Endometriosis 101

Catherine Allaire, MDCM, FRCSC
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Endometriosis is defined as the presence of endometrial stroma and glands outside the endometrial cavity. This abnormal implantation most often occurs on the pelvic peritoneal surfaces and the pelvic organs, but can also occur at distant sites in the body. Hormonal activation of the ectopic endometrium can cause inflammation and scarring, leading to pain and infertility. The lesions have a variety of appearances, pigmentation, and degree of activity.

How does it develop?

Retrograde menstruation and implantation are the most accepted of the many postulated etiologies for the development of endometriosis. Since retrograde menstruation has been documented to occur in 90% of women, other associated factors, such as a genetic predisposition or immunologic failure, are postulated to be present in those who develop endometriosis. A genetic predisposition is supported by studies which have demonstrated a 6.9% prevalence of endometriosis in first-degree relatives of patients diagnosed with endometriosis, versus 1% for sisters or mothers of the patient's husband.[1,2] However, most of the current research is focused on the immune system and its role in the development and manifestation of endometriosis. There are factors, however, which increase the risk of having endometriosis (Table 1).

How prevalent is it?

Studies looking at women undergoing laparoscopic tubal ligation found prevalence rates ranging from

Melanie's case

Melanie, a 34-year-old nulligravid, presents with recurrent severe dysmenorrhea. She had a laparoscopy in 2002, where typical lesions of endometriosis involving the uterosacral ligaments were excised. Her previous deep dyspareunia resolved, and her dysmenorrhea was improved for 1 year but recurred. She has been on a monophasic oral contraceptive pill and nonsteroidal anti-inflammatory drugs, but still misses 1-2 days of work every month at the time of menses. She is not planning any pregnancies in the near future, but may want to get pregnant later. You suggest taking the monophasic oral contraceptive pill continuously, but she returns after 2 months complaining of breakthrough bleeding and constant nausea. You discuss Depo-Provera® but she is concerned about side-effects.

What other medical approach could she try?

Would further surgery help her?

What is her fertility potential?

Is she destined for a hysterectomy?

Table 1
Risks for endometriosis

- Women of reproductive age
- Incidence increases with age
- More common in Asians than Caucasians, and least common in Africans
- Maternal family history
- Greater volume of menstrual flow (short cycles, long heavy flows, early menarche)
- Obstruction of outflow tract (Mullerian anomalies)

Protective Factors
- Smoking
- Use of oral contraceptive pill
- Decreased body fat
- Factors that reduce estrogen levels, such as exercise-induced amenorrhea

Table 2
Symptoms and signs of endometriosis

Symptoms
- Pain: dysmenorrhea
  cyclic non-menstrual pelvic pain
  deep dyspareunia
  micturition or defecation pain
- Infertility
- Bleeding: menorrhagia
  metrorrhagia
  urinary or GI bleeding at time of menses

Physical signs
- Painful pelvic examination
- Uterosacral thickening or nodules
- Fixed, retroverted uterus
- Tender adnexal mass
- Coloured lesions of vulva, vagina, cervix, or surgical scar

GI: Gastrointestinal

2% to 20%. When an infertile population is studied, those rates range from 20% to 50%. Studies have shown a high prevalence of the disease (up to 47%) in adolescents with severe pelvic pain.[3]

There is an apparent increase in the prevalence of endometriosis over the last few decades. This may result from a more accurate diagnosis with increased recognition of more subtle or atypical appearances of endometriosis at laparoscopy. It may also be a consequence of delayed childbearing in combination with contraception methods that do not suppress ovulation.

How do you know it's endometriosis?

Cyclic pelvic pain and infertility are the most common symptoms of endometriosis (Table 2). Endometriosis is the most common cause of chronic pelvic pain in women of reproductive age. Other causes of chronic pelvic pain include pelvic adhesions, chronic pelvic inflammatory disease, pelvic congestion syndrome, pelvic or abdominal neuromuscular problems, interstitial cystitis, and irritable bowel syndrome. The history and physical exam should aim to diagnose these other causes of pain which often may be coexisting with endometriosis, especially if the patient's symptoms do not respond to treatments targeted at endometriosis alone.

