

## Minimal to mild endometriosis: 4 treatment options

Since even limited disease can cause infertility or substantial pain, it should be taken as seriously as severe endometriosis. An expert details diagnosis and the pros and cons of 4 management approaches.

**A 30-year-old woman** complains of dysmenorrhea and severe dyspareunia and reports a lingering ache after coitus. When the pain began several months earlier, she was given a presumptive diagnosis of endometriosis and advised to take nonsteroidal anti-inflammatory drugs (NSAIDs). Although the drugs provided relief initially, they are no longer effective. An examination reveals tenderness in the posterior cul-de-sac. The patient asks about the advisability of surgical treatment to eliminate the pain once and for all.

### KEY POINTS

- Signs of minimal or mild endometriosis include tenderness or nodularity in the posterior cul-de-sac, especially at the uterosacral ligaments, and anterior cul-de-sac nodularity.
- Endometriosis can be associated with infertility at all stages of disease.
- Indications for laparoscopy include infertility of more than 1 year without other symptoms or after 6 months if the patient has other symptoms or is more than 35 years of age. Patients with pelvic pain that has not responded after 3 months of nonsteroidal anti-inflammatory drugs and/or oral contraceptives also are candidates.
- Following adequate surgical extirpation of disease, no further postoperative medical treatment is necessary for patients with either pain or infertility. However, oral contraceptives have benefits for many patients who are not attempting to conceive.

**T**his case represents 1 of the challenges of treating minimal to mild endometriosis—disease without adhesions, invasive lesions, or endometriomas. Endometriosis is suggested in this patient by tenderness or nodularity in the posterior cul-de-sac, especially at the uterosacral ligaments, and anterior cul-de-sac nodularity. The patient's complaint of pain does not necessarily indicate severe disease. Rather, the relationship between minimal or mild disease and symptoms is unclear. The patient may report significant pain when only superficial implants and minimal adhesions are present.

Although hysterectomy is the definitive treatment for patients with recurrent or intractable pain associated with endometriosis, I make every effort to avoid this operation in young women with minimal to mild disease. This article describes 4 other options—no treatment, ovarian suppression, surgical treatment, and combined treatment—and points out potential pitfalls associated with each approach.

CONTINUED

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### Endometriosis: A snapshot

**Prevalence.** Endometriosis affects about 7% of reproductive-aged women—approximately 5 million Americans. Most of these women are unaware that they have the disease, although many may suffer symptoms ranging from pelvic pain to infertility.

**Symptoms.** Endometriosis is suggested by a variety of symptoms, including dysmenorrhea, dyspareunia (especially with aching following coitus, as in the case described at the opening of this article), dyschezia, dysuria, mittelschmerz, or focal or generalized pelvic pain. Hematuria and hematochezia also may be present. About 30% of patients with endometriosis have no pain.<sup>1</sup>

**Diagnostic challenges.** Deeply invasive endometriosis that is overlooked or develops outside the posterior cul-de-sac can be inappropriately staged as minimal or mild disease.

**Causes of pain.** Pain symptoms often do not correlate well with disease severity. Pain may be due to secretion of irritating factors (eg, histamine), adhesions that cause scarring or retraction, immunologic reactivity, or other unknown entities.

**Infertility can occur at any stage.** Not surprisingly, patients who have severe or extensive disease have a poorer prognosis than those with minimal or mild disease.

**Endometriosis is a progressive disease,** but the rate of progression and nature of lesions vary from patient to patient. Adhesions develop due to the inflammatory process caused by longstanding endometriosis, becoming more extensive and dense over time. Complete cul-de-sac obliteration can result from longstanding invasive and adhesive disease or may stem from abnormal müllerian development.

### Diagnosis

The diagnosis of endometriosis often can be difficult, and the extent of disease is thought to be underestimated in as many as 50% of patients.<sup>1-3</sup>

**Clinical presentation.** Endometriosis presents as pelvic pain in about 50% of patients, infertility in about 25%, pain and infertility in about 25%, and as ovarian endometrioma in less than 5% of cases.<sup>1-3</sup> Asymptomatic disease is frequent: from 1% to 40%.<sup>1-3</sup> The disease may occur any time after puberty, including adolescence. For other symptoms and characteristics, see “Endometriosis: A snapshot,” above.

