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Easily Missed: Endometriosis, an update

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Authors

Louie Ye[1,2]
Job title: RANZCOG Trainee/Clinical Fellow
Lucy H R Whitaker[3]
Job title: NES/CSO Clinical Lecturer in Obstetrics & Gynaecology
Rebecca L Mawson[4]
Job title: GP & Academic Training Fellow
Martha Hickey[1,2]
Job title: Professor of Obstetrics and Gynaecology

Affiliations

1. The Royal Women's Hospital, Melbourne, Victoria, Australia
2. The Department of Obstetrics and Gynaecology, University of Melbourne and the Royal Women's Hospital, Victoria, Australia
3. MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, 49 Little France Crescent, EH16 4TJ
4. The Academic Unit of Primary Medical Care, The University of Sheffield, Samuel Fox House, Sheffield, S5 7AU, UK.

Corresponding author: hickeym@unimelb.edu.au

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Within our article, we use the terms 'women' and 'women's health'. However, we acknowledge that it is necessary for all assigned female at birth, including those whose gender identity does not align with the sex they were assigned at birth, to access evidence-based care in order to maintain their gynaecological health and reproductive wellbeing.

Case presentation

A 24-year-old woman presents to a new GP with several years of pain during sexual intercourse and increasingly painful periods affecting her mood, relationships and work. The pain persisted despite simple analgesia. She has had multiple contacts with healthcare professionals without a diagnosis or effective management. Her new GP suspects endometriosis. A transvaginal ultrasound (TVUS) and a three-month trial of combined oral contraceptive (COCP) is recommended. No pathology is identified on ultrasound. After three months, there was little improvement, and a gynaecology referral was offered. Subsequent laparoscopy reveals superficial peritoneal endometriosis, and the patient opted for concurrent excisional surgery with insertion of a levonorgestrel-releasing intrauterine system, a choice reflecting her previous treatment experiences and current contraceptive requirements.

What is it?

Endometriosis is defined as the “presence of endometrial-like tissue outside the uterus”(1). There are three sub-types: Superficial peritoneal, deep and ovarian (endometrioma cysts) though symptom severity and disease sub-type and extent are commonly discordant (1). Less frequently, endometriosis occurs in other anatomical locations such as the thorax or previous surgical incision sites (1).

Estimates of disease prevalence vary widely due to inconsistent presentation compounded by diagnostic challenges. In particular, the requirement of laparoscopy to make a diagnosis. The estimated population prevalence of endometriosis is 1 in 10 (2) but is higher in selected populations. For example in those with subfertility prevalence may be up to 50% (3).

Typical gynaecological presentations include painful periods and sub-fertility (1,4). Other symptoms include pain with sex and with defecation or urination which may be cyclical, and systemic manifestations such as fatigue (1,4,5). Sensitisation of central pathways may lead to chronic pain syndromes (6). Long-term consequences include impaired quality of life, anxiety, depression and self-harm(7,8). However, not all individuals with endometriosis have pain symptoms, particularly in the context of sub-fertility.

Factors contributing to sub-fertility may include reduced ovarian reserve, altered implantation and adhesion-related tubal occlusion, as well as decreased frequency of coitus due to associated pain(9). Endometriosis is commonly missed, leading to diagnostic delays. This article will discuss how the protean presenting symptoms and diagnostic criteria contribute to this delay. Endometriosis associated infertility will not be explicitly discussed because this diagnosis is commonly made during fertility investigations.

Why is it missed?

The average diagnostic delay is seven years from the onset of symptoms to definitive diagnosis with variation between countries (10). In 2020, the UK diagnostic delay was eight years, which is unchanged in a decade (11). An important contributing factor is the delay between primary presentation and diagnostic testing (12–15). One third of patients had consulted their GP six or more times before referral, with 39% having two or more gynaecological referrals before a definitive diagnosis (14).

Endometriosis is difficult to diagnose clinically as symptoms are both common and non-specific(15,16) and may be attributed to other conditions (17). For example, endometriosis may mimic or cause IBS, a common condition in primary care(17). The variable nature of presenting symptoms may lead them to be dismissed as functional or psychosomatic (12,13). Women consistently report difficulties in convincing doctors about the severity of their symptoms. This is compounded by clinicians dismissing or normalising symptoms such as painful periods (11,18). Affected women may also believe that their menstrual symptoms are normal (15). Diagnostic delay is even more common in adolescents(19), possibly due to a false belief that endometriosis takes time to cause symptoms after the onset of menarche(20). Cultural barriers may lead to reluctance or difficulty in reporting menstrual and sexual symptoms (11,18). The lack of reliable non-invasive tests likely contributes to delays in diagnosis and treatment(21,22). This is intensified by the variation and methodological quality of endometriosis guidelines leading to different diagnostic criteria(23).

