Endometriosis: improvements and challenges in diagnosis and symptom management

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Commentary

Endometriosis: Improvements and challenges in diagnosis and symptom management

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Endometriosis is a chronic disorder with debilitating symptoms that is difficult to diagnose and treat. Advances in imaging technologies and strategies for the management of symptoms are improving the quality of life of patients by reducing the time taken for diagnosis and offering a more balanced approach to therapy.

Introduction

Endometriosis is a chronic neuroinflammatory disorder characterized by the growth of lesions (tissue which appears to phenocopy endometrium) in sites outside the uterus. The prevalence of endometriosis is estimated to be 2%–10% within the general female population—which is higher in those who are infertile (~50%)—thought to represent ~190 million individuals worldwide.[1] Endometriosis lesions are usually found in the pelvic cavity and assigned to three subtypes depending upon location: superficial peritoneal, ovarian (endometriomas/cysts), and deep (may invade tissues, such as the wall of the bladder and intestine). While it can be asymptomatic, individuals with endometriosis typically report a variety of symptoms (alone or in combination) including chronic pain, fatigue, problems with the urinary and digestive system, and anxiety and depression. Genetic studies have identified shared risk factors with disorders that have shared symptoms including migraine (headache), depression, irritable bowel syndrome, and asthma.

Definitive diagnosis, based on laparoscopic surgery, takes 7–9 years on average.[1] Current therapeutic options are limited to surgical excision/destruction of lesions with high recurrence rates and drugs with unwanted side effects,[1] prompting patients to explore alternative and self-management strategies, some of which are discussed below.

In this commentary, we briefly summarize current standard clinical practice before focusing on new approaches to address diagnostic delay and symptom management that are not dependent on hormone-suppressive drugs.

Current recommendations for diagnosis and treatment

Endometriosis is a persistent condition without a known cure. Research suggests that the variation in pelvic pain stems from different types of pain, including nociceptive, neuropathic, and nociplastic pain. This underscores the importance of tailoring treatment to each individual through collaborative decision-making. Standard treatments involve hormonal medication to suppress symptoms during reproductive years (except when trying to conceive) and surgical removal of lesions (https://www.eshre.eu/Guideline/Endometriosis). However, there is increasing recognition of the role of non-hormonal drugs and behavioral therapies in a holistic treatment plan.[2] Deciding on the best approach involves considering patient preferences while addressing symptom management, functional improvement, side effects, risks, and fertility goals.

Prognostic markers of surgical success in women with superficial peritoneal endometriosis

While laparoscopy is considered the gold standard for diagnosis of endometriosis, the benefit of therapeutic laparoscopy for treating pain associated with superficial peritoneal disease (the most common endometriosis subtype) has been challenged.[3] To address the lack of high-quality data regarding treatment of superficial peritoneal disease to improve pain, a UK multicenter, randomized clinical trial (RCT) (ESPRIT2; ISRCTN27244948) is underway. This double-blind study aims to randomize 400 participants with chronic pelvic pain and a diagnosis of isolated superficial peritoneal endometriosis to surgical removal versus diagnostic laparoscopy alone.[4] It aims to determine whether surgical removal is of overall benefit to women with superficial peritoneal disease and whether there are prognostic markers that predict positive surgical outcomes.

Accelerating time to diagnosis—New opportunities based on imaging and biomarkers?

Advances in application of imaging technologies appear promising

Endometriosis specialists have been evaluating the evidence that imaging can be used as a reliable/robust alternative to laparoscopy for diagnosis, and many believe it should be more widely adopted.[1] Specifically, the latest clinical guidance from Canada supports the use of advanced pelvic ultrasound or magnetic resonance imaging (MRI) for the diagnosis of ovarian or deep disease, although endometriosis cannot be completely excluded if results appear normal and the individual has symptoms consistent with the disease such as pain or infertility.[5] As deep endometriosis lesions also contain substantial areas of fibrosis concomitant with the increase in tissue stiffness, transvaginal elastosonography (TVESG) has been suggested as a better method of diagnosis than either transvaginal ultrasound (TVUS) or MRI with 100% success in detecting lesions in a recent study of 30 patients,[6] although it is yet to be tested more widely.