**Physical examination.** Pelvic examination should be performed at the time of menses, when disease is more easily identified. The location of tenderness often corresponds to the location of the pain. As in the example case, signs of minimal or mild disease include:

- tenderness or nodularity in the posterior cul-de-sac, especially at the uterosacral ligaments
- anterior cul-de-sac nodularity

**Diagnostic tests.** The only definitive test for pelvic endometriosis is diagnostic laparoscopy. Biopsy of lesions is sometimes necessary and always advisable to confirm the diagnosis. Ultrasonography and cancer antigen 125 levels are not helpful in the diagnosis of minimal or mild disease except to rule in more severe disease.

**Indications for laparoscopy** include infertility of more than 1 year without other symptoms or after 6 months if the patient has other symptoms or is more than 35 years of age. Evaluation for other female factors and sperm quality should be conducted prior to laparoscopy. Patients with pelvic pain that has not responded after 3 months of NSAIDs and/or oral contraceptives (OCs) also are candidates for laparoscopy. In the case described above, I would recommend at least a 3-month trial of OCs and NSAIDs before performing laparoscopy.

**Staging the disease.** The American Society for Reproductive Medicine has developed a

staging system with scores from 1 to 150. Minimal and mild disease ranges from 1 to 15.<sup>4</sup>

**Management options.** Depending on the woman's reproductive goals, 1 of the 4 options discussed below may be recommended.

### Option 1

#### No treatment

This option includes expectant management and/or limited use of analgesics and NSAIDs, which may be especially helpful for women with dysmenorrhea, particularly when infertility is the primary complaint. In other instances, this approach may fail to provide adequate relief from pain.

Almost all patients should undergo an initial trial of NSAIDs and/or OCs, using NSAIDs no more than 3 days per month and taking OCs continuously for 12 weeks followed by 1 week of withdrawal. Repeat the OC regimen so that the patient has only 4 withdrawal "periods" per year.

Monitor patients every 3 to 6 months the first year and annually thereafter if they are doing well. If this approach fails, laparoscopy usually is the next step, although a 3-month trial of gonadotropin-releasing hormone (GnRH) agonists may be attempted.

### Option 2

#### Ovarian suppression

Achieve this using OCs, progestins, danazol, or GnRH agonists or antagonists.

**Oral contraceptives** can be given cyclically, but many patients do better with continuous active-ingredient tablets for 3 months, followed by withdrawal for 1 week and then repetition. Monophasic OCs are superior to triphasic formulations.

The best beginning dosage usually is 35  $\mu\text{g}$  of ethinyl estradiol, but this can be decreased if the patient is symptomatic with headaches; it also can be increased for breakthrough bleeding. Norethindrone 0.35 to 0.5 mg daily may be added if the patient is still symptomatic with bleeding.

Transdermal estradiol (0.05 mg or 0.1 mg twice weekly) also may be used if it is better tolerated. Treatment lasts 3 to 6 months.

**Progestins alone** such as medroxyprogesterone acetate (20 to 30 mg daily) or depot medroxyprogesterone acetate (150 mg every 3 months) suppress gonadotropin secretion and ovarian function but can be associated with breakthrough bleeding, mastalgia, bloating, weight gain, and depression.

**Danazol** (200 to 400 mg twice daily) functions primarily by suppressing follicle-stimulating hormone and luteinizing hormone from the pituitary gland, thereby creating a hypoestrogenic state. Unfortunately, danazol also is associated with androgenic side effects and for that reason is rarely used today. Still, it can be an effective second-line drug.

**Laparoscopic treatment is sometimes combined with ovarian suppression to improve success or facilitate surgery.**

**GnRH agonists** include nafarelin acetate nasal spray (200  $\mu\text{g}$  twice daily), leuprolide acetate as an intramuscular injection (3.75 mg monthly), and goserelin implant (for 3-month release).

GnRH agonists cause hypoestrogenemia (ie, estradiol less than 40 pg/mL) and resultant amenorrhea, which permits regression of endometriosis and relief of symptoms. Side effects include hot flashes in about 90% of patients, decreased libido, vaginal dryness, headaches, emotional lability, and insomnia.

