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Endometriosis: An update on diagnosis and medical management

A shift toward early clinical diagnosis of endometriosis, one of the most prevalent gynecological disorders, and initiation of empiric medical treatment without the need for laparoscopy is critical to improving the care and quality of life of patients who suffer from the disease.

ABSTRACT: Endometriosis is a common condition of reproductive-aged women that negatively impacts their quality of life. The gold standard for diagnosing endometriosis is direct visualization at laparoscopy; however, current guidelines support the initiation of empiric treatment prior to laparoscopy in patients with suspected endometriosis. Clinically diagnosing endometriosis can be challenging because the signs and symptoms are

nonspecific. A thorough history and a comprehensive assessment of a patient's pain experience is recommended. A stepwise pelvic exam may reveal anatomic features of endometriotic implants, and imaging, predominantly transvaginal ultrasound, can be a useful adjunct. First-line medical management of endometriosis-related pain includes combined hormonal contraceptives or progestin-only hormone treatment. If there is no improvement in symptoms after a 3-month trial, a referral to a gynecologist is appropriate in order to consider gonadotropin-releasing hormone (GnRH) agonist, GnRH antagonist, or laparoscopic treatments. In patients with more complex disease, a referral to the Centre for Pelvic Pain and Endometriosis at BC Women's Hospital and Health Centre should be made.

Endometriosis is a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterus, and estrogen-dependent inflammation.¹ It is estimated that 1 in 10 reproductive-aged women suffer from endometriosis, making it one of the most prevalent gynecological disorders.² The extent of disease varies considerably from isolated peritoneal lesions to widespread pelvic adhesions, infiltrating lesions, and ovarian cysts. Most endometriotic disease is located on the pelvic peritoneum; a smaller percentage involves the bowel, bladder, and upper abdomen. The disease rarely occurs beyond the peritoneal cavity (e.g., cutaneous, thoracic).³

Women with endometriosis may experience severe pelvic pain, including dysmenorrhea, dyspareunia, and nonmenstrual chronic pelvic pain. However, some women with endometriosis are asymptomatic.⁴ In addition, infertility may occur in up to 30% of women with endometriosis.⁵ Affected women may also report fatigue, lower back pain, and urological and/or gastrointestinal symptoms.^{5,6} These symptoms are often chronic and are a major cause of disability and impaired quality of life because they can negatively affect women's work productivity, social lives, and intimate relationships, in part by reducing the quality of their sex lives.⁷ Studies also suggest that there are higher rates of depression, anxiety, and emotional distress in women with the condition.⁷ The direct and indirect annual costs, including health care resources and lost productivity, in Canada are estimated to be \$1.8 billion.⁸

Diagnosing endometriosis is particularly challenging in the community setting because it presents with a variety of nonspecific symptoms that overlap with other gynecological and nongynecological disorders. Historically, a definitive diagnosis has necessitated surgical removal and histological examination of tissue. As a result, the diagnosis of endometriosis is often delayed up to 10 years after the initial onset of symptoms, and thereby postpones appropriate treatment and causes psychological distress.^{9,10} Qualitative studies that have explored other reasons for the significant delay

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This article has been peer reviewed.

in diagnosis attribute it in part to normalization of pain by both the patients and physicians and to the lack of access to specialized examinations.^{10,11} There is a need for further education about endometriosis for both health care providers and patients, with the goal of reducing diagnostic delay by making a clinical diagnosis and enhancing women's experiences of care.¹¹⁻¹⁴

With the move away from a surgical diagnosis toward a clinical diagnosis of endometriosis, family physicians and other primary care medical professionals play an important role in identifying patients earlier after development of clinical symptoms, validating their concerns, and directing them to appropriate investigations or treatment. There is emerging evidence that the early recognition and treatment of symptoms may prevent long-term morbidity such as chronic pain.¹⁵ This article reviews the contemporary diagnosis and management of endometriosis, and provides information on when and how to access the BC Women's Centre for Pelvic Pain and Endometriosis to obtain specialized diagnosis and treatment.