How do you make the diagnosis?

The gold standard for diagnosis remains laparoscopy combined with pathologic identification of two or more of the following histologic criteria on biopsy: endometrial glands, endometrial stroma, endometrial epithelium, and hemosiderin-laden macrophages.

Because of the wide variety of appearances, a biopsy of the more atypical forms is important as they may look similar to other pathologic processes. The Revised American Fertility Society Classification (Stages I-IV) is the most commonly used staging system and assigns points based on severity of anatomical distortion, particularly in the adnexa and depth of the disease. Unfortunately, the staging system has a poor correlation with the severity of pain, and only mild correlation with fertility prognosis. Though it is commonly thought that endometriosis is always progressive over time, there is good evidence that the lesions can remain stable or recede spontaneously.[4]

Ancillary tests that may also be useful are endovaginal ultrasound. Occasionally, magnetic resonance imaging (MRI) can be used to further help delineate the nature of an adnexal mass, but this is not a cost-effective test, and it should be used selectively. Cystoscopy or colonoscopy should be performed if there is suspicion of significant bladder or bowel involvement with endometriosis. Serum measurement of Ca-125 antigen

Dr. Allaire is a clinical assistant professor, obstetrics and gynecology, division of reproductive endocrinology and infertility, University of British Columbia, UBC Centre for Reproductive Health, Vancouver, B.C.

is often elevated in patients with moderate to severe endometriosis and particularly in the presence of endometriomas. It can be used to distinguish between endometriomas (which have elevated Ca-125 in 78% of cases)[5] and corpus luteal cysts, or in predicting the persistence or recurrence of significant endometriosis. Overall, it has a low sensitivity and a variable specificity.

What about medical therapy?

The primary goals of medical therapy should be pain control and/or cytoreduction of the disease. No improvement in fertility rates has been demonstrated following medical therapy. Simple measures may help in providing symptomatic relief, and an initial therapeutic trial of analgesics, oral contraceptives, or progestins is acceptable without a diagnosis if the examination is normal. Some patients seem to gain relief of symptoms through lifestyle changes, such as dietary modifications and exercise, though this is difficult to prove scientifically. Cytoreduction of endometriosis lesions is usually achieved only by endocrine manipulations that prevent their cyclic stimulation. Endometriomas do not respond well to medical therapy and require surgical treatment.

Analgesics

Prostaglandin production may account for some of the symptoms of endometriosis, particularly dysmenorrhea and gastrointestinal disturbances. Nonsteroidal anti-inflammatories (NSAIDs) inhibit prostaglandin synthesis, and have been shown to provide pain relief in endometriosis patients. A placebo-controlled trial of naproxen sodium showed substantial relief in 83% of treated patients versus 41% of placebo cycles, and the effect was not correlated to the stage of disease.[6] NSAIDs are generally safe and inexpensive, and should constitute the first line of therapy for symptom relief. Other less conventional and unproven methods of pain relief may be tried, including acupuncture, biofeedback, or transdermal electrical nerve stimulation. Narcotic preparations for pain relief should be used under close supervision for short periods at a time once a diagnosis has been established. In a patient with no history of addictive behaviour, there is little risk of inducing addiction, and these medications can significantly improve quality of life.

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Table 3
Medical therapies for endometriosis

Medication/generic	Dosage	Common side-effects
Monophasic combined oral contraceptive	One daily, up to 3 daily for BTB	Nausea, bloating, mastodynia, weight gain, BTB
Provera®/ medroxyprogesterone acetate	20-100 mg orally/day	As above
Depo-Provera®	100-150 mg IM every 2-6 weeks	As above; possible decrease in bone density Delayed return of fertility
Megace®/ megestrol acetate	40 mg orally/day	As above; decreases HDL-C
Cyclomen®/danazol	200-800 mg orally/day	Weight gain, oily skin, acne, muscle cramps, breast atrophy, adverse lipid profile, elevated liver enzymes, voice deepening, cliteromegaly
GnRH Agonists		
Lupron Depot®/ leuprolide acetate	3.75 mg IM monthly	Hot flushes, vaginal dryness, bone loss, decreased libido, depression, fatigue, headaches
Synarel®/ nafarelin acetate	200 µg nasal spray twice daily	As above
Zoladex®/ goserelin acetate	3.6 mg subcutaneous depot monthly	As above
Suprefact®/ buserelin acetate	200-400 µg nasal spray three times daily, or 200 µg subcutaneous per day	As above