■ **The problem of bone loss.** The major concern with GnRH agonists is the loss of bone density—about 3% to 8%—which occurs over 6 months of drug therapy, with a 2% to 3% loss persisting approximately 1 year after treatment.<sup>5</sup> While only one 6-month course of GnRH agonist is approved by the US Food and Drug Administration, studies have shown that 3 months of treatment—both initially and for subsequent retreatment (if symptoms recur)—is as effective as 6 months of treatment

**TABLE**

**Reports of pain in patients with laparoscopically diagnosed endometriosis treated with nafarelin acetate or danazol**

| TREATMENT                     | DYSMENORRHEA |        |         | DYSPAREUNIA |        |         |              | PELVIC |        |         |
|-------------------------------|--------------|--------|---------|-------------|--------|---------|--------------|--------|--------|---------|
|                               | NO.          | %      |         | NO.         | %      |         |              | NO.    | %      |         |
|                               |              | ABSENT | PRESENT |             | ABSENT | PRESENT | NOT REPORTED |        | ABSENT | PRESENT |
| <b>Nafarelin 800 µg daily</b> | 45           |        |         | 26          |        |         |              | 40     |        |         |
| Admission                     |              | 0      | 100     |             | 0      | 100     | 0            | 0      | 100    |         |
| Treatment*                    |              | 100    | 0       |             | 62     | 31      | 8            | 65     | 35     |         |
| Posttreatment†                |              | 36     | 64      |             | 62     | 35      | 4            | 45     | 55     |         |
| <b>Nafarelin 400 µg daily</b> | 45           |        |         | 31          |        |         |              | 37     |        |         |
| Admission                     |              | 0      | 100     |             | 0      | 100     | 0            | 0      | 100    |         |
| Treatment*                    |              | 98     | 2       |             | 65     | 32      | 3            | 57     | 43     |         |
| Posttreatment†                |              | 33     | 67      |             | 71     | 29      | 0            | 49     | 51     |         |
| <b>Danazol 400 mg bid</b>     | 34           |        |         | 23          |        |         |              | 28     |        |         |
| Admission                     |              | 0      | 100     |             | 0      | 100     | 0            | 0      | 100    |         |
| Treatment*                    |              | 94     | 6       |             | 70     | 17      | 13           | 64     | 36     |         |
| Posttreatment†                |              | 50     | 50      |             | 65     | 30      | 4            | 50     | 50     |         |

bid = twice a day  
 All subjects reported pain on admission.  
 \*Treatment was continued for 6 months  
 †Posttreatment period was 6 months follow-up  
 Source: Adamson and Kwei<sup>20</sup>

**Surgical treatment completed at the time of diagnosis has a distinct advantage over medical therapy.**

and is associated with less bone loss.<sup>6,7</sup> Patients generally should undergo dual-photon absorptiometry to confirm that they have normal bone density before beginning GnRH-agonist retreatment. In addition, patients should be fully informed of the potential risks of therapy. Subsequent symptoms also may be treated with OCs, danazol, and/or surgery.

▪ **Hot flashes can be effectively managed** with norethindrone (2.5 mg daily). Low doses of estrogen (conjugated estrogen 0.6 mg or estradiol 1 mg per day) have also been used as “add-back” therapy to reduce bone loss. More recently, add-back therapy for 6 to 12 months with norethindrone (2.5 mg daily) and alendronate (10 mg daily) has been suggested, along

with calcium (1,000 mg per day).<sup>8</sup> While these appear to be effective, the long-term impact of such add-back therapy is still being evaluated.

**Option 3  
 Surgical treatment**

Laparoscopy enables treatment to be initiated, when appropriate, and possibly completed at the same time as diagnosis. Surgical therapy usually is conservative, consisting of excision, laser vaporization, or electrosurgical coagulation of endometriosis. Adjunctive procedures such as salpingo-ovariectomy also may be performed.

Other controversial but occasionally indicated procedures for pain include uterosacral nerve ablation and, for severe midline dysmenorrhea, presacral neurectomy.

Medical and surgical treatments sometimes have the same results, but surgical treatment completed at the time of diagnosis

Minimal to mild endometriosis: ■  
4 treatment options

has a distinct advantage over medical therapy because of the decreased time, cost, and side effects associated with it.

