Endometriosis Unmasked: Rethinking Diagnosis and Management

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Abstract
Endometriosis is a chronic, estrogen-dependent inflammatory disorder affecting 6–10% women of reproductive age and possibly one of the most under-recognized causes of chronic pelvic pain and infertility. Although awareness is increasing, the average time between symptom onset and a diagnosis confirmed through surgery remains 5 to 10 years (because of heterogeneous clinical presentation and reliance on invasive laparoscopy for definitive diagnoses). In the past years, there has been tremendous movement in both diagnostic and therapeutic paradigms. Newer guidelines by the European Society of Human Reproduction and Embryology (ESHRE), National Institute for Health and Care Excellence (NICE) and national societies now lean towards a clinical, history- and imaging-based diagnostic pathway, with laparoscopy being recommended only in equivocal or treatment-refractory cases. This review focuses on: the role of transvaginal ultrasonography and pelvic magnetic resonance imaging in detecting deep infiltrating disease; the ongoing investigation of circulating and menstrual-effluent biomarkers towards a non-invasive diagnostic test. On the therapeutic front, second-line medical options have extended beyond combined hormonal contraceptives, progestins and GnRH agonists to include oral gonadotropin-releasing hormone (GnRH) antagonists-elagolix, relugolix and linzagolix-whereas deep and bowel endometriosis is better managed via refinement in minimally invasive excisional surgery. The review provides an overview of recent evidence on the epidemiology and pathogenesis involved in endometriosis, advances in clinical and imaging detection methods, promising non-invasive biomarkers, medical and surgical management updates as well as current gaps in care.

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1. Introduction

For endometriosis, the definition is any presence of endometrial-like glandular and stromal tissue outside of the uterine cavity (such as on the pelvic peritoneum, ovaries, and rectovaginal septum), with much rarer extra pelvic disease. It impacts an estimated 190 million women globally and is associated with dysmenorrhea, chronic pelvic pain, dyspareunia, and subfertility leading to significant reduction in quality of life, work productivity, and mental health [1]. US population-based data suggest that both the incidence and prevalence of diagnosed endometriosis increased over the past decade, reflecting growing clinical awareness and greater use of imaging [2].

However, the disease continues to be characterised by delayed diagnosis. Several cohorts continue to demonstrate mean delays between symptom onset and definitive diagnosis of 5–10 years, a lag attributable to normalization of symptoms, overlap with other etiologies of pelvic pain, and the historical reliance on surgical confirmation [3, 4]. Even after diagnosis, care pathways continue to be poorly integrated as only 45% of patients in a recent national audit in the United Kingdom were on treatment concordant with guidelines and around one third faced long-term opioids [3]. Gabapentinoids, which provide little benefit for endometriosis-associated pain remain prescribed with nearly one in ten receiving these medications highlighting sustained deficits in guideline-concordant management [3]. In these aspects, the present review introduces recent guideline changes all over

world including a 2024 revision of the Korean Society of Endometriosis national guideline reflecting on such great findings [5]

2. Pathogenesis: A Brief Overview

The pathogenesis of endometriosis remains incompletely understood and is now considered multifactorial instead. Sampson's retrograde menstruation theory, whereby shed endometrial fragments implant on pelvic surfaces, is the most cited explanation but fails to account for extrapelvic disease and the fact that retrograde menstruation occurs in almost all menstruating women without developing endometriosis [1, 4]. Concerned theories involve coelomic metaplasia, lymphovascular dissemination, stem cell trafficking and genetic as well as epigenetic susceptibility. A consensus concept indicates that both lesion formation and maintenance depend on a dysfunctional immune environment in the peritoneal cavity and at eutopic endometrium, characterized by poor immune clearance, chronic low-grade inflammation and progesterone resistance [1, 4]. Specifically, progesterone-resistance is now a targeted biomarker and drug-gene of research.