Positron emission tomography (PET) used in combination with computed tomography (CT) (PET-CT) and the radiotracer 18F-FDG can provide both biological and anatomical data and is

being applied in oncology to improve characterization of tumors. These methods have now been extended to studies of small numbers of women with known or suspected endometriosis. In a recent study[7] of 18 women, application of 18F-FDG PET-CT confirmed the presence of lesions in 13 out of 18 participants (72%), although the lesions did show an inconsistent 18F-FDG uptake. Method refinement using newer radiotracers, such as ^{18}F-fluoroestradiol, and candidates derived from oncological and cardiovascular disease will be needed if we are to improve diagnostic accuracy, but the rapid development of these methods does offer real hope that imaging can reduce the need for surgical diagnosis.

The hunt for a reliable and reproducible diagnostic biomarker is still underway

Finding a biomarker for endometriosis has been something of a holy grail for more than 20 years; the aim has been to develop a protocol to detect one (or more in a panel of biomarkers) in a biological fluid such as blood, saliva, or urine, preferably using a home self-collection kit.

A recent systematic analysis summarized the many biomarkers reported in studies conducted between 2005 and 2022 that included multiple tissues/fluids, including peripheral blood.[8] A sub-analysis of those in properly controlled cohorts of 30 or more patients found only four biomarkers (TNFalpha, MMP-9, TIMP-1, and miR-451) that fit their strict criteria (found to be significantly different by two or more research teams in three or more tissue/fluids). They commented on the poor harmonization in sample collection methods, which may explain the inconsistencies. Another study looked at potential biomarkers in blood by combining markers of inflammation with genome-wide association studies (GWASs), next-generation sequencing, and machine learning.[9] Unfortunately, this study highlighted the failure of many biomarkers to achieve validation before commercialization, with most biomarkers remaining at the discovery phase.

MicroRNAs (miRNAs) found in blood or saliva are a type of biomarker that has received considerable attention. The latest systematic review of results from blood/serum identified 298 records in Pubmed (up to November 2023), with data extracted from 32 that were of high quality (had both cases and controls, hormone status known). These studies reported 141 miRNAs as differentially expressed, although there was considerable variation and only has-miR-17-5p was reported in 6 (19%) studies.[10] In other studies, investigators have analyzed 200 saliva samples collected as part of a prospective clinical trial (ENDO-miRNA study (ClinicalTrials.gov identifier: NCT04728152). Their analysis was based on a panel of 109 miRNAs as a biomarker test for endometriosis, and they reported that this test had predictive value, specificity, and sensitivity all greater than 95%.[11] Similar to these studies, a diagnostic kit based on measurement of miRNAs in saliva has been developed and is being marketed to health care professionals (https://ziwig.com/en/endometriosis/). The kit still requires validation in larger independent cohorts.

In patients with endometriosis wishing to get pregnant, blood levels of anti-Müllerian hormone (a protein secreted by actively growing ovarian follicles) are often measured during clinical evaluation. The justification for measuring this protein is based on several lines of evidence, including reports that levels are lower in those with ovarian endometriosis as well as in those who have had ovarian surgery. Hence, this protein can be considered as a useful biomarker when assessing whether *in vitro* fertilization (IVF) is likely to be necessary/successful.[12]

Reframing the treatment of endometriosis-associated pain

Researchers and clinicians are frustrated by the poor rates of translation from preclinical models into novel therapies compounded by poor trial design (patient heterogeneity/low numbers) and failure to report results of trials. Recognizing the imperative "not to repeat past mistakes," there has been a major shift in research efforts, with a greater emphasis on the management of symptoms that matter most to the patient, revisiting/repurposing existing medicines, and a more open-minded approach to the value of physical and self-help strategies.[1]

Cannabis-derived products

Many patients with chronic pain, including those with endometriosis, use cannabis-derived products or medical cannabis for symptom relief. Survey data suggest these products can be highly effective, although access and cost remain a factor in their widespread use in most countries. Notably, the biological basis for their activity is backed up by the presence of receptors that can bind cannabinoids in endometriosis lesions and by the well-known role of these receptors in pain and inflammatory pathways known to be dysregulated in endometriosis.[1] Available evidence supports the use of cannabis-based products for treatment for pelvic pain, gastrointestinal issues, and mood,[13] and phase III clinical trials are being conducted to support the adoption of products with appropriate formulations into routine clinical practice under medical supervision (Table 1).