Why does it matter?

Endometriosis may cause considerable suffering, distress and economic hardship for individuals(6,24). Diagnostic delays may have a significant impact socially and psychologically (25) and longer delay is associated with more advanced disease (26). Chronic pain may impair quality of life, reduce productivity and workforce participation, and contribute to financial hardship (Figure 1)(6,7,11). In the UK, the economic impact of endometriosis is estimated at around £8.2 billion per year, primarily due to absenteeism from work and healthcare costs (27). Direct treatment costs are comparable to conditions such as Type 2 diabetes or rheumatoid arthritis (27).

Around 30% of women with infertility have endometriosis (28), increasing to 50% in those with regular menstrual cycles and male partners normospermia(3). Delayed diagnosis may reduce the chance of pregnancy by 33% (29).

With such profound consequences for individuals and society, "reducing delayed diagnosis" is a priority area for research (11,30). Early diagnosis and prompt treatment might mitigate the psychosocial and economic burden associated with delayed management of endometriosis-related pain (12,15,29). However, it is not known whether earlier treatment affects the natural history of endometriosis or reduces the incidence of chronic pain syndromes

How is it diagnosed?

There is a lack of consensus about how endometriosis should be diagnosed. In the UK, guidelines from the National Institute for Health and Care Excellence (NICE) and the European Society of Human Reproduction and Embryology (ESHRE) advise that laparoscopy is the gold standard diagnostic tool with histological confirmation (4,13). Limited access and cost of laparoscopy contribute to delayed diagnosis and others have argued that clinical and radiographic features are sufficient particularly for ovarian and deep sub-types (18). Improving diagnosis and non-invasive screening tools is a top 10 research priority for the UK (30).

Clinical features

Initial suspicion and clinical diagnosis of endometriosis relies on a combination of clinical history, physical examinations, and imaging findings. Isolated pelvic examination in primary care is often uninformative (5). A normal pelvic exam or inability to perform an examination should not delay gynaecological referral(4).

Management in primary care may include ruling out conditions such as pelvic infection, pregnancy, and inflammatory or irritable bowel disease. Previous presentations may also be informative. A study of primary care records found that women subsequently diagnosed with endometriosis were likely to have had multiple consults with menstrual pain within a 12-month period, as well as gastrointestinal symptoms associated with menstruation (31). Managing complexity and uncertainty within the initial presentations of endometriosis symptoms underpins consultations in general practice(32).

Investigations

There are currently no biomarkers for endometriosis with adequate specificity or sensitivity, although this is an active area of research (21)(33). NICE and ESHRE guide against measuring Ca125 due to lack of sensitivity and specificity (4). NICE recommends transvaginal ultrasound (TVUS) as first-line imaging for suspected endometriosis (4). TVUS may exclude other potential conditions such as cysts and may identify ovarian endometriomas. Specialists in TVUS report a sensitivity of 79% and specificity of 94% for deep endometriosis and 3-D ultrasound may increase sensitivity to 87% (22,34). However, Access to specialist ultrasonography is limited in most settings.

Where TVUS is declined or inappropriate trans-abdominal ultrasound should be offered but has a lower sensitivity and specificity than TVUS (4). Ovarian and deep endometriosis may be visible on MRI (22). However, only around 17-44% of women with endometriosis present with endometriomas (35,36).

Laparoscopy for direct visualisation of lesions remains gold standard diagnostic tool(4,13). However, access to laparoscopy contributes to the delay in diagnosis, is costly, invasive and carries surgical risks (37). In view of this, laparoscopy may not be required for diagnosis if imaging identifies endometriomas or deep disease. Similarly, laparoscopy may not be indicated for women with symptoms controlled by medical therapy if the patient is in agreement with a ‘working diagnosis’ of endometriosis(38).

How is it managed?

Management in primary and tertiary care should be holistic, addressing symptoms and offering psychological support, individualised to patient wishes and fertility priorities. In primary care, NICE recommends a 3-month trial of paracetamol or NSAIDs alone or combined with a COCP or continuous progestogen for pain suggestive of endometriosis(39). Patient Decision aids have been developed to support the choice of hormonal preparation (4).

