

# About the Authors



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# Endometriosis: A Narrative Review

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## Introduction

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Although much progress has been made since endometriosis was first scientifically described centuries ago, numerous unanswered questions still surround this chronic, inflammatory condition.<sup>1</sup> For instance, one theory on the pathogenesis of endometriosis suggests that the condition begins from retrograde menstrual flow implanting on surfaces in the abdomen and pelvis (Samson's theory), which is a logical mechanism given the high rates of endometriosis in patients with obstructive anomalies of the lower genital tract and significant retrograde flow. This explanation has many shortcomings however, as retrograde menstruation occurs more commonly than the reported 10% prevalence of endometriosis. Additionally, endometriosis lesions can be found in areas quite remote from the pelvis, such as the thoracic cavity. As such, research has been increasingly focused on identifying immune, genetic, and local environmental factors that likely play critical roles in the development of endometriosis. This growth of benign endometrial-like tissue outside of the uterus can sometimes be asymptomatic, but it can also cause debilitating pain, infertility, ovarian cysts (endometriomas), and can invade surrounding organs such as the bowel or bladder. There are three main phenotypes of endometriosis: superficial lesions, deeply infiltrating endometriosis (including nodules), and ovarian endometriomas.

While the exact etiology may be obscure, the societal and economic impacts of this condition are undeniable. Patients diagnosed with endometriosis are at a significantly higher risk of absenteeism from work or school, lower quality of life, chronic pelvic pain, and are more likely to receive a mental health diagnosis such as depression or anxiety.<sup>2,3</sup> Apart from direct and indirect incurred costs to patients (estimated at approximately \$5000 per patient annually), at a national level the economic burden of endometriosis exceeds \$2 billion annually in Canada, and approaches \$80 billion in the USA.<sup>4,5</sup>

## Diagnosis

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The difficulty in diagnosing endometriosis is two-fold. Firstly, abnormally painful periods, the hallmark of endometriosis, are commonly normalized or discounted by patients or physicians; this can result in a lengthy delay both in seeking and obtaining a diagnosis that can range from 4–11 years.<sup>6</sup> Secondly, in the absence of endometriomas, imaging for endometriosis is extremely dependent on how the radiological exam is performed and on the interpretation of the images. Apart from imaging, endometriosis can be diagnosed during surgery, however, current guidelines and societies uniformly recommend against diagnostic laparoscopy for the sole purpose of establishing a diagnosis.<sup>7,8</sup> In appropriate patients, a presumptive diagnosis based on a patient's history and physical exam findings can safely expedite clinical management and improve patient symptoms.

## Ultrasound

Transvaginal ultrasound typically can detect ovarian endometriomas, with their pathognomonic ground-glass contents, absence of flow within these lesions, and ovaries which are abnormally adherent to one-another ("kissing ovaries"). More subtle signs such as the sliding-sign (assessing the mobility of the uterus and vagina against the rectosigmoid) or the presence of bowel, bladder or uterosacral nodules require more specific expertise not widely available in the community. The overall sensitivity of ultrasound to detect endometriosis ranges from 80–90%, with a specificity of approximately 90%; however, for deep disease (including bowel nodules and ovarian endometriomas) the sensitivity and specificity exceed 90%.<sup>9-11</sup>

## Magnetic Resonance Imaging

Compared to ultrasound, magnetic resonance imaging (MRI) has the advantage of visualizing extrapelvic disease (i.e. lower lung fields, diaphragm, abdomen, and bowel lesions beyond the reach of pelvic ultrasound) and does

not rely on the sonographer's dynamic use of the ultrasound probe to generate images. If advanced ultrasound is not available, MRI may improve the accessibility of diagnostic imaging for patients. For deep disease, MRI has a sensitivity and specificity of approximately 94% and 77%, respectively. Classically, T2-hypointense lesions, occasionally with T1-hyperintense spots, signal nodules of endometriosis. Besides its diagnostic role, MRI can also help with operative planning, such as the need for colorectal resection or urological procedures if surgery for endometriosis is being considered.

### Molecular Testing

Novel tests are currently under development for the diagnosis of endometriosis using salivary micro-ribonucleic acid (miRNA) signatures. Although these tests have shown promising preliminary results, with a sensitivity and specificity of >95%, these remain investigational and are not yet available for commercial use.<sup>12,13</sup>

### Treatment of Endometriosis

The approach to managing endometriosis hinges on whether the patient's main concern is pain, fertility, or both. Apart from the significant impact on quality of life that endometriosis can cause, there are no immediate health concerns unless the endometriosis is compromising another organ such as the bowel or the urinary tract. As such, treatment must be guided by the patient's priorities, keeping in mind that asymptomatic endometriosis generally does not require intervention.