BTB: Breakthrough bleeding
GnRH: Gonadotrophin-releasing hormone
IM: Intramuscularly
HDL-C: High-density lipoprotein cholesterol

Hormonal Therapy

The most commonly used hormonal treatments for endometriosis and their side-effects are listed in Table 3. The primary care physician may be initiating or managing cyclic or continuous oral contraceptive pill use or progestin treatment for their patients. Table 4 is a trouble-shooting guide for the use of these medications. The usual contraindications apply for the use of these treatments. Patients taking danazol or gonadotrophin-releasing hormone analogues should have a gynecologist involved in their care.

One of the newer medical options being investigated is the levonorgestrel-releasing intrauterine device that has become available in Canada. A few small studies have shown efficacy in treating dysmenorrhea and deep dyspareunia symptoms of endometriosis.

Table 4
Troubleshooting medical therapy

Continuous OCP
- Use monophasic pill
- Breakthrough bleeding: take 2-3 pills/day for a while until bleeding stops. If bleeding continues, stop for a week, and have a full withdrawal bleed.
- Moodiness: change pills until a well-tolerated one is found
- Nausea: try vaginal administration using double dose

Provera®/ Depo-Provera®:
- Start with oral Provera (20-30 mg) for 6-8 weeks; if well-tolerated, one can switch to Depo-Provera 150 mg IM every 6-10 weeks (cheaper and easier)
- Breakthrough bleeding: Add low-dose estrogen until bleeding stops

If these methods fail, consider trial of GnRH analogue or danazol, or look for other source of pain.

OCP: Oral contraceptive pill
IM: Intramuscularly
GnRH: Gonadotrophin-releasing hormone

Is surgery an option?

The surgical management of endometriosis patients can be conservative or radical. With conservative surgery, the goal is to remove all the diseased tissue while restoring normal pelvic anatomy. The surgery can be performed by laparoscopy or by laparotomy. Both approaches offer a similar outcome, though a laparoscopic approach leads to a shorter hospital stay, with quicker recovery and less discomfort.

There is Level 1 evidence that the surgical treatment of even mild or minimal endometriosis can improve fertility.[7] There is Level 1 evidence that laparoscopic ablation of minimal-moderate endometriosis improves pelvic pain symptoms.[4] There is also Level 1 evidence that presacral neurectomy can help with central pelvic pain and dysmenorrhea in these patients.[8] In general, surgical treatment seems to have better success, and results in a lower and more delayed recurrence rate than medical therapy. However, multiple conservative surgeries for pain or infertility are not justified by the evidence available.

Radical or "definitive" surgery is the closest there is to a cure for this disease, and can be offered once fertility is not desired anymore. Following pelvic clean-out, the patient can be started on hormone replacement therapy immediately. It is recommended that combined estrogen-progestin regimens be used to prevent stimulation of possible residual disease by unopposed estrogen.

Though progress has been made in the medical and surgical management of endometriosis, we still have much to learn. The avenues for research abound, and, luckily, many good clinical studies are being done to help us in the prevention and management of this disease. CME

Take-home message

- Endometriosis is a common, sometimes debilitating, problem affecting women of reproductive age.
- Cyclic pelvic pain and infertility are the most common symptoms of endometriosis.
- The primary goals of medical therapy should be pain control and/or cytoreduction of the disease.

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Suggested Readings
1. The Canadian Consensus Conference on Endometriosis, Journal SOGC suppl, April 1993
2. The Canadian Consensus Conference on Endometriosis, Journal SOGC suppl, May 1999
3. Endometriosis: The Enigmatic Disease, S.L. Corson, EMIS-Canada, London,1992
4. The Endometriosis Sourcebook. Endometriosis Association