REVIEW

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Endometriosis: Still tough to diagnose and treat

ABSTRACT

Endometriosis is a chronic disease that may have life-altering implications such as chronic pelvic pain and infertility. The following review will familiarize the practicing physician with available therapies to maintain and enhance reproductive potential and control pelvic pain in women with endometriosis.

KEY POINTS

Medical treatments for endometriosis include oral contraceptives, progesterone, testosterone derivatives, and gonadotropin-releasing hormone (GnRH) agonists.

The antiestrogenic side effects of GnRH agonists (eg, bone loss, hot flushes, vaginal dryness) can be mitigated by giving back estrogen in replacement doses, making long-term GnRH therapy possible.

Laparoscopic surgical resection of endometriotic lesions is as effective as open surgery, but recurrence is common with either method.

Endometriosis is the most common cause of chronic pelvic pain in adolescents.

Medical and surgical treatments for endometriosis do not restore normal fertility rates, although surgery can improve the patient's chances of fertility.

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DESPITE ADVANCES, endometriosis is still tough to diagnose, tough to treat, and tough to live with.

Defined as the presence of endometrial glands and stroma outside the uterine cavity, endometriosis can only be diagnosed definitively by seeing the endometriotic lesions on laparoscopy or laparotomy. Medical therapy is far from ideal. Despite surgical ablation, many patients experience recurring pelvic pain and infertility.

In this article we explore the management of chronic pelvic pain in adult women and adolescents and infertility due to endometriosis.

PATHOGENESIS IS UNCLEAR

Various theories have been proposed to explain the pathogenesis of endometriosis.

In the 1920s, Sampson[1] proposed that in endometriosis, the pelvic peritoneum is "seeded" by retrograde menstruation. However, 90% of women have been shown to have retrograde menstruation; therefore, some authors propose that women with endometriosis have an immune deficiency that leads to inappropriate clearance of endometrial cells from the pelvic peritoneum.

Endometriosis in distant sites has been explained by metastasis of endometrial cells through lymphatic or blood vessels. In addition, some believe in the existence of totipotential cells that can transform into endometrial cells.

CHRONIC PELVIC PAIN

The most common clinical manifestation of endometriosis is chronic pelvic pain. (Pelvic pain is usually deemed chronic if it persists for

TABLE 1

Medical therapies for pelvic pain due to endometriosis

MEDICATION	DOSAGE	SIDE EFFECTS
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Variable	Gastrointestinal irritation
Oral contraceptives	20–35 µg ethinyl estradiol (cyclic or noncyclic)	Breakthrough bleeding, nausea, fluid retention
Progestational agents		Breakthrough bleeding, fluid retention, acne, weight gain
Medroxyprogesterone acetate (oral)	30–50 mg/day	
(depot injection)	150 mg/3 months	
Megestrol acetate	40 mg/day	
Testosterone derivatives		
Methyltestosterone	5–10 mg/day	Masculinization, fluid retention, irregular menses
Danazol	800 mg/day	Weight gain, hirsutism, acne, irregular menses, abnormal lipid profile
GnRH agonists		Hot flushes, vaginal dryness, decreased bone density
Leuprolide (depot suspension)	3.75 mg/4 weeks	
Nafarelin	1 puff twice daily	
GnRH agonist plus "add-back" therapy	A GnRH agonist, as above plus (a) conjugated equine estrogens 0.625 mg/day and medroxyprogesterone 2.5 mg/day or (b) an oral contraceptive	Possible decreased bone density

more than 6 months.) Some patients with endometriosis may suffer from a concomitant pain syndrome, which is defined as pain that:

- Does not respond to over-the-counter analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs)
- Disrupts the patient's life, preventing her from functioning in the family or on the job
- Is accompanied by depression or other psychologic disorder
- Is out of proportion to any identifiable abnormality found on examination or imaging studies.

Consider other causes of chronic pain

Even if a patient has been diagnosed with endometriosis, it is important to consider other causes of chronic pain. Endometriosis is a common finding on laparoscopy performed for indications other than pelvic pain. Often, physicians simply assume that any pelvic pain in a patient with endometriosis is related to the endometriosis itself and do not consider alternative diagnoses, treating the patient with medication or surgery—with significant side effects and very little relief.

Many disorders can cause chronic pelvic pain: irritable bowel syndrome, interstitial cystitis, musculoskeletal problems, and others. Think about consulting a gastroenterologist if the symptoms are focused in the gastrointestinal system, or a urologist if the symptoms are in the urinary system.

