Diagnosis and Management of Endometriosis

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Abstract

Signs and symptoms of endometriosis are non-specific, and an acceptably accurate non-invasive diagnostic test has yet to be reported. Serum markers do not provide adequate diagnostic accuracy. The preferred method for diagnosis of endometriosis is surgical visual inspection of pelvic organs with histologic confirmation. Such diagnosis requires an experienced surgeon because the varied appearance of the disease allows less-obvious lesions to be overlooked. Empiric use of non-steroidal anti-inflammatory drugs or acetaminophen is a reasonable symptomatic treatment, but the effectiveness of these agents has not been well-studied. Oral contraceptive pills, medroxyprogesterone acetate, and intrauterine levonorgestrel are relatively effective for pain relief. Danazol and various gonadotropin-releasing hormone analogues also are effective but may have significant side effects. There is limited evidence that surgical ablation of endometriotic deposits may decrease pain and increase fertility rates in women with endometriosis. Presacral neurectomy is particularly beneficial in women with midline pelvic pain. Hysterectomy and bilateral salpingo-oophorectomy definitively treat pain from endometriosis at 10 years in 90 percent of patients.

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Introduction

Endometriosis is characterized by the presence of endometrial tissue outside the endometrial cavity. These ectopic deposits of endometrium may be found in the ovaries, peritoneum, uterosacral ligaments, and pouch of Douglas *(Figure 1)*. Rarely, extrapelvic deposits of endometrial tissue are found.

Morbidity rates associated with endometriosis are considerable. Between 1990 and 1998, endometriosis was the third most common gynaecologic diagnosis listed in hospital discharge summaries of women 15 to 44 years of age.[1] The prevalence of endometriosis in the general population is estimated to be 10 percent.[2] A much higher prevalence of up to 82 percent occurs in women with pelvic pain, and in women undergoing investigation for infertility the prevalence is 21 percent.[2-4] The prevalence in women undergoing sterilization is 3.7 to 6 percent.[3,5]

Figure 1: Laparoscopic view of deposits of endometrial tissue (arrow) on the ovary.

Etiology and Pathophysiology

Several theories have been suggested to explain the pathogenesis of endometriosis. The most widely held theory involves the retrograde reflux of menstrual tissue from the fallopian tubes during menstruation. Two other possibilities are the celomic metaplasia and embryonic rests theories. Celomic metaplasia hypothesizes that the mesothelium covering the ovaries invaginates into the ovaries, then undergoes metaplasia into endometrial tissue. The embryonic rests theory hypothesizes that Müllerian remnants in the rectovaginal region differentiate into endometrial

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
The preferred method for diagnosing endometriosis is direct visualization of lesions with histological confirmation.	C	15
Danazol may be used for pain relief in patients with endometriosis.	A	22
OCPs, progesterone-only OCPs, and medroxyprogesterone acetate (Provera) should be used as first-line therapies for treating pain associated with endometriosis.	A	24-26
Because gonadotropin-releasing hormone analogues provide equivalent pain relief as OCPs and progestogens with more side effects, they should be used only as second- or third-line agents.	A	27
Surgical ablation of endometrial deposits with or without laparoscopic uterine nerve ablation can be performed for pain relief.	B	30, 31
Laparoscopic surgery can be performed in women with subfertility and endometriosis.	B	32
Presacral neurectomy can be performed in women with midline abdominal pain from endometriosis.	B	31
Laparoscopic cystectomy is preferred over drainage for pain relief in women with endometriosis.	B	33

OCPs = oral contraceptive pills.
A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 542 or http://www.aafp.org/afpsort.xml.

tissue. A woman's risk for endometriosis increases with increased exposure to endometrial material; thus, shorter menstrual cycles, longer bleeding, and early menarche are risk factors *(Table 1)*.[2,6-10] Being overweight and smoking have been associated with a lower risk of endometriosis.[11]

Table 1: Risk factors for endometriosis

Risk factor/comparrison	Odds ratio	95% Confidence interval
Mother or sister has endometriosis/mother and sister do not have endometriosis	7.2	2.1 to 24.3[6]
Menstrual flow six days or more/flow less than six days	2.5	1.1 to 5.9[7]
Menstrual cycle less than 28 days/cycle of 28 to 34 days	2.1	1.5 to 2.9[8]
Consuming one or more alcoholic drinks per week/no alcohol consumption	1.8	1.0 to 3.2[9]
Never used OCPs/ever used OCPs	1.6	1.2 to 2.2[10]
Use of pads and tampons/use of either pads or tampons	1.4	0.9 to 2.0[2]

OCPs = oral contraceptive pills.
Information from references 2 and 6 through 10.

