

# Managing Endometriosis in the Primary Care Setting

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With nonspecific symptoms and no definitive, noninvasive diagnostic tool, prompt recognition of this condition requires a combination of vigilance, knowledge, and clinical detective work.

**T**oday, federal practitioners are treating more female patients than ever. According to recent estimates, approximately 15% of active duty military personnel, 16% of reservists, and 20% of new military recruits are women.<sup>1</sup> Between 1990 and 2000, the number of female veterans increased 33% from 1.2 million to 1.6 million, with women now accounting for about 7% of the total veteran population.<sup>2</sup> And by the year 2010, this percentage is expected to rise to 10%.<sup>1</sup> Given these demographic changes, as well as the substantial number of female dependents treated by military providers, women's health issues are becoming more and more prominent in the federal setting.

Endometriosis is one of the most significant gynecologic conditions encountered in primary care. Defined as the presence of endometrial tissue outside of the uterus, endometriosis is most common in women of reproductive age, and its major consequences are pelvic pain and infertility. Although the true incidence of the disease is not known, endometriosis has been found in 5% to 50% of infertile women and 5% to 21% of

women admitted to the hospital with pelvic pain.<sup>3</sup>

While common, endometriosis can present a diagnostic challenge. With potentially nonspecific symptoms and a lack of a readily available, noninvasive diagnostic tool, the condition may not be recognized immediately and treatment may be delayed. For this reason, it's essential that primary care providers know when to suspect endometriosis, how to interpret the clinical picture for the most accurate diagnosis, and what treatment options are available based on the patient's individual needs.

This article provides a general overview of endometriosis, including etiology, presentation, diagnosis, treatment, and prognosis. The purpose is to raise awareness of these issues among primary care providers in federal practice and, in so doing, improve the care their female patients receive.

## POSSIBLE ORIGINS OF THE DISEASE

Classically, three theories have been used to explain the etiology of endometriosis: (1) retrograde menstruation, in which endometrial cells are refluxed through the fallopian tubes and into the abdominal cavity; (2) metaplasia of fetal developmental cells, in which peritoneal epithelium is changed into endometrial tissue due to chronic inflammation; and (3) growth of embryonic remnants in the

peritoneum into mature endometrial tissue. Currently, the mechanism of retrograde menstruation is the dominant theory.<sup>4</sup>

Although the majority of women undergo some degree of retrograde menstruation, fewer than 10% develop clinical endometriosis. Normally, these refluxed endometrial cells are destroyed by the immune system. An abnormal immune response to these cells—whether due to alterations in the peritoneal fluid, the number or activity of peritoneal macrophages, or the endometrial cells themselves—prevents normal clearance. In such cases, an overactive yet ineffectual inflammatory process develops, encouraging the growth of the abnormal endometrial cells.<sup>5</sup>

The relationship between ectopic endometrial tissue and the classic presentations of pelvic pain and infertility is not well understood. The fact that implanted endometrial cells bleed in response to normal stimulation from the hypothalamic-pituitary-ovarian axis has been postulated to explain the worsening pain from endometriosis around the time of menstruation. Although it is recognized that endometriosis and infertility are related, causality has not been established.<sup>6</sup>

No specific genome defect has been identified with endometriosis, but there is an increased risk of endometriosis in members of the same family. No specific lifestyle or socio-

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economic factors have been linked to the incidence of the disease.<sup>3</sup>

## RECOGNIZING THE SIGNS AND SYMPTOMS

The most common presentation of endometriosis is pelvic pain in a woman of reproductive age. Patients usually describe their pain as deep and central in location (though it can be unilateral), and they typically report worsening of pain during the menstrual period. In addition to this dysmenorrhea, women may report dyspareunia, dysuria, and dyschezia.<sup>6</sup> As a general rule, clinicians should suspect endometriosis in any woman who develops dysmenorrhea after years of painless menstrual cycles.

The other common presentation of endometriosis is infertility. In such cases, the patient may have minimal or no pelvic pain, and the diagnosis frequently is made during the routine infertility workup. Recent studies suggest that even minimal disease may adversely affect fertility.<sup>5</sup>

## MAKING THE DIAGNOSIS

Diagnosis usually is based upon a clinical presentation that is consistent with endometriosis in a woman of reproductive age. Clinical features of endometriosis include pain with motion of the uterus, ovaries, and uterine adnexa; decreased mobility of the uterus and uterine adnexa; and palpable uterosacral nodules.

On its own, no laboratory test or noninvasive imaging procedure is diagnostic of endometriosis. Pelvic ultrasound, computed tomography, and magnetic resonance imaging may be used to identify specific collections of ectopic endometrial cells (which are called endometriomas). None of these modalities, however, can be used reliably to assess the extent of endometriosis, especially disease on the peritoneal surface.<sup>5</sup>

Patients who present with a spectrum of symptoms and physical exam findings that are consistent with endometriosis may be treated by the primary care physician without further workup or specialty consultation. If the diagnosis is in doubt, however, evaluation by a gynecologist may be warranted. Overall, laparoscopy with tissue biopsy remains the most accurate tool for confirming suspected endometriosis.

