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Canada
+15878858911
editorial-office@sciformat.ca

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DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN ENDOMETRIOSIS: A NARRATIVE REVIEW

Adrianna Krupska (Corresponding Author, Email: adriannakrupska@gmail.com)

Non-Public Healthcare Provider "Przychodnia" Medical Clinic Ltd., Chorzów, Poland

ORCID ID: 0009-0008-1710-1381

Karina Kinga Brzózka

University Clinical Center in Gdańsk, Department of Emergency Medicine, Gdańsk, Poland

ORCID ID: 0009-0004-2338-1827

Katarzyna Ledwożyw

Gabriel Narutowicz City Specialist Hospital in Cracow, Cracow, Poland

ORCID ID: 0009-0000-6911-3001

Alicja Pieluć

Medical University of Gdańsk, Gdańsk, Poland

ORCID ID: 0009-0003-1150-2241

Zuzanna Pyrka

Gabriel Narutowicz City Specialist Hospital in Cracow, Cracow, Poland

ORCID ID: 0000-0001-5688-1036

Weronika Elżbieta Cionżyńska

Stefan Żeromski Specialist Hospital in Cracow, Cracow, Poland

ORCID ID: 0009-0007-1464-4957

ABSTRACT

Endometriosis is a multifactorial inflammatory disease associated with altered estrogen signaling, immune dysregulation, and the presence of endometrial-like tissue outside the uterine cavity. It affects nearly 10% of women of reproductive age and can substantially reduce quality of life through chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. Despite its prevalence, diagnosis and treatment remain difficult because symptoms are heterogeneous and frequently nonspecific, contributing to an average diagnostic delay of seven to ten years. This review summarizes the shift from invasive diagnostic laparoscopy toward non-invasive multimodal imaging, particularly transvaginal sonography (TVS) and magnetic resonance imaging (MRI), for disease assessment. It also discusses current medical, surgical, and fertility-preservation strategies aimed at improving symptom control and treatment outcomes in affected patients. Early diagnosis and a multidisciplinary approach may help reduce delays in treatment and improve long-term clinical outcomes.

KEYWORDS

Endometriosis, Chronic Pelvic Pain, Non-Invasive Diagnostics, Fertility

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1. Introduction

Endometriosis is characterized as a multifaceted, chronic inflammatory disorder driven by the ectopic growth of endometrial-like glands and stroma. Clinically, endometriosis is associated with persistent pelvic pain, fatigue, and impaired fertility (Becker et al., 2022). One of the major clinical challenges in endometriosis is the long delay between symptom onset and diagnosis. While traditional diagnostic approaches relied on invasive laparoscopy for definitive diagnosis, current clinical practice increasingly favors non-invasive diagnostic pathways. This shift may help reduce the psychosocial and socioeconomic burden of delayed treatment and promote long-term multidisciplinary care.

2. Pathophysiology and Risk Factors

Current evidence suggests that the pathogenesis of endometriosis can be understood as a disruption in cellular and immunological homeostasis, involving interactions between hormonal, immune, and inflammatory mechanisms. While Sampson's retrograde menstruation hypothesis provides the primary mechanism, recent data indicates this mechanism requires a permissive peritoneal microenvironment or "fertile soil" sustained by systemic immune dysregulation and local endocrine signaling to promote lesion development (Bulun et al., 2019). Recent evidence suggests that shed epithelial clones carry specific somatic driver mutations (such as *KRAS*) that interact with epigenetically altered stromal cells and may contribute to lesion persistence and remodeling.

Immune Dysregulation

In the peritoneal environment, macrophages and NK cells display impaired phagocytic activity. Rather than clearing ectopic tissue, these immune cells promote a pro-inflammatory cytokine cascade (including IL-1 β , IL-6, IL-8, and TNF- α) that contributes to lesion survival, vascularization, and nerve fiber growth.

Localized Endocrine Circuits

Ectopic implants develop autonomous local estrogen production. Upregulated expression of steroidogenic acute regulatory (StAR) protein and aromatase, combined with a severe downregulation of 17 β -hydroxysteroid dehydrogenase type 2 (17 β -HSD2), fuels continuous local estradiol production. This hyper-estrogenic environment is further compounded by progesterone resistance, which disrupts normal cellular differentiation (Bulun et al., 2019).

3. Clinical Presentation and Information Heterogeneity

Clinical presentation varies considerably among patients, with symptom severity often not correlating with disease extent. This discrepancy between symptoms and disease extent where minimal lesion volumes trigger intractable pain profiles - highlights the involvement of neuroinflammatory networks and central nervous system sensitization (Zondervan et al., 2018).

Pain Phenotypes and Central Sensitization

Chronic pelvic pain may present as dysmenorrhea, deep dyspareunia, dyschezia, and dysuria. Over time, persistent nociceptive stimulation can alter central nervous system processing and contribute to central sensitization, leading to persistent pain despite surgical treatment.

Gastrointestinal Mimicry and Diagnostic Noise

Visceral cross-sensitization between the pelvic organs and the lower gastrointestinal tract may complicate the diagnosis of endometriosis. Symptoms such as cyclical bloating ("endo-belly"), constipation, and diarrhea frequently mimic Irritable Bowel Syndrome (IBS), often leading to misdiagnosis and delayed referral to gynecological care.