Table 2: Differential Diagnosis of Endometriosis by Symptom

Dysmenorrhea	**Generalized pelvic pain**
Primary	Endometritis
Secondary (e.g., adenomyosis, myomas, infection, cervical stenosis)	Neoplasms, benign or malignant
Dyspareunia	Nongynecologic causes
Diminished lubrication or vaginal expansion because of insufficient arousal	Ovarian torsion
Gastrointestinal causes (e.g., constipation, irritable bowel syndrome)	Pelvic adhesions
Infection	Pelvic inflammatory disease
Musculoskeletal causes (e.g., pelvic relaxation, levator spasm)	Sexual or physical abuse
Pelvic vascular congestion	**Infertility**
Urinary causes (e.g., urethral syndrome, interstitial cystitis)	Anovulation
	Cervical factors (e.g., mucus, sperm, antibodies, stenosis)
	Luteal phase deficiency
	Male factor infertility
	Tubal disease or infection

Diagnosis

CLINICAL PRESENTATION

Endometriosis usually becomes apparent in the reproductive years when the lesions are stimulated by ovarian hormones. Symptoms tend to be strongest premenstrually, subsiding after cessation of menses. Pelvic pain is the most common presenting symptom; other symptoms include back pain, dyspareunia, loin pain, dyschezia (i.e., pain on defecation), and pain with micturition. A patient survey of women in the United Kingdom and United States who were referred to university-based endometriosis centers found that 70 to 71 percent presented with pelvic pain, 71 to 76 percent with dysmenorrhea, 44 percent with dyspareunia, and 15 to 20 percent with infertility.[12] In a British study of women with pelvic pain, many patients who eventually were diagnosed with endometriosis had been diagnosed previously with irritable bowel syndrome.[13] Endometriosis is associated with infertility because of adhesions that distort the pelvic anatomy and cause impaired ovum release and pickup. However, tubal distortion is not the only cause of infertility, because patients with endometriosis seem to have poor ovarian reserve with low oocyte and embryo quality. A meta-analysis of 22 studies evaluating in vitro fertilization outcomes found that patients with endometriosis had a pregnancy rate of nearly one half that of patients without endometriosis, with decreases in fertilization, implantation, and oocyte production rates.[14]

SURGICAL PRESENTATION

The preferred method for the diagnosis of endometriosis is direct visualization of ectopic endometrial lesions (usually via laparoscopy) accompanied by histological confirmation of the presence of at least two of the following features: haemosiderin-laden macrophages or endometrial epithelium, glands, or stroma.[15] Diagnosis based solely on visual inspection requires a surgeon with experience in identifying the many possible appearances of endometrial lesions; nonetheless, there is relatively poor correlation between visual diagnosis and confirmed histology. For example, microscopic endometrial lesions may be found in normal-appearing peritoneal samples.

DIFFERENTIAL DIAGNOSIS

Given the non-specific symptoms of endometriosis, the differential diagnosis is lengthy (Table 2).[16] The possibility of malignancy must be considered.

PHYSICAL EXAMINATION

There are few well-studied clinical manoeuvres for use in the diagnosis of endometriosis. Signs may be absent or may include tender nodules in the posterior vaginal fornix, uterine motion tenderness, a fixed and retroverted uterus, or tender adnexal masses resulting from endometriomas. One study determined the usefulness of clinical signs and symptoms in the diagnosis of endometriosis in women who present with infertility.[17] Although no test provides strong evidence for the presence of endometriosis, the symptom of uterosacral pain has the highest positive likelihood ratio.