Pathogenesis

The main hypotheses for the cause of endometriosis are retrograde menstruation, coelomic metaplasia, and hematological/lymphatic dissemination.¹ In addition, affected women likely have alterations in multiple biological pathways that establish and support the proliferation of this disease. These include the downregulation of apoptotic pathways and an impaired immune response that prevents clearance of refluxed menstrual debris, which promotes implantation and growth of endometrial cells.¹⁶ Endometriosis is also characterized by a positive feedback loop between local estradiol production and inflammation.¹⁷

There is a 5% to 8% increase in the risk of developing endometriosis in those with an affected first-degree relative. Other risk factors include in utero exposure to diethylstilbestrol and longer lifetime exposure to estrogen, such as in early menarche or late menopause.^{1,17} Historically, there has been a perception that endometriosis is a disease of primarily Caucasian women. However, it can be present in all

ethnicities, although there are some interesting differences between ethnic groups, including the possibility of more severe anatomic disease in East and Southeast Asians.¹⁸

History

The first step in diagnosing a woman with suspected endometriosis is to take a thorough history, and both acknowledge and evaluate her symptoms. Dysmenorrhea, chronic pelvic pain, deep dyspareunia, and infertility are the most common symptoms of endometriosis [Box 1].⁵ A national case-control study of more than 5500 women with endometriosis reported that the likelihood of endometriosis increased with the number of symptoms present, from an odds ratio of 5.0 with one symptom to 84.7 when seven or more symptoms were present.⁶

The differential diagnosis for these symptoms is lengthy and includes gynecological conditions such as primary dysmenorrhea, adenomyosis, ovarian cysts, and pelvic inflammatory disease, as well as chronic pain syndromes, including irritable bowel syndrome, interstitial cystitis, myofascial pelvic pain, and fibromyalgia. These conditions may also co-occur with endometriosis. In the context of persistent pain, endometriosis has recently been recognized as one of the chronic overlapping pain conditions that affect mostly women and reflect a sensitization process of the central nervous system (central sensitization).¹⁹

Asking about the temporal relationship between pain and the menstrual cycle may prove helpful because primary dysmenorrhea typically occurs with the onset of menstrual flow, is nonprogressive, and lasts approximately 8 to 72 hours, while menstrual pain associated with endometriosis has been described as progressive, cyclic, or acyclic, and it may extend beyond 72 hours.²⁰ The Society of Obstetricians and Gynaecologists of Canada guidelines recommend using tools such as the patient questionnaire provided by the International Pelvic Pain Society (www.pelvicpain.org) for evaluating pelvic pain. History of infertility, benign ovarian cysts, and previous pelvic surgery are associated with endometriosis, and a family history of the disease should further increase suspicion of the diagnosis.¹⁴

BOX 1. Symptoms associated with endometriosis.^{14,21}

- Dysmenorrhea
- Deep dyspareunia
- Chronic pelvic pain
- Cyclic dyschezia
- Cyclic dysuria
- Lower back or abdominal pain
- Abnormal bleeding
- Fatigue
- Infertility
- Cyclic catamenial symptoms, including cyclic leg pain, rectal bleeding, hematuria, and dyspnea

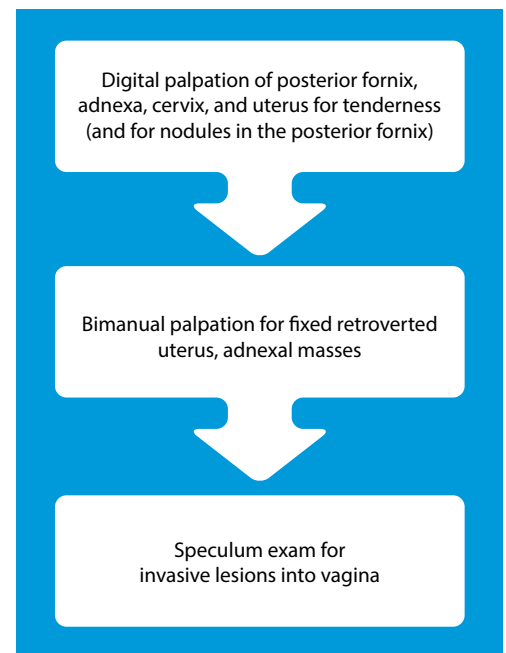


FIGURE 1. Stepwise pelvic exam for endometriosis.