#### Pain: Non-Surgical Management

Non-pharmacological options for managing the pain associated with endometriosis include an anti-inflammatory diet, mindfulness, and pelvic physiotherapy, the latter of which has significant benefits for chronic pelvic pain as well as dyspareunia.<sup>14</sup> First-line pharmacological management of endometriosis-associated pain typically starts with non-hormonal options such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), which can be taken as needed, whether during menstruation or otherwise.

Hormonal treatments for endometriosis aim to suppress menstruation and shift the balance toward progestogens from estrogen, which is the dominant hormone driving this

condition. Combined hormonal contraceptives (administered either orally, transdermally, or via vaginal ring) are a popular and simple option. These contraceptives are recommended to be taken continuously (without a break for a period) in order to maximize their efficacy for endometriosis-associated pain. Progestin only options, whether approved for contraception (i.e. norethindrone, drospirenone, depot medroxyprogesterone acetate, or levonorgestrel intrauterine system) or not (i.e. norethindrone acetate, or dienogest), have all shown efficacy in treating endometriosis associated pain.<sup>15,16</sup> Dienogest, a synthetic fourth-generation progestin, remains a popular first-line choice for endometriosis owing to its excellent oral bioavailability and tolerability, absence of systemic androgenic effects, and a comparable reduction in pain when evaluated against a gonadotropin releasing hormone agonist (GnRH agonist).<sup>17,18</sup>

GnRH agonists suppress menstruation centrally and induce a temporary menopausal state. Leuprolide acetate and triptorelin pamoate are two commonly used preparations in Canada that are administered as intramuscular injections, either monthly or every 3 months depending on the dose prescribed. An initial flare effect is possible if these GnRH agonists are administered in the follicular phase, therefore timing the injection after ovulation but before menses is preferable. To avoid a flare in the follicular phase, a 5-day course of low dose aromatase inhibitor (e.g. letrozole 2.5 mg by mouth daily) can be used.<sup>19</sup>

Side-effects of GnRH agonist therapy are significant, including hot flashes, mood changes, and decreased bone density with prolonged use. As such, a low dose hormonal replacement, similar to what is used in menopausal women, may be employed as an "add-back" therapy to improve tolerability while still benefiting from globally reduced systemic estrogen. Add-back therapy is recommended if treatment duration exceeds 6-months in order to protect bone density, or earlier to mitigate the side-effects of treatment. Novel oral GnRH antagonists have also been developed either combined with "add-back" therapy (relugolix/estradiol/norethindrone acetate – Myfembree®) or without combined "add-back" therapy (elagolix sodium – Orilissa®). These treatments have proven efficacy for mild-to-moderate symptoms of endometriosis.

Apart from the novel GnRH antagonists, all of the above hormonal preparations have also shown efficacy in reducing ovarian endometrioma

diameter or volume over time, as well as reducing the risk of recurrence of endometriomas and pelvic pain after surgery.<sup>20-22</sup> Other medications that were previously used to treat endometriosis, such as danazol and aromatase inhibitors, have generally, fallen out of favour due to poor tolerability.

### **Pain: Surgical Management**

Surgery generally carries more risks than medical management, and many patients may experience a significant improvement in their symptoms with medication such that they decide against surgery altogether, making medical management a compelling first-line option. Nonetheless, surgery for endometriosis associated pain can be offered with or without an initial course of medical therapy based on patients' informed decision making. Additionally, regarding patients with large endometriomas, significant visible pathology on imaging, or impingement on the urinary or digestive tract, surgery may be the most effective treatment option.

Without any clear signs of endometriosis on imaging, a laparoscopy may still be offered with the goal of both identifying and treating lesions of endometriosis, if found. Patients with pelvic pain in the absence of endometriosis, and a negative laparoscopy (i.e. no lesions identified) may warrant a referral to a pain centre.

Discussing surgery for endometriosis with patients requires consideration of many variables such as the desire for future childbearing, anticipated years remaining until menopause, and any site-specific symptoms (such as dyschezia or hematuria). Pre-operative planning and obtaining a thorough, informed consent, are of paramount importance to avoid patients undergoing a suboptimal or incomplete surgery.