DIAGNOSTIC TESTS

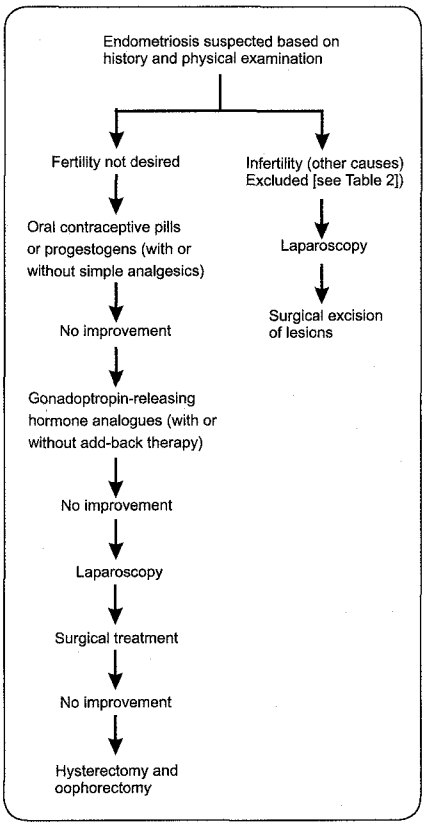
Two tests, serum cancer antigen 125 (CA 125) and magnetic resonance imaging (MRI), have been closely studied for endometriosis, but neither have shown impressive diagnostic accuracy. The use of MRI for diagnosis of an endometrial cyst is much more accurate than for endometriosis. Although there is a wealth of interest in the use of serum markers to diagnose endometriosis, none are accurate enough to be used in routine clinical practice. Elevation in levels of CA 125 (i.e., greater than 35 IU per mL), more commonly known for its use in the diagnosis or monitoring of ovarian cancer, is of limited diagnostic value; however, given its high specificity, CA 125 may be useful as a marker for disease monitoring and treatment follow-up. In addition, a well-designed meta-analysis found that measurement of serum CA 125 levels may be useful in identifying patients with infertility who may have severe endometriosis and

could benefit from early surgical treatment.[18]

One report on the use of serum cancer antigen 19-9 (CA 19-9) in the diagnosis of endometriosis found that CA 19-9 has inferior sensitivity to CA 125 but may be of some use in determining disease severity.[19] There is emerging interest in a variety of other markers. One relatively small study found that the cytokine interleukin-6 (at a cut-off value of 2 pg per mL) may be more sensitive and specific than CA 125.[20] Measurement of tumor necrosis factor a in the peritoneal fluid also has shown diagnostic promise, with sensitivity and specificity of 1 and 0.89, respectively. However, this test requires an invasive procedure to obtain the fluid. It may prove useful as an adjunct to less-obvious surgical diagnosis.

Transvaginal ultrasonography has been proven useful in the diagnosis of retroperitoneal and uterosacral lesions, but it does not accurately identify peritoneal lesions or small endometriomas.[21] Computed tomography (CT) has not been studied rigorously or promoted as a diagnostic imaging modality.

Figure 2: Steps to consider for treatment of women with endometriosis.



DIAGNOSTIC STRATEGY

There are no sufficiently sensitive and specific signs and symptoms or diagnostic tests for the clinical diagnosis of endometriosis, and no diagnostic strategy is supported by evidence of effectiveness. The American College of Obstetricians and Gynecologists recommends a pretreatment diagnostic strategy to exclude other causes of pelvic pain such as chronic pelvic inflammatory disease, fibroid tumours, and ovarian cysts.[15] Non-gynaecologic causes of pain also should be excluded. Pelvic and rectal examinations should be performed, although the yield of the physical examination is low. Findings of a retroverted uterus, decreased uterine mobility, cervical motion tenderness, and tender uterosacral nodularity are suggestive of endometriosis when present, but these findings often are absent. Laboratory tests and radiologic examinations usually are not warranted. Measurement of CA 125 levels may be useful for monitoring disease progress, and MRI has a high sensitivity in detecting endometrial cysts but poor diagnostic accuracy for endometriosis in general. Empiric diagnosis and treatment of endometriosis is reasonable, based on clinical suspicion and presentation. Patients with persistent symptoms after empiric treatment should be referred for laparoscopy, the preferred method for diagnosis of endometriosis.

Treatment

MEDICAL TREATMENT

Standard medical therapies for patients with endometriosis include analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen), oral contraceptive pills (OCPs), androgenic agents (e.g., danazol [Danogen®]),[22] progestogens (e.g., medroxyprogesterone acetate [Provera]), gonadotropin-releasing hormone analogues (GnRHas; e.g., leuprolide [Lucrin®], goserelin [Zoladex®], triptorelin [Not in RSA], nafarelin [Synarel®]), and anti-progestogens (e.g., gestrinone). *Table 3*[23] lists the indications and standard dosages for medications used in the treatment of endometriosis. *Figure 2* presents a decision tree for treatment of endometriosis in select patients.