Physical examination

The physical examination, which includes abdominal, pelvic, and in some cases rectovaginal examination, helps further refine the differential diagnosis and determine the appropriate imaging. Digital pelvic examination should be performed as a single-digit palpation for tenderness [Figure 1]. Deep infiltrating endometriosis nodules (palpable thickening) may be felt in the posterior vaginal fornix. On bimanual exam (digital pelvic exam plus abdominal palpation together), findings suggestive of endometriosis include a fixed, retroverted uterus, and

ovarian endometriomas manifesting as fixed adnexal masses.^{2,21} The pelvic examination is limited in identifying early-stage superficial disease, and normal examination findings are not sufficient to exclude endometriosis.¹⁴ Patients with chronic overlapping pain conditions and central sensitization may have other findings on examination, including bladder/pelvic floor tenderness on digital palpation, pelvic floor spasm, abdominal or vulvar allodynia, abdominal wall myofascial trigger points, and positive findings on examination of the back/hips.

Investigation

Transvaginal (TV) ultrasound is regarded as the first-line investigational tool for suspected endometriosis.²¹ While TV ultrasound cannot detect superficial peritoneal disease, it has a high sensitivity and specificity for the diagnosis of ovarian endometriomas [Figure 2].²² The ability to detect deep infiltrating endometriotic lesions is shown to improve significantly when the TV ultrasound is performed by an endometriosis specialist.²³ Magnetic resonance imaging (MRI) has high diagnostic accuracy in detecting endometriomas and deep

infiltrating endometriosis, and is less operator dependent.^{22,24} However, MRI is considered a second-line imaging technique after TV ultrasound because of higher costs and reduced availability.²⁴ Finally, while many biomarkers are being researched, there is currently no biomarker recommended as part of routine investigation of endometriosis.²¹

Diagnosis

Current guidelines created by professional societies, including the Society of Obstetricians and Gynaecologists of Canada, state that direct visualization at laparoscopy, preferably with histologic verification, is the diagnostic gold standard.^{20,21} However, the guidelines also advocate for medical treatment of clinically suspected endometriosis without a surgical diagnosis. There has been a push by experts in the field to move away from a surgical diagnosis and toward a clinical diagnosis, where patients' symptoms and signs are emphasized.^{14,20} This does not diminish the value of laparoscopy as a diagnostic tool, particularly when diagnosis is uncertain. Laparoscopy is also a valuable treatment option for endometriosis in women

who do not attain symptomatic relief through medical management.

During laparoscopy, endometriosis is surgically staged, most commonly by using the revised American Society for Reproductive Medicine staging system, which classifies the disease as minimal, mild, moderate, or severe (Stage I to IV).²¹ Of note, surgical staging only marginally correlates with severity of pain or risk of infertility, and an accurate diagnosis of endometriosis highly depends on surgical skill.^{4,5} Despite being a minimally invasive procedure, a laparoscopy still carries a 7.5% risk of minor complications and a 1.4% risk of major complications.²¹ Most societies advocate a see-and-treat approach to surgery for endometriosis, and state that a purely diagnostic surgery (without treatment at the same time) is not in the best interest of the patient. In patients with signs of advanced disease (ovarian endometrioma or deep infiltrating disease), a referral to a gynecologist with expertise in surgical management of endometriosis is indicated.

Current treatment

Treatment of patients with endometriosis pain may include medical therapy, surgical therapy, or both. Medical treatment is intended to reduce pain through hormonal suppression and reduction or elimination of menses.¹ Fertility-sparing surgical treatment aims to relieve symptoms through ablative techniques or excision of lesions, while still conserving reproductive function, and therefore, may be indicated as first-line therapy for temporary pain relief in women seeking spontaneous conception.²⁵

The first-line treatment for women who do not wish to conceive in the near future is combined hormonal contraceptives or progestin-only hormone treatment, with analgesics as needed. Other hormonally suppressive treatment options include injectable gonadotropin-releasing hormone (GnRH) agonists plus add-back therapy, but this is generally viewed as a second-line treatment due to cost and side effects. An oral GnRH antagonist (elagolix) for endometriosis was approved in Canada after promising results of the randomized controlled trial were published in the *New England Journal of Medicine* in 2017.²⁶ Danazol was an early treatment for endometriosis; however, its