DIAGNOSIS

Symptoms that suggest endometriosis are menstrual cycle-related pain (eg, midcycle pain or dysmenorrhea) and deep dyspareunia (pain during sexual intercourse). However, women with endometriosis do not have a

higher prevalence of menstrual dysfunction. The pain can be diffuse or localized.

Areas of tenderness can be better identified by performing a physical examination during a menstrual period. Nodularity of the cul-de-sac can be felt in patients with deeply infiltrating disease.

Imaging studies, such as ultrasonography or magnetic resonance imaging, will not show peritoneal disease or adhesions unless there are large endometriomas.[2] Serum markers such as cancer antigen (CA) 125 are not sensitive enough to be used for screening.[3] The definitive diagnosis of endometriosis can only be made by laparoscopy or laparotomy.

FOUR STAGES OF ENDOMETRIOSIS

In the classification system developed by the American Society of Reproductive Medicine,[4] endometriosis has four stages, based on the location and extent of disease: stage 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe).

Perception of pain is related to both somatic and psychologic components. Patients with deeply infiltrating disease of the cul-de-sac often have significantly higher pain scores; however, the stage of disease often does not correlate with the severity of the pain.

MEDICAL TREATMENT OF ENDOMETRIOSIS ASSOCIATED WITH PELVIC PAIN

A variety of medical therapies are available for patients with recurring pelvic pain due to endometriosis (TABLE 1). With recurrence of dysmenorrhea, a trial of NSAIDs may be all that is necessary to control the symptoms.

Oral contraceptives are the most common form of medical treatment. No specific formulation is superior.

In an open-label, randomized clinical trial,[5] a cyclic low-dose oral contraceptive was inferior to the gonadotropin-releasing hormone (GnRH) agonist goserelin in relieving deep dyspareunia but similar in relieving nonmenstrual pain. (The women in the goserelin group had no menstrual pain because the drug suppressed the menses completely.) Pain scores fell significantly from baseline in the oral contraceptive group, but some patients still had dysmenorrhea. Six months after stopping treatment, pain scores did not differ between the two groups.

Patients who still have significant dysmenorrhea while on cyclic oral contraceptives may take it continuously to prevent menstruation and its associated pain.

Danazol is a derivative of 17-alpha ethinyltestosterone that inhibits the midcycle gonadotropin surge and ovarian steroidogenesis. The net effect is a hypoestrogenic, hyperandrogenic environment. Danazol is as effective as the GnRH agonists,[6] but has side effects related to hypoestrogenemia and hyperandrogenemia. Irreversible hepatocellular damage has been reported.

Progestins. Medroxyprogesterone acetate was as effective as danazol in relieving pain symptoms in a placebo-controlled trial.[7]

Gonadotropin-releasing hormone (GnRH) agonists, after a brief stimulatory phase, suppress estradiol levels to castrate levels. Subcutaneous and inhalational forms may be taken on a daily basis; intramuscular preparations can be given once a month or once every 3 months.

Randomized clinical trials have shown excellent short-term results. Leuprolide, a GnRH agonist, was shown in a placebo-controlled trial to be effective in treating endometriosis-associated pain.[8]

The main side effects of GnRH agonists are due to low estrogen levels. Patients lose trabecular bone density, which can take up to 2 years to restore after 6 months of treatment.[9] In addition, they notice symptoms such as hot flushes and vaginal dryness.

These side effects initially precluded long-term use of GnRH agonists, until "add-back" therapy was developed in which the patient is given enough estrogen to relieve the flushes and prevent bone loss. A combination of conjugated estrogens 0.625 mg and medroxyprogesterone 2.5 mg daily has been shown to be effective in preventing the hypoestrogenic side effects of GnRH agonists and maintaining their efficacy. Other agents such as bisphosphonates have been used successfully to prevent bone loss.

These add-back regimens have introduced the possibility of long-term therapy in some patients. Long-term results of therapy with GnRH agonists showed a 5-year recurrence rate of 37% with minimal disease and 74%

Even if the patient has endometriosis, consider other causes of chronic pain

with severe disease.[10] In another retrospective review,[11] the median time to recurrence of symptoms after medical therapy (danazol or a GnRH agonist) was 6 months.

GnRH agonist therapy has also been used to prevent postoperative recurrence of symptoms, although the results have been contradictory. Hornstein et al,[12] in a placebo-controlled trial, found that a GnRH agonist increased the median time to initiation of alternative treatment (24 months with the GnRH agonist nafarelin vs 11 months with placebo). However, at 6 months, the two groups did not differ in their pain scores.

SURGICAL TREATMENT OF ENDOMETRIOSIS ASSOCIATED WITH PELVIC PAIN

Conservative surgical treatment of endometriosis entails removing or destroying the lesions.