Gynaecology referral is recommended when this initial management is ineffective or contraindicated. Women with severe or recurrent symptoms, endometriomas (>3cm), urinary tract/bowel involvement or infertility plus symptoms of endometriosis should also be referred to a specialist endometriosis centre if available(4). Medical treatments such as

LNG-IUS and GnRHa may be used alone or in addition to surgery (pre- & post-operatively) to manage pain and reduce recurrence (40,41).

Laparoscopic excisional/ablative surgery is the mainstay of surgical treatment. Complex surgery for deep endometriosis involving the bowel, bladder or ureter is best managed within a specialist endometriosis centre(42). The risk of serious surgical complications depends on the extent, distribution and depth of disease, but is around 7% for surgical resection of deep endometriosis(42). Surgery may not be definitive and up to 50% report persistent symptoms at 5 years, indicating the importance of informed choice and follow-up care (43,44). Surgery has not been shown to improve fertility(39). A 2020 systematic review concluded that laparoscopic surgical management did not improve live birth rates and ovarian surgery may impair fertility (43). There are currently ongoing clinical trials examining the risks and benefits of sub-type specific surgery to improve pain, quality of life and fertility outcomes to inform evidenced-base and joint-decision making.

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How common is it

A US cross-sectional survey estimated the prevalence of diagnosed endometriosis at 6.1%(24), with a predominant symptom burden in those aged 18-29. This was corroborated by an Australian study reporting that 6.3% of women aged 40-44 years have confirmed endometriosis (45).

More prevalent in certain patient groups (2)

- Asymptomatic women - 2 to 11%
- Women with infertility - 5 to 50%
- Women hospitalised for pelvic pain - 5 to 21%
- Women with chronic pelvic pain - 50%–75%

What you need to know

1. No non-invasive diagnostic tools are available to identify endometriosis, laparoscopic biopsy of endometriotic lesions remains the gold standard for diagnosis
2. Consider endometriosis in women of reproductive age with abdomino-pelvic pain associated with menstruation, sexual intercourse, urination, defecation, and infertility.
3. Pain from suspected endometriosis can be managed in primary care with initial treatment with hormonal contraceptive methods including LNG-IUS combined with analgesia without laparoscopic confirmation

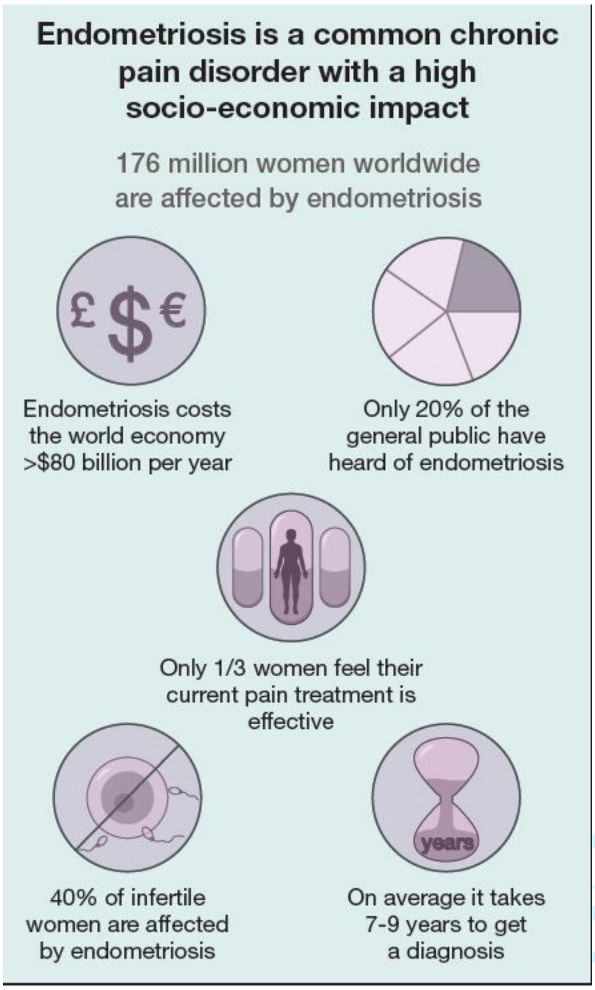
How patients were involved in the creation of this article

We asked two people living with endometriosis in the UK for comments on an early draft of this paper. In response to their comments, we revised the case to highlight the fact it often takes several years and many visits for endometriosis to be suspected & investigated. We also sought to highlight the impact of endometriosis on quality of life and the recurrence/ongoing impact after surgical excision.

Education into practice

- How do you communicate with your patients about their menstrual symptoms?
- How do you make a provisional diagnosis of endometriosis?
- What are the initial treatments you can offer and how would you adapt these for different patients?

Figure 1



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