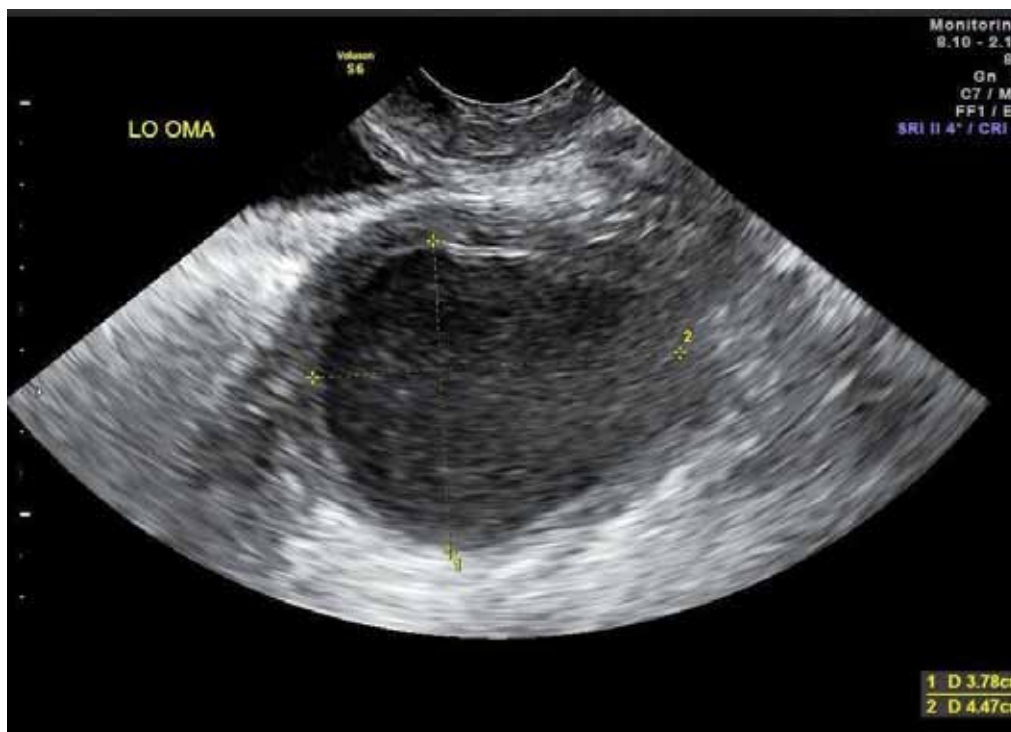


FIGURE 2. Transvaginal ultrasound. Endometriomas contain old brown blood, which is why they have been referred to as “chocolate cysts.” On transvaginal ultrasound, endometriomas often display a characteristic ground glass appearance.

androgenic side effects limit its clinical usefulness, and it has now fallen out of favor. Because these hormonal therapies have similar clinical effectiveness in treating endometriosis-related pain, patient preference, cost, and side effect profiles are important in treatment selection.²⁷ Recurrence of pain upon discontinuation limits the usefulness of hormonal therapy.²⁸ Common treatment options are summarized in **Table 1**.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common first-line treatment that work by reducing the production of prostaglandins, which are believed to be responsible for causing dysmenorrhea and cramps.²⁹ While NSAIDs effectively treat primary dysmenorrhea, a Cochrane review did not find any high-quality evidence to support NSAID efficacy in treating endometriosis-related nonmenstrual pain.²⁹ Despite this, NSAIDs are still widely used in the management of endometrioses due to their low cost, few side effects, and ready availability; however, women should be counseled on the increased risk of gastrointestinal ulceration and cardiovascular disease.²⁸

Combined hormonal contraceptives

Combined estrogen and progestin contraceptives (combined hormonal contraceptives), including combined oral contraceptive pills, transdermal patches, and vaginal rings, are considered first-line treatment for endometriosis in women without contraindications.²¹ Combined hormonal contraceptives inhibit ovulation, reduce menstrual flow, and cause decidualization and atrophy of endometriosis implants, which leads to a reduction in pain.²⁸ The efficacy of combined oral contraceptive pills in providing relief from endometriosis-related pain has been confirmed in several randomized control trials.³⁰ Either cyclic or continuous administration of combined oral contraceptive pills is acceptable. However, continuous regimens may be more beneficial in reducing pain symptoms.³¹ Advantages of prescribing a combined hormonal contraceptive include relative affordability, ease of use, contraceptive benefits, and noncontraceptive benefits such as a reduced risk of endometrial and ovarian cancer.³² Combined hormonal contraceptives can be taken safely for

TABLE 1. Common hormonal medications used for the management of endometriosis.