3. Advances in Diagnosis

3.1. Clinical Evaluation and the Move Away from Laparoscopy as the Diagnostic Standard

Direct visualization at laparoscopy, with histological confirmation has been viewed as the gold standard in diagnosis. This paradigm has now shifted. The 2022 ESHRE guideline clearly indicates that laparoscopy should no longer be performed for diagnostic purposes, but it should still be carried out only with inconclusive imaging or failure of empiric medical therapy [6]. A 2024 position statement supports this stance, stating that a presumptive diagnosis of endometriosis in adolescents and young women with moderate to severe dysmenorrhea necessitates empirical treatment without surgical confirmation [7]. The updated NICE guideline revision in 2024 also state similar recommendations, clinicians should initiate management based on history and examination findings, despite normal imaging, and it upgraded referral language from 'consider referral' to 'refer' for suspected cases in an effort to shorten the diagnostic pathway. A comprehensive history is key to this method; cyclical and non-cyclical pelvic pain, dysmenorrhoea, dyspareunia, dyschezia and infertility together with family history, since a first-degree relative with endometriosis substantially raises pretest probability [8, 9]

3.2. Imaging: Vulvovaginal Ultrasound and Magnetic Resonance Imaging

In our clinical practice we recommend the use of transvaginal ultrasonography (TVUS) performed by an experienced sonographer as the first-line imaging modality in suspected endometriosis, with good sensitivity for ovarian endometrioma and reasonable accuracy achieved for deep infiltrating disease of the rectovaginal septum, bladder and bowel using structured scanning protocols [6, 10]. Pelvic MRI is recommended as an adjunctive or second-line modality, especially for surgical planning of deep infiltrating endometriosis or where technical limitation to TVUS is a consideration [8, 9]. One key point made by both updates, is that a normal pelvic ultrasound or MRI does not rule out superficial peritoneal endometriosis given that this type of disease will often be below the resolution of current imaging, thus reinforcing their recommendations that treatment should not be denied based on unremarkable imaging [9]. A Systematic assessment of available imaging modalities has concluded that none yet meets the accuracy threshold required to fully replace laparoscopy as a confirmatory test, which is why current strategies pair imaging with clinical judgment rather than relying on imaging alone [11].

3.3. Classification Systems

Staging systems standardize communication and management once endometriosis is suspected or diagnosed; however, the existing systems do not adequately reflect severity of symptoms nor the impact on fertility. The modified American Society for Reproductive Medicine (ASRM) classification has continued to be used extensively for surgical staging of endometriosis [29], while the #Enzian classification has gained traction [30] specifically for describing deep infiltrating disease of the rectovaginal septum, bladder, and ureters, complementing rather than replacing ASRM staging [12]. For the patient requiring fertility treatment after surgery, ESHRE recommends the use of the Endometriosis Fertility Index (EFI) as a valid, reproducible tool for counselling on chances of spontaneous conception compared to those achieving pregnancy with assisted conception [6].

3.4. Emerging Non-Invasive Biomarkers

There is still an unmet need for a valid, non-invasive biological marker to shorten the diagnostic delay. Serum CA-125 remains the most investigated single circulating marker, but in isolation, its diagnostic performance is only moderate and can increase significantly when used together with other markers including soluble adhesion molecules, growth factors, and inflammatory cytokines [13]. Proteomic and lipidomic profiling of plasma, recently linked to the #Enzian anatomical annotation system, has identified candidate protein signatures that differ by disease stage, offering a possible route toward stage-specific, blood-based screening [12]. Menstrual effluent has emerged as a particularly promising, minimally invasive biospecimen, Women with endometriosis have stromal cells derived from their menstrual effluent that exhibit impaired decidualization capacity and altered expression of genes in the retinoic-acid and progesterone-signaling pathways relative to controls [4,11], phenotypes that can be recapitulated in healthy cells exposed to inflammatory cytokines that stimulate peritoneal inflammation – supporting a model whereby chronic peritoneal inflammation drives progesterone resistance. Analogous work has assessed menstrual-blood expression of candidate transcriptomic biomarkers—aromatase [14], steroidogenic factor-1, and HSD17B2—and a recent systematic review of menstrual-effluent-based diagnostics reported that several biomarker classes "demonstrated biological plausibility" but also highlighted the need for prospective multicenter validation with reference gene selection as well as standardization of collection protocols before broader clinical uptake [11]. Together, these efforts represent a transition from single-marker discovery to multi-analyte and plasticity-biospecimen investigation; however, none have yet been validated as standard-of-care to replacing either imaging or laparoscopy.