Staging of endometriosis is problematic. The most widely used staging system for endometriosis is the revised American Society for Reproductive Medicine (formerly the American Fertility Society) classification system.<sup>7</sup> This system was designed, however, to predict the likelihood of pregnancy and does not correlate with the severity of pelvic pain.

## TREATMENT STRATEGIES

Since medical therapy has not been demonstrated to improve fertility, surgery is the preferred treatment for women who are infertile. Therefore, such women should be referred to a gynecologist with expertise in the treatment of endometriosis-associated infertility.

For women who do not plan to have children in the future, definitive surgical therapy (total abdominal hysterectomy with bilateral salpingo-oophorectomy) or semidefinite therapy (total abdominal hysterectomy with unilateral oophorectomy) may be considered. Although these two procedures were once considered to be equally effective in the appropriate clinical setting, the definitive procedure currently is preferred because it is associated with a lower rate of recurrence.<sup>5</sup>

Medical therapy is the initial treatment of choice for women who present with pelvic pain or dyspareunia (Table).<sup>4</sup> First-line medication con-

sists of oral contraceptives (OCs), which are believed to improve the pain of endometriosis by suppressing follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and by directly thinning endometrial tissue. No one OC preparation has been shown to be superior to another, and each can be taken continuously or cyclically. If a patient fails to respond to a three-month trial of OCs, progesterone preparations (oral progesterone acetate or intramuscular depot medroxyprogesterone acetate) may be tried.<sup>8</sup> Progesterone has similar effects on FSH, LH, and endometrial tissue.

When there is a lack of response to either OCs or progesterone, the patient may be given a trial of second-line medication, which traditionally consist of danazol or gonadotropin-releasing hormone (GnRH) agonists. While these drugs have shown greater effectiveness than OCs and progesterone in treating endometriosis, they are more expensive and are associated with some serious adverse effects.

Danazol is a synthetic androgen that suppresses the pituitary production of FSH and LH by a negative feedback mechanism. Its use has been curtailed due to adverse androgenic effects and a high cost—though a less expensive, generic formulation is now available.

GnRH agonists (such as depot leuprolide) inhibit the secretion of gonadotropin, resulting in a disruption of the normal pituitary stimulation from the hypothalamus. The net result of both synthetic androgens and GnRH agonists is a reduction of estradiol, a potent stimulant of endometrial growth. Due to significant adverse effects, which include bone loss and cardiovascular changes, the FDA limits the use of GnRH agonists to six months.<sup>8</sup>

Researchers have investigated the effects of GnRH agonists beyond six

**Table. Options for medical management of endometriosis<sup>4,5</sup>**

Drug	Dosage	Common adverse effects
Oral contraceptives	1 pill daily	Headache, nausea, blood clots
Medroxyprogesterone acetate	50–100 mg PO per day	Weight gain, breakthrough bleeding
Depot medroxyprogesterone	150 mg IM every three months	Weight gain, breakthrough bleeding
Danazol	800 mg/day	Acne, hot flashes, weight gain
GnRH* agonists		Hot flashes, sleep disturbances, bone loss
Leuprolide	3.75 mg IM monthly for six months	
Gosarelin	3.6 mg SC monthly	
Nafarelin	200 µg intranasally twice daily	

\*GnRH = gonadotropin-releasing hormone.

months when used in conjunction with estrogen add-back therapy to reduce bone loss. In one small, randomized, placebo-controlled trial comparing GnRH agonists alone versus GnRH agonists plus estrogen add-back therapy, the researchers found that patients in the dual treatment group experienced less bone loss.<sup>9</sup> This benefit, however, came at the cost of a reduced response to the GnRH agonists.<sup>9</sup>

Limited studies have investigated the off-label use of aromatase inhibitors in the treatment of endometriosis that is refractory to other medical therapies, with reported improvement in symptoms. These medications block the conversion of androgen precursors to estradiol.<sup>5</sup>

**DISEASE RECURRENCE**

Up to 90% of women with painful endometriosis experience a reduction in pain with ongoing medical treatment.<sup>8</sup> Response to medical therapy is inversely proportional to the severity of endometriosis, with recurrence rates as high as 85% in women with advanced disease who discontinue therapy (for any reason other than lack of pain improvement).<sup>5</sup>

Some authorities consider endometriosis to be a progressive disease and recommend aggressive medical therapy aimed at minimizing both symptoms and adverse effects. If medical therapy fails, they advocate definitive surgical therapy rather than continuing medical therapy that is only partially effective.

**KEEPING AWARENESS HIGH**

Federal practitioners can expect to see more female patients and, as a result, more cases of endometriosis. In order to achieve prompt diagnosis, it's essential for clinicians to maintain a high index of suspicion in women with either pelvic pain or infertility. Medical therapy is effective for most women, but it should be considered suppressive and not curative. Surgical therapy is reserved for women who fail medical therapy and for those who present with infertility.

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*Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

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