Type	Dose
Cyclic combined hormonal contraceptives	
Monophasic, biphasic, or triphasic pill	1 tablet/day
Continuous combined hormonal contraceptives	
Monophasic pill	1 tablet/day
Progestins	
Norethindrone	0.35 mg, 1–3 tablets/day
Norethindrone acetate	5 mg, 0.5–2.0 tablets/day
Dienogest	2 mg, 1 tablet/day
Depot medroxyprogesterone acetate	150 mg IM every 6–8 weeks
Levonorgestrel intrauterine system	52 mg released over 5 years

BOX 2. Tips for breakthrough bleeding.³³

- Counsel about consistent pill use and smoking abstinence to reduce risk of breakthrough bleeding.
- Switch to a different combined hormonal contraceptive (higher dose of estrogen or different type of progestin).
- Add a 7-day course of oral estrogen.
- If on a continuous regime for ≥ 21 days, discontinue the combined hormonal contraceptive for 3 to 4 days.

prolonged periods of time and are well tolerated. Adverse events are generally mild and include nausea, headaches, weight changes, and mood changes, and importantly, a small increased risk of venous thromboembolism.³² The most frequent reason for discontinuing combined hormonal contraceptives is breakthrough bleeding or spotting, which is treatable [**Box 2**].^{32,33}

Progestins

Progestin-only therapies are another first-line option that inhibit ovulation and induce decidualization and atrophy of endometriotic lesions.²⁸ Several progestins are available in Canada, in a variety of formulations, including oral, parenteral, and intrauterine systems; most are used off-label for treatment of endometriosis symptoms [**Table 1**].

Dienogest is the only progestin currently approved in Canada for the indication of endometriosis treatment. Norethindrone acetate is another available effective progestin, with early studies showing its efficacy in relieving chronic

pelvic pain and dysmenorrhea in women with endometriosis.³⁴ The most common side effect with progestin-only therapies is menstrual cycle disturbance, which can be managed with a 10- to 14-day course of low-dose estrogen to counteract endometrial atrophy.²⁸ Mood changes and weight gain are also clinical concerns.³⁵ However, progestins do not have the same thrombotic risk that combined contraceptives have. If a patient has responded well to these endometriosis-specific progestin therapies and wishes to have long-term therapy (e.g., 5 years or longer), potential long-term impacts on bone and lipid metabolism should be discussed. Another clinically useful but less studied progestin is the norethindrone-only contraceptive pill (mini-pill), which can be titrated up to obtain amenorrhea. Medroxyprogesterone acetate can be prescribed as an oral agent or an intramuscular injection (e.g., Depo-Provera). The Depo-Provera form has been associated with a reversible decrease in bone mineral density.³⁵

The levonorgestrel intrauterine system (levonorgestrel-IUD) releases levonorgestrel locally in the pelvis, thereby reducing the risk of systemic side effects.²¹ Because the levonorgestrel-IUD does not provoke hypoestrogenism and is applied once every 5 years, it has been suggested as a favorable treatment for women not planning to conceive.³⁶ However, because the levonorgestrel-IUD does not typically suppress ovulation, it is not helpful in treating ovulation pain.³⁶ Furthermore, the levonorgestrel-IUD carries a risk of expulsion, pelvic infection, and perforation.²¹

The following second-line therapies are usually initiated by a gynecologist, but ongoing administration may be provided by the family physician.

GnRH agonists with add-back therapy

Several GnRH agonists are available in Canada and can be administered via intramuscular, subcutaneous, or intranasal routes. GnRH agonists suppress gonadotropin secretion (follicle-stimulating hormone and luteinizing hormone), which stops estrogen production by the ovaries. Subsequent hypoestrogenism leads to amenorrhea and hypo-atrophic regression of the endometrium.³⁷ GnRH agonists cannot be safely administered for longer than 6 months due to symptoms of estrogen deficiency, including a possible irreversible loss of bone mineral density. The concurrent use of add-back hormone therapy, such as low-dose continuous estrogen with progestin, has enabled extended therapy with maintenance of bone mineral density.³⁸ While GnRH agonists with add-back therapy are an effective treatment

for endometriosis, they should be considered second-line because they are an expensive and complex form of therapy.³⁷