4. Advances in Management

4.1. First-Line Medical Therapy

Now, a first-line approach for suspected or confirmed endometriosis-associated pain has been proposed by an empirical medical therapy without needing surgical diagnosis before [6,7]. NSAIDs are still a prudent first-line choice but evidence for their efficacy should be endorsed with caution as evidence is only limited to endometriosis-associated pain. In their respective guidelines, ESHRE supports the use of combined hormonal contraceptives (oral or as a transdermal or vaginal ring) and progestogens (intrauterine system releasing levonorgestrel and oral dienogest; etonogestrel implants) as strong first-line treatment options based on efficacy, tolerability, and long-term suitability [6,15]. Among the progestins, dienogest in particular has a large real-world safety database supporting its long-term utility for pain control and a favorable bleeding and bone-density profile when compared with GnRH agonists [15, 16].

4.2. GnRH Agonists and the New Generation of Oral GnRH Antagonists

GnRH agonists have traditionally been used as second-line therapy; however, their use is limited by hypoestrogenic side effects and the development of bone mineral density loss, usually limiting continuous treatment to six months without add-back therapy [6]. The biggest pharmacological advancement in the last couple of decades is seen with oral, non-peptide GnRH antagonists like elagolix, relugolix (as monotherapy or fixed-dose combination with estradiol and norethindrone acetate), and linzagolix that induce a rapid, dose-dependent, reversible suppression of ovarian estrogen production without the initial flare phenomenon associated with agonists [17,18]. Clinically meaningful reductions in dysmenorrhea and non-menstrual pelvic pain have been shown in the Phase 3 SPIRIT 1 and 2 trial of relugolix combination therapy [19]. ELAGOLIX AND RELUGOLIX A network meta-analysis of these agents demonstrated that among patients treated with elagolix, those receiving the highest dose and patients treated with relugolix had the largest decreases in pelvic pain, dysmenorrhea, and dyspareunia, but they also experienced higher rates of hot pushes on treatment compared to placebo (headache was more common at the two lower dosages only); additionally, weight-adjusted doses at the top elagolix (200 mg) level caused significant reductions in spinal bone mineral density from baseline [18,20]. These efficacy findings were supported in a recent updated meta-analysis, which also noted that much of the pain benefit seems to be mediated through decreased uterine bleeding and this may be an important consideration when counseling patients about expected treatment response [20,21]. ESHRE now recommends GnRH agonists and antagonists as second-line choices that are selected through shared decision-making considering patient preference, side effect profile, cost and availability [6,21].

4.3. Surgical Management

Surgery remains indicated for endometriomas, deep infiltrating disease causing organ dysfunction, or pain refractory to medical therapy, and laparoscopic excision is generally preferred over ablation for deep and ovarian disease given lower recurrence rates. For deep infiltrating endometriosis involving the bowel, current practice is conservative for minor lesions (shaving excision if confined to the serosa or muscularis ; disc excision for more focal full-thickness disease), and aggressive when necessary (segmental resection with stricture/stenosing lesions) with a view towards minimizing morbidity but preserving bowel and bladder function [22]. large single-center series describe durable improvement in dysmenorrhea, dyspareunia, and pelvic pain with laparoscopic bowel resection over long-term follow-up [23], while a more contemporary single-center cohort reports similar short- and long-term functional outcomes following peritoneal stripping via laparoscopy or laparotomy but emphasize that technique selection (shaving, disc or segmental resection) should be driven by pre-operative imaging data, such as MRI colonography to characterize lesion depth, number and the presence of associated bowel stricture [24]. A contemporary retrospective cohort combining gynecologic and colorectal surgery found that segmental resection was used in roughly six in ten patients, with a low major-complication rate (one anastomotic leak among 108 patients) and a sonographic recurrence rate of about 22% during one year follow up; recurrence was not significantly associated with the type of resection performed and was managed medically without need for reoperation in this study. [25] Refinement of techniques: for rectal endometriosis, a randomized trial reported that natural-orifice specimen extraction colectomy vs conventional laparoscopic segmental resection was associated with better digestive functional outcomes with the latter while recovery was faster after surgery performed through the natural-orifice approach, exemplifying an ongoing trade-off between functions and recovery [26]. This involves incorporating nerve-sparing dissection techniques for lesions at the level of the rectal bulb and pelvic autonomic plexus, which may promote a decrease in postoperative bladder and bowel dysfunction [22,27]. Bowel-involving disease is now treated with new surgical techniques, multidisciplinary input from gynecologic and colorectal surgery is regarded as standard [22].