Laparoscopic surgery. Several observational studies found laparoscopy to be just as effective as laparotomy in treating endometriosis, regardless of severity.[13]

Sutton et al[14] performed one of the few randomized double-blind clinical trials to evaluate the results of surgery for endometriosis. Patients were randomized to undergo either diagnostic laparoscopy or laparoscopy with treatment. Pain scores improved in 22% of the patients in the control group (owing to a placebo effect), compared with 63% of the treated women, of whom 90% continued to report pain relief 1 year later.[15]

The stage of disease often does not correlate with the severity of the pain

Nerve ablation. If pain persists, other surgical options include denervation procedures such as uterosacral nerve ablation ("LUNA" if performed laparoscopically) or presacral neurectomy.

The LUNA procedure involves transecting nerves near the cervix. A recent review by the International Cochrane Collaboration concluded there is no evidence that the LUNA procedure adds benefit to surgery for endometriosis ablation.[16]

Presacral neurectomy involves transecting nerves below the bifurcation of the aorta. A randomized clinical trial found that this procedure did show some benefit in relieving midline pelvic pain.[17]

Depending on the extent of disease and completeness of resection, patients may be started on medical therapy immediately after surgery.

ENDOMETRIOSIS IN ADOLESCENTS

Endometriosis is the most common cause of chronic pelvic pain in adolescents,[18] accounting for up to 70% of cases.[19] The likelihood of finding endometriosis in an adolescent with pelvic pain increases with age.[20] Unlike in adult women, definitive therapy (removal of all reproductive organs) to manage endometriosis pain is not an option for adolescents.

Endometriotic lesions are different in adolescents

Endometriotic lesions in adolescents do not have the typical "powder-burn" appearance found in adults. Therefore, the surgeon must maintain a high level of suspicion when perusing the pelvis. Lesions may be clear, vesicular, white, or hemorrhagic. With time, they are believed to progress to the typical powder-burn lesions seen in adults.[20] Redwine[21] showed that black lesions are usually noted 10 years later than red and clear lesions.

Most adolescents with endometriosis present with stage 1 disease.[18] Indeed, in most series, none of the adolescent patients had stage 3 or 4 disease.

The degree of pain and discomfort in these patients does not correlate with the amount or location of endometriosis.[22] One study[23] showed that a higher amount of prostaglandin F2-alpha is released from hemorrhagic lesions, possibly explaining the increased dysmenorrhea in adolescents.

Müllerian anomalies

Patients with obstructive müllerian anomalies such as imperforate hymen, transverse vaginal septum, cervical agenesis, or a noncommunicating uterine horn have a higher incidence of endometriosis. An obstruction in the outflow tract will lead to increased backflow of blood into the peritoneal cavity, which is likely to increase the probability of endometriosis.[24]

These adolescents are more likely to present with stage 3 or 4 endometriosis as compared with adolescents without müllerian

anomalies who have endometriosis. Müllerian anomalies are likely to be first detected in adolescence, when, at menarche, the patient is likely to begin experiencing symptoms. Initially she may complain of cyclic pain, which gradually progresses to pain throughout the cycle.

The physician's index of suspicion must be very high to diagnose these patients appropriately. An adolescent presenting with pelvic pain or amenorrhea or menstrual irregularities should have an evaluation of her reproductive organs. Early diagnosis is mandatory, since relief of the müllerian obstruction leads to resolution of endometriosis and pain.[24] In addition, the earlier the abnormality is detected, the greater the chance that damage to reproductive organs can be minimized and fertility potential maintained.

Therapy for adolescent endometriosis

A combination of medical and surgical therapy is used to manage adolescent endometriosis. The goal is to control pain, minimize the number of surgical procedures, and preserve all reproductive organs.

Surgery. At the time of diagnosis during laparoscopy, all endometriotic lesions should be destroyed through excision, endocoagulation, or laser vaporization. Women managed with laser laparoscopy vs expectant management have significant relief of pain.[14] However, results are poorest for stage 1 patients.[14]

Since adolescents are more likely to have low-stage endometriosis, they are less likely to experience complete resolution of symptoms with surgical destruction of lesions. Concomitant diagnoses such as irritable bowel syndrome and lactose intolerance must be considered. Also, a thorough sexual history must be obtained, since girls with a history of sexual abuse are more likely to have pelvic pain.

Medical treatment of pelvic pain due to endometriosis in adolescents is similar to its management in adults (TABLE 1). However, danazol and methyltestosterone are rarely used in adolescents, owing to their unacceptable side effects.

