginal Ultrasound (TVUS)

Expert-performed transvaginal ultrasound has demonstrated high accuracy in detecting ovarian endometriomas and deep infiltrating endometriosis involving the bowel, bladder, and uterosacral ligaments (44). Recent international consensus statements and guidelines increasingly recommend TVUS as a first-line diagnostic tool, supporting earlier diagnosis without surgical confirmation (21).

4.2.2. Magnetic Resonance Imaging (MRI)

MRI offers superior soft-tissue contrast and enables comprehensive pelvic mapping, particularly in complex or deep disease. Recent consensus recommendations confirm MRI as a reliable, non-invasive modality for diagnosing and staging deep infiltrating endometriosis, especially when performed using standardized protocols in experienced centers (45).

4.2.3. Emerging Imaging Technologies

Innovative imaging approaches, including photoacoustic imaging and near-infrared fluorescence techniques, are under preclinical and early clinical evaluation. These technologies aim to improve lesion detection and characterization by targeting vascular and molecular features of endometriotic tissue (46).

4.3. Artificial Intelligence and Machine Learning Applications

AI and machine learning have emerged as transformative tools in non-invasive endometriosis diagnosis.

AI-assisted image analysis has been shown to improve the detection of subtle endometriotic features on ultrasound and MRI, reducing operator dependence and inter-observer variability (47). Deep learning algorithms trained on imaging datasets demonstrate promising sensitivity for identifying deep infiltrating disease (42).

Beyond imaging, machine learning models integrating clinical symptoms, demographic data, and laboratory findings have been developed to predict endometriosis risk and support early triage in primary care settings (25). These tools may be particularly valuable in identifying patients who would benefit most from specialist referral or advanced imaging.

4.4. Multimodal and Integrated Diagnostic Models

The future of non-invasive diagnosis likely lies in integrated diagnostic frameworks combining biomarkers, imaging, clinical data, and AI-based analytics. Recent reviews emphasize that multimodal models outperform single-modality approaches and better reflect the biological heterogeneity of endometriosis (3, 17).

International discussions, including those at recent ESHRE congresses, support the adoption of integrated diagnostic pathways to reduce diagnostic delay and facilitate earlier, personalized intervention (21, 48).

4.4.1. Challenges and Clinical Translation

Despite substantial progress, several challenges remain. These include lack of standardized biomarker assays, limited external validation of AI models, variability in imaging expertise, and regulatory barriers to clinical adoption (1, 23). Addressing these limitations will be critical to translating non-invasive diagnostic advances into routine clinical practice.

5. Precision Medicine in Endometriosis

5.1. Molecular Stratification and Personalized Therapy

Precision medicine aims to tailor prevention, diagnosis, and treatment to individual biological profiles. In endometriosis, molecular stratification based on hormone receptor expression, inflammatory signatures, and genetic risk factors may predict treatment response (3).

For example, altered progesterone receptor expression is associated with resistance to progestin therapy, while increased aromatase activity may indicate responsiveness to estrogen-suppressive treatments (49). Predictive biomarkers may enable clinicians to select optimal medical therapies and avoid ineffective interventions.

5.2. Novel Therapeutic Strategies

Beyond conventional hormonal therapy and surgery, innovative precision-based approaches are under development. These include targeted drug delivery systems, immunomodulatory therapies, and gene-based interventions aimed at modifying disease pathways rather than suppressing symptoms alone (50).

Bioengineering strategies, such as nanoparticle-based drug delivery, may enhance therapeutic efficacy while minimizing systemic side effects (51). Precision approaches also extend to fertility preservation and management of endometriosis-associated infertility (52).

5.3. Toward Integrated, Patient-Centered Care

Precision medicine in endometriosis must incorporate not only molecular data but also patient-reported outcomes, psychosocial factors, and reproductive goals. Multidisciplinary care models involving gynecologists, pain specialists, fertility experts, and mental health professionals are essential for optimal management 28.

Education of healthcare providers and public awareness initiatives remain critical to reducing diagnostic delay and improving early intervention.

6. Conclusion

Endometriosis is a complex, systemic, and highly heterogeneous disease that continues to be burdened by substantial diagnostic delay and unmet clinical needs. Its multifactorial pathophysiology encompassing hormonal dysregulation, chronic inflammation, immune dysfunction, neuroangiogenesis, and genetic and epigenetic alterations explains the wide variability in clinical presentation and treatment response. Persistent delays in diagnosis, driven by symptom normalization, limited awareness, reliance on invasive procedures, and structural healthcare barriers, result in disease progression, chronic pain, impaired fertility, psychological distress, and significant socioeconomic impact.

Recent advances in non-invasive diagnostics, including biomarkers, advanced imaging, and artificial intelligence–based tools, alongside integrative "omics" approaches, are reshaping the diagnostic and therapeutic landscape of endometriosis. These innovations support a transition toward precision medicine, enabling earlier diagnosis, molecular stratification, and personalized treatment strategies. Achieving meaningful improvements in patient outcomes will require rigorous validation of emerging technologies, improved education and awareness, and the implementation of multidisciplinary, patient-centered care models.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interests.

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