4.4. Postoperative Medical Therapy and Fertility Concerns

Evidence indicating that this reduces both symptom and endometrioma recurrence after surgery [6] underpins updated ESHRE guidance allowing postoperative hormonal suppression in women not wishing to conceive. In contrast, the prior standard of prolonged (ultralong) GnRH-agonist pretreatment before assisted reproductive technology is no longer recommended due to uncertainty regarding its benefit on live-birth rates [6]. Clomiphene citrate and letrozole (but not FSH) can be used for moderate stimulation. No specific stimulation protocol is preferable to another between GnRH agonist and antagonist protocols among infertile women with endometriosis undergoing *in vitro* fertilisation, as neither has been shown to provide additional benefit over live birth rate outcomes. The Endometriosis Fertility Index continues to be the recommended tool for counseling on natural conception probability after surgical staging [6].

4.5. Adjunctive and Multidisciplinary Approaches

As endometriosis-associated pain has a central sensitization component, complementary and alternative medicine (CAM) approaches are becoming increasingly used in conjunction with hormonal and surgical management. Recent systematic review/meta-analyses have shown benefit from pelvic floor physiotherapy, psychological support, and, in selected patients with features of neuropathic pain,

neuropelveological techniques targeting somatic and autonomic pelvic nerves with improvements reported for pain intensity, sexual function and quality of life; however the majority of studies remained small scale (with a heterogenous evidence base) thus requiring further controlled trials [28]. Dietary changes and well-structured psychological support are also recommended in recent reviews of obesity management primarily focused on the primary care perspective, but with lower overall strength of supporting evidence compared to medications or surgery [10].

5. Persistent Gaps and Future Directions

Despite the recent advances in guidelines summarised above, implementation in practice remains behind. The 2024 UK national audit revealed considerable inequalities in access to specialist endometriosis services, ongoing dependence on opioids and gabapentinoids despite scant evidence supporting their use, and failure to consistently apply validated measures of pain and quality-of-life in routine follow-up [3,31]. Diagnostic delay, while theoretically addressable through the updated clinical- and imaging-based pathways, will require sustained investment in ultrasound training, primary-care education, and public awareness to translate guideline recommendations into shorter time-to-diagnosis at the population level [9]. No candidate marker or panel in the biomarker context has yet achieved sensitivity and specificity needed for regulatory approval as a stand-alone diagnostic, and similar rigorous prospective, adequately powered, multicenter validation studies remain important goals especially for those addressing menstrual-effluent [11] and multi-analyte plasma panels [12]. Finally, longer term comparative data between oral GnRH antagonists versus agonists and progestins, especially with regard to bone health with long-term use and add-back therapy outcomes will be needed to help refine the sequencing of medical therapy along the female reproductive life -span [20,21].

6. Conclusion

Over the last few years, there have been significant development in the way we diagnose and manage endometriosis. Diagnosis has evolved from a surgically based model to an empirical treatment approach within a clinical and imaging-based pathway, facilitated in part by new ESHRE, NICE, and national society guidelines, as well as ongoing progress toward a truly non-invasive diagnostic test owing to research focused upon circulating and menstrual-effluent biomarkers. In terms of treatment, oral GnRH antagonists have expanded second-line medical therapies in addition to traditional hormonal treatments, while surgical approaches for deep and gastrointestinal involvement of endometriosis are continually improved to maximize symptom alleviation whilst preserving organ function and reproductive capability. However, diagnostic delay and variability of guideline-concordant care persist in practice, highlighting that while these advances are substantial steps toward better outcomes, more research is needed to understand their implementation along with concerted efforts to change clinical training, referral pathways and multidisciplinary service delivery.

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