GnRH antagonists

In contrast to the other medical therapies, GnRH antagonists have only recently become available, with the oral GnRH antagonist elagolix approved by Health Canada in 2018. Oral GnRH antagonists produce a dose-dependent hypoestrogenic environment via pituitary gonadotropin suppression, which inhibits endometriotic cell proliferation.²⁸ The efficacy and safety of elagolix for the treatment of pain associated with endometriosis were established in two 6-month, phase 3 clinical studies.²⁶ Two different doses, 150 mg once daily or 200 mg twice daily, were compared against placebo. Both doses of elagolix significantly improved dysmenorrhea and nonmenstrual pelvic pain during a 6-month period. Both doses resulted in hypoestrogenic effects, including hot flashes and reduced bone mineral density, and the differences were significant when compared with placebo. However, the difference between the lower dose of elagolix and placebo was smaller than that for the higher dose. The potential for balancing effectiveness and tolerability by individually titrating the dosage of elagolix, as well as its oral route of administration, are potential advantages of this medication. Add-back therapy may also be used to counter the hypoestrogenic effects.

When to refer

Pelvic pain management should not be delayed in order to obtain surgical confirmation

of endometriosis. Based on the available evidence and in keeping with national guidelines, combined hormonal contraceptives, preferably used continuously, and/or progestin-only therapies should be considered as first-line options and may be started as empirical therapy by the family physician. They may also be combined with NSAIDs. If there is no improvement in symptoms and no signs of advanced endometriosis after a 3-month trial, a referral to a community gynecologist is appropriate. In women with suspected endometriosis who are actively pursuing a pregnancy or have impaired fertility, referring to a fertility clinic is recommended.²⁷

The BC Women’s Centre for Pelvic Pain and Endometriosis is an interdisciplinary tertiary care centre founded in 2011 to treat those patients with the most challenging cases of pelvic pain and endometriosis [Table 2]. The centre has gynecologists with expertise in endometriosis surgery and pelvic pain who collaborate with in-house physiotherapy, counseling, and nursing to provide interdisciplinary care.³⁹ The centre’s website provides additional information for patients and providers (www.bcwomens.ca/our-services/gynecology/pelvic-pain-endometriosis).

Summary

There is consistent evidence that endometriosis, particularly endometriosis-related pain, can have a significant detrimental impact on a woman’s quality of life. Because women with endometriosis may suffer physically, socially, and emotionally, there is a considerable need for earlier diagnosis and treatment. We are shifting toward a clinical diagnosis of endometriosis and initiation of empiric medical treatment without the need for laparoscopy. A patient who presents with dysmenorrhea, chronic pelvic pain, or dyspareunia should raise suspicion for a diagnosis of endometriosis, particularly if they have other associated symptoms, such as cyclical intestinal or urinary complaints, fatigue, or infertility. It is essential that these symptoms are not normalized or dismissed. Dysmenorrhea that interferes with a woman’s ability to function in her daily life and is not responsive to over-the-counter medication needs to be taken seriously. A recent systematic review of the effects of endometriosis on women’s lives

TABLE 2. Criteria for referring to the Centre for Pelvic Pain and Endometriosis.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Advanced endometriosis (ovarian endometrioma, deep endometriosis, extra-pelvic endometriosis) diagnosed either with imaging or surgically <p>AND/OR</p> <ul style="list-style-type: none"> Persistent pelvic pain that is unresponsive to first-line management (treated by a gynecologist within the last 3 years) 	<ul style="list-style-type: none"> Age < 16 or > 55 years Postmenopausal Currently pregnant or postpartum < 6 months Vestibulitis/vulvodynia/introital dyspareunia only Myofascial/back pain only Neuropathic pain only Unstable or untreated psychiatric issues Untreated or ongoing substance abuse

reported that even if primary care physicians lacked in-depth knowledge of endometriosis, women were satisfied if they felt heard, were treated with sympathy, and were referred appropriately.¹¹ It is important to inquire about areas of life known to be adversely affected by endometriosis to better provide patient-centred treatment, including adaptive coping strategies, stress reduction, emotional and social support, and career counseling. Ultimately, primary care physicians should feel empowered to clinically diagnose endometriosis. Recognizing endometriosis and initiating empiric treatment earlier is a critical step to improving not only the care but also the quality of life of the patients who suffer from this disease. ■

Competing interests

Dr Allaire has participated in a clinical trial within the last 2 years, is a member of an advisory board with the commercial organization Abbvie, and has received an honorarium from the commercial organization Hologic. Dr Dunne is a member of the *BCMJ* Editorial Board but did not participate in the decision making regarding the review and acceptance of this article for publication.

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