Although the use of NSAIDs for pain relief seems logical, their effectiveness

Table 3: Drug treatment for endometriosis

Medication	*Indications*	*Dosing*	*Comment*
Depot MDPA	Pain relief	150 mg intramuscularly every three months	Common usage in primary care
MDPA	Pain relief	30 to 100 mg daily, given orally	Common usage in primary care
Combined OCPs	Pain relief	0.02 to 0.03 mg ethinyl estradiol and 0.15 mg desogestrel daily (cyclically) for six months*	Common usage in primary care
Levonorgestrel intrauterine system (Mirena®)	Pain relief after surgery	Intrauterine system	Can be placed easily in primary care setting
Gonadotropin-releasing hormone analogues	Pain relief	3.75 mg of leuprolide injected every four weeks or 3.6 mg of goserelin implanted subcutaneously for six months	Expensive; significant side effects (hypoestrogenic symptoms)
Nafarelin	Pain relief	200 mcg intranasally twice daily for six months	Expensive; significant side effects
Danazol	Pain relief	200 mg given orally three times daily; 400 mg given orally twice daily for six months	Significant androgenic side effects
Gestrinone	Pain relief	2.5 mg given orally twice weekly for six months	Hot flashes

MDPA = medroxyprogesterone acetate; OCPs = oral contraceptive pills.
**-In one study, combined OCPs were given continuously for two years.[23]*

has not been studied well or compared with other treatments. For empiric medical therapy, OCPs and medroxyprogesterone acetate have apparent therapeutic equivalence and should be used as first-line therapies.[24-26]

Many sources support the empiric use of GnRHas for treatment of the pain associated with endometriosis;[27] however, a systematic review found them to be no more effective than OCPs or progestogens[24] (Table A: Medical treatment for endometriosis: summary of studies is available at http://www.aafp.org/afp/20060815/594.pdf) Furthermore, GnRHas can have hypoestrogenic side effects.[28] These side effects may be alleviated somewhat with add-back therapy (i.e., replacement of hormones blocked by the action of GnRHas) without diminishing the effect of the GnRHa; however, the optimal method of add-back therapy has not been established.[27] One small study found the levonorgestrel-releasing intrauterine system (Mirena®) to be effective in postoperative treatment for dysmenorrhoea.[29]

SURGICAL TREATMENT

No randomised controlled trials (RCTs) have evaluated ablation of endometrial deposits alone. Ablation of endometrial deposits with or without laparoscopic uterine nerve ablation decreases pain. (Table B: Surgical treatment for endometriosis: summary of studies is available at http://www.aafp.org/afp/20060815/594.pdf)[30,31] Presacral neurectomy, a procedure in which the sympathetic nerves from the uterus are divided, may decrease midline abdominal pain.[31] Laparoscopic surgery with ablation of endometrial deposits also may increase fertility in women with endometriosis.[32] No systematic reviews or meta-analyses have compared laparoscopic drainage and laparoscopic cystectomy for the treatment of ovarian endometriomas. One RCT found cystectomy to be superior to drainage in pain relief at two years.[33]

Hysterectomy and bilateral salpingo-oophorectomy are definitive treatments for endometriosis, although there are no RCTs to support this. In a retrospective analysis of women 10 years after hysterectomy and bilateral salpingectomy, there was a 10 percent incidence of recurrent symptoms; women who had only hysterectomy had a 62 percent incidence of recurrent symptoms.[34]

CRITERIA FOR APPROPRIATE REFERRAL

Referral is required for definitive diagnosis of endometriosis by laparoscopy or laparotomy and biopsy, or for surgical ablation. Medical treatment with GnRHas or danazol (if the use of OCPs or progestogens proves ineffective) may be expensive with many possible side effects, and these therapies may be outside the range of usual primary care pharmacotherapy. Physicians experienced in the use of GnRHas and danazol may be comfortable prescribing such medications; otherwise, referral is appropriate.

Prognosis

The natural history of endometriosis suggests that the disease may stabilize or resolve on its own. In a small study that randomized patients with endometriosis to progestin or placebo, follow-up laparoscopy after one year showed that regardless of the treatment arm, 47 percent of patients had progression of their endometriosis, 25 percent had disease resolution, and 25 percent were unchanged.[35] Endometriosis may recur after surgery whether or not the patients are treated with estrogen replacement. Likewise, postmenopausal women may develop endometriosis if they use hormone therapy.

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See CPD Questionnaire, page 39

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