Education. Some adolescents may need to be seen by a pediatric psychologist, not only to detect any psychologic issues that may be contributing to lack of pain control, but also to teach methods of pain control.

It is imperative to spend additional time with adolescents to explain endometriosis and its possible clinical implications. Multiple visits should be scheduled to answer questions and concerns that arise as the adolescent attempts to understand her disease.

ENDOMETRIOSIS AND INFERTILITY

From 25% to 40% of women undergoing diagnostic laparoscopy because of infertility are found to have endometriosis, compared with 2% to 5% of women undergoing laparoscopic tubal ligation.[25] In addition, the disease is more severe in the infertile group.

How does endometriosis impair fertility?

In advanced endometriosis, large endometriomas and extensive pelvic adhesions can disrupt the normal anatomic relationship between the fallopian tubes and the ovaries, creating an obvious impediment to conception. However, in minimal or mild disease it is unclear how a few superficial lesions can reduce the monthly fecundity rate from a normal of about 20% down to 2% to 3%.

A possible mechanism of infertility is that endometriosis generates a local peritoneal inflammatory response, leading to immune dysfunction and altered levels of prostaglandins, growth factors, and cytokines.[26] Increased numbers of peritoneal macrophages may phagocytose sperm and reduce their fertility potential.

Other possible mechanisms:

- Endometriosis may interfere with ovulation and oocyte pickup by its association with the luteinized unruptured follicle syndrome and a factor that inhibits capture of the ovulated oocyte by the fimbria of the fallopian tube, although the evidence for this is very weak.[26]
- Endometriosis may impair fertilization and embryo quality.
- It may also reduce implantation of the embryo by reducing endometrial alpha-v-beta-3 integrin (an adhesion molecule necessary for implantation of the fertilized egg) and leukemia inhibitory factor.[27]

Without estrogen replacement, patients lose bone density and have hot flushes on GnRH agonists

Treatments to enhance fertility

Infertile patients have three options short of in vitro fertilization: medical, surgical, and superovulation with intrauterine insemination.

Medical and surgical treatment. Although minimal and mild endometriosis reduces monthly fecundity rates, medical and surgical treatments have not been shown to restore normal fertility. In fact, placebo-controlled trials have not shown suppressive therapy with GnRH agonists, danazol, or progestins to enhance fertility for any stage of endometriosis.[28,29]

A meta-analysis of pregnancy rates with endometriosis treatment found that surgical treatment with laparotomy or laparoscopy resulted in significantly higher pregnancy rates than medical treatment or expectant management.[30,31] However, the improvement was limited to patients with moderate to severe disease.

Two randomized studies—one from Italy and the other from Canada—compared surgical treatment with no treatment at the time of diagnostic laparoscopy for minimal to mild endometriosis. The Canadian study[32] followed patients for 36 weeks postoperatively. The control group had a monthly fecundity rate of 2.4% compared with 4.7% for the treatment group. Although this difference was statistically significant, 4.7% is still a long way from the normal 20%.

Medical treatment of endometriosis does not improve fertility

The pregnancy rates at 1 year in the Italian study were 24% in the control group vs 29% in the treatment group; the difference was not statistically significant.[33]

Superovulation with intrauterine insemination. Tummon et al[34] randomized patients with minimal to mild endometriosis to undergo superovulation with intrauterine insemination or no treatment. The live birth rate per cycle was significantly better with treatment: 11% vs 2%.

A similar study[35] compared three cycles of superovulation with intrauterine insemination to six cycles of expectant management and found that the monthly fecundity rate was significantly higher with treatment (15% vs 4.5%), but the cumulative pregnancy rate was not (37.5% vs 24%).

Does endometriosis affect in vitro fertilization success rates?

Studies comparing pregnancy rates with in vitro fertilization between patients with endometriosis vs tubal infertility yielded inconsistent results. Several noted reduced pregnancy and implantation rates in women with endometriosis,[36–38] while others showed no difference.[39,40] The stage of disease does not seem to affect pregnancy rates.[40,41] The presence of endometriomas also did not impair pregnancy rates.

Lower fertilization rates were reported in some studies.[38] One study[36] also observed that embryos from women with endometriosis contained fewer blastomeres and that more embryos arrested in culture.

The same study also noted no difference in pregnancy rates between women with or without endometriosis who received oocytes donated from women without endometriosis. On the other hand, oocytes donated from women with endometriosis yielded lower pregnancy rates than oocytes from donors without the disease.[36] Another study confirmed that oocyte recipients with and without endometriosis had the same pregnancy rates.[41]

These findings suggest that endometriosis impairs oocyte and subsequent embryo quality but not endometrial receptivity.

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