#### Option 4

##### Combined treatment

Laparoscopic treatment of endometriosis is sometimes combined with ovarian suppression to improve success or facilitate surgical procedures.

**Preoperative medical therapy**, for example, suppresses ovulation so that functional cysts are not present, since they may be confused with endometriosis. Metastatic or extensive superficial disease is suppressed and becomes atrophic. Other uses of GnRH agonists prior to surgery include reducing symptoms, increasing the time available for adequate preoperative evaluation, facilitating scheduling, and even delaying or avoiding surgery for a woman nearing menopause.

Potential disadvantages of preoperative medical treatment include the changed appearance of endometriosis, which may make the disease more difficult to diagnose; drug cost and side effects; delay of diagnosis; and delay in attempting pregnancy.

**Postoperative medical treatment.** GnRH agonists may be indicated postoperatively if complete resection of disease has not been accomplished or for treatment of pain. Preoperative or postoperative treatment usually is given for 2 to 6 months, but 3 months is adequate for most women. An especially successful treatment approach for patients who do not desire pregnancy is to give OCs continuously for 2 to 3 months after surgery, withdraw for 1 week, and repeat the 2 to 3 months of treatment. In a few cases, where indicated, OCs can be continued until menopause or until the patient wishes to attempt pregnancy. It is the most cost-effective approach for many patients.

##### Treatment outcomes

**Pain.** If a woman has persistent pain after several months of expectant management,

■ Minimal to mild endometriosis: 4 treatment options

such as the patient described at the opening of this article, continuous OCs (3 months on, 1 week off) and GnRH agonists appear to be similarly effective. Approximately 80% to 90% of patients experience significant relief while on OCs or GnRH agonists, but more than 50% have some dysmenorrhea by 6 months after the agent is discontinued.<sup>9</sup>

■ **Laparoscopic treatment** also is effective in treating pelvic pain, with approximately 60% to 100% of patients showing significant clinical improvement following complete resection of disease.<sup>10</sup> Of patients who have relief of pain at 6 months after conservative surgery, 90% continue to have decreased pain at 1 year.<sup>11</sup>

**If the patient has adequate surgical extirpation of disease, no further post-operative medical treatment is indicated.**

■ **Hysterectomy** with oophorectomy results in a very high probability of “cure,” but should be avoided, if possible, in young women with minimal or mild disease. There is a small recurrence rate after hysterectomy, in the range of 5% to 8%.<sup>12</sup> This rate may be reduced by meticulous resection of all endometriosis at the time of hysterectomy and by performing concomitant oophorectomy.

**Infertility.** Pregnancy rates are higher 9 months after laparoscopic treatment than after no treatment in women with minimal to mild endometriosis, according to a large, multicenter, prospective randomized trial that was excellently designed and executed.<sup>13</sup> Laparoscopically treated patients had a 37.5% pregnancy rate versus 22.5% in the expectantly managed group ( $P = .002$ ).

However, pregnancy rates at 3 years are not different for no treatment, laparoscopy, and laparotomy when 3-year estimated cumulative life-table pregnancy rates are calculated.<sup>14</sup> Similarly, no treatment or surgery is superior to medical treatment for infertility associated with minimal to mild endometriosis.<sup>14</sup>

Meta-analysis also has shown no significant difference in crude pregnancy rates between no treatment and medical treatment.<sup>15</sup> Therefore, selected young patients with minimal or mild disease and a short duration of infertility can forego treatment, although superior pregnancy rates can be achieved with laparoscopic surgery.

■ **Fertility treatment.** Controlled ovarian hyperstimulation with clomiphene citrate (150 mg every day from cycle day 3 to 7) or gonadotropins and intrauterine insemination improves pregnancy rates in this group. Most patients will conceive within 3 to 6 cycles of clomiphene treatment; thus, therapy should not continue past that time.

Patients with minimal to mild disease who undergo assisted reproductive technology have pregnancy rates similar to women in other diagnostic categories. Pregnancy rates depend on patient age, ranging from approximately 40% per egg retrieval at age 30 to 20% at age 40.<sup>16</sup>

■ **Medical treatment delays conception.** Ovarian suppression for minimal and mild endometriosis merely delays the possibility of pregnancy by the duration of the therapy and is associated with additional cost and undesirable side effects. For that reason, medical therapy should not be used to treat minimal and mild endometriosis when the only symptom is infertility.