Classification Systems

For decades, the Revised American Society for Reproductive Medicine (rASRM) score was the most widely used classification system for endometriosis. However, it correlates poorly with pain severity and does not adequately describe deep infiltrating endometriosis (DIE). To improve disease assessment, clinicians increasingly use both the Enzian classification and the Endometriosis Fertility Index (EFI). The Enzian system provides detailed assessment of DIE in subperitoneal compartments, while the EFI helps estimate reproductive outcomes after surgery.

4. Diagnostic Approaches: Multimodal Diagnostic Approach

Modern diagnostic approaches increasingly favor non-invasive imaging methods over surgical confirmation of endometriosis (Guerriero et al., 2016; Bazot & Daraï, 2017).

Transvaginal Sonography (TVS)

Transvaginal sonography (TVS), performed according to the International Deep Endometriosis Analysis (IDEA) consensus recommendations, serves as the first-line imaging modality. By assessing dynamic "soft markers" (e.g., ovarian mobility and compartment-specific tenderness) together with the "sliding sign," clinicians can accurately identify rectosigmoid and retrocervical involvement.

Role of MRI

Magnetic Resonance Imaging (MRI) is an important imaging technique in the evaluation of deep infiltrating endometriosis. T2-weighted and fat-suppressed T1-weighted sequences allow accurate assessment of deep subperitoneal lesions, the sacral plexus, and diaphragmatic involvement, which is important for preoperative planning.

The Peritoneal Blind Spot

An important diagnostic limitation remains: neither TVS nor MRI can reliably detect superficial peritoneal lesions (SUP). Consequently, negative imaging results cannot completely exclude early-stage disease.

Biomarkers

Serum CA-125 serves as a basic biomarker for advanced ovarian disease but lacks the sensitivity required for early-stage screening. Current research focuses on microRNA panels and liquid biopsies to establish a reliable non-invasive diagnostic tools (Nisenblatt et al., 2016).

5. Treatment Strategies: Multidisciplinary Management

Treatment of endometriosis requires balancing long-term symptom control with preservation of reproductive function (Taylor et al., 2017).

Medical Therapy

Medical therapies aim to reduce inflammation and suppress the hypothalamic-pituitary-ovarian axis.

- **First-Line Suppression:** Combined oral contraceptives (COCs) and continuous progestins (dienogest, 2 mg daily) remain standard first-line therapies. Dienogest reduce local inflammatory activity, suppresses proliferation, and inhibits lesion angiogenesis.
- **Second-Line GnRH Modulators:** Oral GnRH antagonists (e.g., elagolix, relugolix) allow controlled estrogen suppression. To reduce the risk of bone mineral density loss, these therapies are usually combined with continuous add-back therapy (low-dose estrogen/progestin combinations) to maintain systemic safety (Taylor et al., 2017).

Surgical Management: Principles of Surgical Excision

Surgery is indicated when lesions impair organ function or symptoms are refractory to medical treatment.

- **Excision vs. Ablation:** Current evidence suggests that laparoscopic excision may provide superior long-term outcomes compared with ablation (Bafort et al., 2020). Excision allows complete removal of infiltrating lesions and provides tissue for histopathological confirmation.
- **Nerve-Sparing Protocols:** Complex cases often require nerve-sparing surgical techniques. Preserving the hypogastric nerves and the inferior hypogastric plexus is essential for maintaining postoperative urinary and bowel function.

Fertility Preservation

Surgical intervention on the ovaries requires balancing symptom control with preservation of ovarian reserve. While removal of endometriomas may reduce local pelvic inflammation, aggressive capsule stripping often diminishes ovarian reserve, causing a significant decline in Anti-Müllerian Hormone (AMH) levels. Therefore, patients with low ovarian reserve are often referred for ART or IVF to avoid repeated surgical procedures.

Future Non-Hormonal Therapies

To avoid the contraceptive effects of current hormonal therapies, researchers are exploring non-hormonal molecular targets. Current studies investigate Selective Progesterone Receptor Modulators (SPRMs), aromatase inhibitors, and anti-angiogenic therapies. Additionally, blocking localized PGE2 receptor pathways and modulation of the gut-pelvic microbiome may offer promising future treatment options.

6. Discussion

Endometriosis management should involve multidisciplinary care because the disease has substantial physical, psychological, and socioeconomic effects on patients (Culley et al., 2013). A major diagnostic limitation is the limited ability of non-invasive imaging to detect superficial peritoneal implants. To address this limitation, clinicians increasingly rely on classification tools such as the EFI and Enzian system. Because symptomatic recurrence is common after discontinuation of medical therapy, endometriosis should be managed as a chronic condition. Improving patient outcomes requires replacing fragmented care with multidisciplinary specialist centers that integrate gynecologists, radiologists experienced in endometriosis imaging, pain management specialists, and psychologists.

7. Conclusions

The management of endometriosis requires reducing diagnostic delays through combined imaging approaches (TVS/MRI) and the development of non-invasive biomarkers. Future therapies may focus more on targeted molecular approaches while preserving reproductive function. Improved patient outcomes will depend on greater clinical awareness and individualized multidisciplinary care.

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