Diet and the microbiome

Surveys of patients have confirmed that many are well informed that diet can have an impact on pain and gastrointestinal symptoms including bloating. Studies are also providing evidence that changes to diet are effective,[14] although much larger studies with more diverse populations and diets are required. Links between diet, the gut microbiome, and the brain (pain, mood, and neurological activity) are now well established for a range of disorders including those, like endometriosis, where inflammation plays a key role. The impact of the microbiome on the bioavailability of oestrogens is particularly relevant to endometriosis given the evidence that steroids play a key role in its etiology.[1] This is an ideal time for the field of endometriosis to incorporate novel findings on the role of the gut-brain-microbiome axis in mood and pain disorders and include them in strategies for pain management. This is an area where rapid progress is being made.

Physiotherapy, exercise, and behavioral therapies

The utility of physical therapies (including treatment by a physiotherapist) for the management of endometriosis-associated pain have been supported by evidence from several trials,[15] and their inclusion in standard care is likely to be important for patients wanting to reduce the use of drugs.

Current trials are also testing an increased range of non-medical therapies under evaluation including mindfulness,

Table 1. Selected clinical trials testing impact of cannabinoids and diet for management of endometriosis-associated pain

Trial number	Intervention	Details	Comments
NCT05670353 (DREAMLAND)	cannabinoid derivatives (98% CBD, 2% THC) or placebo (RCT)	10–150 mg daily, 9 weeks, 102 participants (end August 2024)	primary outcome—proportion of patients with reduction in pain
NCT04527003	cannabidiol (CBD) extract	CBD 10 mg or 20 mg, treatment for 8 weeks, 3 groups (placebo, low, or high CBD), all participants receive noretindrone acetate 5 mg/day, 36 participants (end Dec 2024)	primary outcome—pain scores (daily VAS scale); secondary outcome—measurement of inflammatory markers
NCT05714189	low FODMAP (n = 22) or endometriosis diet (n = 21) or normal diet (20)	non-randomized, 62 participants, 6 months on low FODMAP, endometriosis diet or control (end Dec 2022)	participants adhering to a diet reported less pain and less bloating; publication of larger cohort endometriosis diet only (n = 91) vs. control (121) improved QoL domains
NCT05831735 (CRESCENDO)	physical activity	200 participants, randomized, 3 groups: control (video of movement), physical activity (video and 1–3 h of activity via videoconference), physical activity and education (6 sessions, monthly)	primary outcomes—changes in pain/fatigue, quality of life; secondary outcomes—self-image, motivation
NCT05098444	cognitive behavioral psychotherapy (internet delivery)	120 participants, randomized to internet-based CBT (8 modules in total and one per week) or no treatment (waiting list)	primary outcomes—change in pain perception and quality of life; secondary outcomes—stress, illness perception
NCT06211231 (MY-ENDO)	digitally delivered mindfulness and acceptance-based psychological intervention	255 participants randomized to 3 groups: self-guided digital intervention, therapist-guided digital intervention, or none	primary outcome—improvement in quality of life

physical exercise programs, and cognitive behavioral therapies (Table 1). These trials complement those on diets and are important in providing a framework and evidence to support their inclusion in personalized care plans at a time when many patients are already being influenced by reports on social and other media.

Conclusions and future prospects

Endometriosis is a difficult disorder to diagnose and treat in part because it can present with a range of overlapping symptoms that are similar to those of other chronic inflammatory disorders. Investment in endometriosis research has been low compared to that of other disorders with similar prevalence and socioeconomic impact. Progress in finding a biomarker has been hampered by poor replication, while many therapeutic drugs effective in preclinical models have failed in patients from phase II and III trials. Positive progress in reducing diagnostic delay and non-hormonal approaches for the management of symptoms have come from adoption of methods or treatments in use for other conditions that have been informed by the finding of shared genetic risk factors.

DECLARATION OF INTERESTS

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