There are two described approaches to managing lesions of endometriosis: ablation (typically electrosurgical, CO2 laser, or plasma-jet destruction of the lesion *in situ*) and excision (removal of the entire lesion). Excision tends to be favoured by experts on the grounds that it may reduce the risk of future recurrence, which is supported by studies that have shown a lower likelihood of requiring additional therapies post-operatively, and greater improvements in pain and dyspareunia compared to ablation.<sup>23-26</sup> In addition, ablation is not always possible, especially when lesions are deep or nodular and involve other organs. That being said, excision of lesions can be technically challenging due to the location and depth of the invasion, particularly when in close

proximity to structures such as the ureters, pelvic nerves, or bowel.

When deep disease is suspected, referral to an appropriate surgical specialist is important to ensure that a complete excision can be safely performed. For instance, patients with endometriomas are significantly more likely to have an obliterated cul-de-sac and rectosigmoid disease, and therefore may be best served with a specialist in gynecologic surgery.<sup>27</sup>

The goal of surgery is to restore anatomy and excise all visible traces of endometriosis. This may necessitate excision of the pelvic side-walls, uterosacral ligaments, peritoneum, and endometriomas. Incidental discovery of damaged Fallopian tubes occurs not infrequently in these patients and the management of these damaged tubes (either to remove or preserve) should be pre-emptively discussed during the consent process to ensure the patient's wishes are respected. Endometriosis may also affect the ureter, the bladder, the bowel (including the appendix), and the diaphragm; therefore, a thorough evaluation and consent process pre-operatively are imperative to ensure that screening for such lesions has occurred and that a discussion regarding the surgical plan and possible involvement of other surgical specialists at the time of surgery has been fully developed.

Two final special populations are those amenable to hysterectomy and those approaching or in menopause for whom a bilateral oophorectomy can be considered. Concomitantly performing a hysterectomy during a surgery for excision of endometriosis significantly increases the chances of improving a patient's pain symptoms after surgery and decreases the risk of requiring reintervention.<sup>28,29</sup> These benefits are balanced by an incrementally increased surgical risk (i.e. vault related complications) and potential regret – as such, the decision to proceed with a hysterectomy should not be taken lightly. Bilateral oophorectomy has previously been shown to improve patients' symptoms and reduce the risk of endometriosis recurrence; however, the implications of surgical menopause (if relevant) must be explored.<sup>30</sup> Consideration of unilateral oophorectomy if there is significant ovarian disease with a healthy contralateral ovary may also be an appropriate option.

### **Fertility**

Surgery for endometriosis in the context of fertility remains controversial and a heavily



debated field of research. While there is evidence that surgery for deeply infiltrating endometriosis may assist with natural pregnancy rates, any manipulation of the ovaries for endometriomas (whether cystectomy, cyst drainage with sclerotherapy, or cyst ablation) negatively affects the ovarian reserve to varying degrees.<sup>31,32</sup> For those undergoing assisted reproduction with in vitro fertilization (IVF), the role of surgery is controversial, with some studies showing a benefit in the live birth rate while others do not. A recent systematic review and meta-analysis conducted in 2021 did favour surgery for improving IVF outcomes; however, robust randomized controlled trials are lacking.<sup>33</sup> Surgery before IVF does clearly confer an advantage in the clinical pregnancy rate in two specific scenarios. Firstly, if the patient has abnormal Fallopian tubes (e.g., hydrosalpinx), surgery to clip or remove these tubes may improve implantation rates.<sup>34</sup> Secondly, due to severe anatomic distortion from endometriosis or large endometriomas, healthy ovarian tissue may be inaccessible at the time of ovarian stimulation and egg collection. In such instances, surgery may be beneficial to improve access to ovarian tissue for IVF. Surgery may also be offered prior to ovarian stimulation to improve tolerability of the exogenous hormones during IVF cycles, as endometriosis symptoms often worsen during IVF protocols.

## Conclusion

Endometriosis is a common condition with widespread consequences on a patient's quality of life, mental health, reproductive health, and ultimately on society at large. Detection and diagnosis remain challenging, and treatment strategies, whether medical or surgical, depend on patients' priorities and symptoms. An empiric diagnosis and medical management is a reasonable approach for the appropriate patient. In addition, referral to a surgical specialist is recommended should surgery be desired. Research is warranted to facilitate earlier diagnosis, to improve our understanding of the differences between the three phenotypes of endometriosis, and to better clarify the association between lesions and symptoms.

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## Financial Disclosures

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