■ **Pregnancy after laparoscopy.** A review of laparoscopic treatment of endometriosis reported pregnancy rates for minimal and mild disease of 58% whether treated by electrocoagulation or by CO<sub>2</sub> laser.<sup>17</sup>

### **Choosing a management approach**

**Treat disease at time of diagnosis.** Endometriosis cannot be fully diagnosed without laparoscopy. Whether the patient's symptoms involve pain or infertility, surgical treatment involving complete laparoscopic resection of the disease should be performed at the time of diagnosis, provided the surgeon

is sufficiently skilled.<sup>18</sup> The only exceptions to this approach are:

- patients given a presumptive diagnosis of endometriosis who plan to undergo a trial of medical therapy for pain, and
- young women with infertility as the sole symptom and extensive superficial peritoneal and/or ovarian disease. Treatment of such lesions may increase pregnancy rates, but also can lead to pelvic adhesions.

**Postoperative options.** Pain patients generally should receive OCs postoperatively. For infertility patients who have not conceived after 3 to 12 months of attempting pregnancy on their own following laparoscopic surgery, controlled ovarian hyperstimulation with clomiphene or gonadotropins for 3 to 6 months with intrauterine insemination will increase pregnancy rates.

If the patient has adequate surgical extirpation of the disease, no further postoperative medical treatment is indicated (except for OCs), for either pain or infertility. If pain recurs, GnRH agonists usually should be the first line of treatment.

For infertile patients who fail to conceive, a second-look laparoscopy at 6 to 18 months is occasionally indicated, although in vitro fertilization may be more cost-effective, especially if other infertility factors are present.<sup>19</sup>

**When no operative laparoscopy is performed** or when resection of endometriosis is incomplete, pain patients are usually best managed with GnRH agonists or danazol for 3 to 6 months (TABLE). (GnRH agonists are generally preferred because of their more favorable side-effect profile.) If pain continues despite surgical and/or medical treatment, refer the patient to pain specialists for a comprehensive management approach. Discuss this option with the patient at her first consultation and integrate it into the treatment plan.

For infertility patients who have not undergone operative resection or who have had inadequate resection, minimal and mild disease needs no further treatment. Ovarian

suppression should be avoided. Patients who do not conceive within approximately 6 to 15 months should generally move on to in vitro fertilization, although repeat laparoscopy is occasionally indicated if there is residual disease and pain associated with the infertility.

### **Treat the whole patient:**

#### **Lifestyle and other factors**

It is critical that physicians recognize the degree to which endometriosis can physically and emotionally disrupt patients' lives. Understanding, empathy, and a comprehensive management approach are valuable components of successful treatment.

The patient also should be encouraged to develop a healthy lifestyle with respect to diet, exercise, and sleep. Stress reduction through mind-body techniques can be very helpful, as well.

**If pain continues despite surgical or medical treatment, refer the patient to pain specialists for comprehensive management.**

Information about the disease can serve as psychological support and is available from organizations such as the Endometriosis Association ([www.endometriosisassn.org](http://www.endometriosisassn.org)), RESOLVE ([www.resolve.org](http://www.resolve.org)), and the American Society for Reproductive Medicine ([www.asrm.org](http://www.asrm.org)). Personal or group counseling also may be helpful, especially for the patient with chronic pain.

Some patients may seek nontraditional and unproven approaches to treatment, such as acupuncture, herbal medicine, or special diets. Management in these chronic, complex situations should focus on alleviation of symptoms and improved quality of life.

A comprehensive evaluation of gastrointestinal, genitourinary, musculoskeletal, neurologic, and psychological systems may be indicated. Referral to a pain clinic may be helpful for further treatment, including biofeed-

■ Minimal to mild endometriosis:  
4 treatment options

back strategies, nerve blocks, psychotherapy, or other pain-management techniques.

Treatment of reactive depression frequently is necessary and often requires a multidisciplinary approach.

A comprehensive long-range treatment approach should be individualized to the patient. A complete cure can sometimes be achieved only by total hysterectomy and bilateral salpingo-oophorectomy. ■

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OBG MANAGEMENT SUPPLEMENT ON

# Androgen Therapy for Women:

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