



IN A DIFFICULT-TO-TREAT CASE

Have you tried a progestin for your patient's pelvic pain?

📌 Progestins are highly effective for pelvic pain caused by endometriosis that's refractory to other treatments

CASE Your patient is a 26-year-old G0 woman who has a long history of progressively worsening dysmenorrhea, pelvic pain, and dyspareunia. In the recent past, she was treated with nonsteroidal anti-inflammatory drugs, a cyclic estrogen-progestin contraceptive, and a continuous estrogen-progestin contraceptive—in that order, and without appreciable relief of the pain.

Recently, the woman underwent laparoscopy, which demonstrated Stage-II endometriosis, which was ablated.

What would you prescribe for her postoperatively to alleviate symptoms?

Instant Poll



What is your preferred hormone treatment for women who have endometriosis and pelvic pain, and whose symptoms have not been relieved by a cyclic or continuous oral contraceptive?

Send your nomination to me at robert.barbieri@qhc.com. We'll consider publishing it in an upcoming issue.

Please include your name and city and state.



Endometriosis will be diagnosed in approximately 8% of women of reproductive age.¹ Pelvic pain, dysmenorrhea, and deep dyspareunia are common symptoms of endometriosis that interfere with quality of life.

Endometriosis is a chronic disease best managed by developing a life-long treatment plan. Following laparoscopic diagnosis and treatment, many experts strongly recommend postoperative hormone-suppressive therapy to reduce the risk that severe pelvic pain will recur, requiring re-operation.

Options for postoperative hormonal treatment of endometriosis include:

- an estrogen-progestin contraceptive
- a progestin (norethindrone acetate [NEA]; depot medroxyprogesterone acetate [DMPA]; oral medroxyprogesterone acetate; the levonorgestrel-releasing intrauterine system [LNG-IUS; Mirena]; and the progestin-releasing implant [Implanon])
- a gonadotropin-releasing hormone (GnRH) agonist (depot leuprolide [Depot Lupron]; nafarelin nasal spray [Synarel]).

CASE Continued

Considering that both cyclic and continuous estrogen-progestin contraceptives have already failed to provide

adequate pain relief for your patient, you know that you should offer an alternative to her. Taking into account that progestins are significantly less costly than a GnRH agonist, a progestin formulation might, for her, be considered a first-line postoperative treatment of symptoms of endometriosis.

Options when considering a progestin

Norethindrone acetate

This agent is available in a single formulation: a 5-mg tablet; however, dosages ranging from 2.5 mg/d (half of a tablet) to 15 mg/d have been reported to be effective for relieving pain caused by endometriosis.

What is it? NEA is an androgenic progestin that suppresses luteinizing hormone and follicle-stimulating hormone, thus reducing production of ovarian estrogen. In the absence of ovarian estrogen, endometriosis lesions atrophy. In addition, NEA binds to, and stimulates, endometrial progestin and androgen receptors, resulting in decidualization and atrophy of both eutopic and ectopic endometrial tissue.

Importantly, NEA does not appear to cause bone loss, a phenomenon that is common with agents such as the GnRH agonists or DPMA.²⁻⁴

The research record. One randomized study, two pilot studies, and one

large observational study have reported that NEA is effective for pelvic pain caused by endometriosis.

In the **randomized trial**, 90 women who had moderate or severe pelvic pain and rectovaginal endometriosis, and who remained symptomatic after conservative surgery, were randomized to receive NEA, 2.5 mg/d, or a low-dose estrogen-progestin contraceptive (ethinyl estradiol, 10 µg, plus cyproterone acetate, 3 mg) daily for 12 months.⁵ Both treatment groups reported significant and similar decreases in dysmenorrhea, deep dyspareunia, non-menstrual pain and dyschezia.

In a small **pilot study**, 40 women who had pelvic pain and colorectal endometriosis were treated with NEA 2.5 mg/d for 12 months. The drug produced significant improvement in dysmenorrhea, pelvic pain, deep dyspareunia, dyschezia, and cyclic rectal bleeding.⁶

In **another pilot study**, women who had pelvic pain and rectovaginal endometriosis were treated with either an aromatase inhibitor (letrozole, 2.5 mg/d) plus NEA (2.5 mg/d) or NEA (2.5 mg/d) alone for 6 months. Both treatments resulted in a significant improvement in pelvic pain and deep dyspareunia. Improvement in pain scores was greater with letrozole plus NEA; patients were more satisfied with NEA monotherapy than with the combined letrozole-NEA treatment, however, because the former was associated with fewer side effects.⁷

In a large (n = 194) **observational study** of the postoperative use of NEA in young women with pelvic pain and endometriosis, NEA at dosages as high as 15 mg/d significantly diminished pelvic pain and self-reported menstrual bleeding. All subjects were started on a dosage of 5 mg/d, which was increased in 2.5-mg increments every 2 weeks to achieve the goals of amenorrhea and a lessening of pelvic pain; the maximum dosage administered was 15 mg/d. Mean duration of NEA use was 13 months; 75% of subjects took the maximum prescribed dosage of 15 mg at some point during treatment. The most commonly reported side effects were weight gain (16% of women); acne (10%); mood lability (9%); and vasomotor symptoms (8%).⁸

In summary. NEA is effective for treating pelvic pain caused by endometriosis at dosages from 2.5 mg/d to 15 mg/d. An important goal of treatment is a decrease in pain symptoms and amenorrhea; a dosage of 2.5 mg is often insufficient to reliably achieve both of those objectives.

In my practice I begin therapy at a dosage of 5 mg/d; the drug is effective for most patients at that dosage. If 5 mg/d does not reduce pain, I

increase the dosage by 2.5 mg (half of a tablet) daily every 4 weeks, to a maximum dosage of 10 mg/d (two tablets). If that dosage is ineffective, I usually discontinue NEA and switch to a GnRH agonist.

Depot medroxyprogesterone acetate; oral medroxyprogesterone acetate

DMPA is available in two FDA-approved formulations:

- a 150-mg dose given by intramuscular injection every 3 months
- a 104-mg dose given by subcutaneous injection every 3 months.

Research. The results of two large clinical trials, comprising a total of more than 550 subjects, showed that DMPA (104 mg, SC, every 3 months) and depot leuprolide (11.25 mg, IM, every 3 months or 3.75 mg, monthly) were each equally effective in relieving dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and pelvic induration in women who had endometriosis.^{9,10}

DMPA was associated with a greater rate of episodes of irregular bleeding than depot leuprolide; conversely, depot leuprolide was associated with greater loss of bone density and a higher incidence of vasomotor symptoms. Weight gain was in the range of 0.6 kg in both groups.

Of note, DPMA is much less expensive than depot leuprolide.

Another study showed that increasing the dosage of DMPA did not improve efficacy over the standard dosage¹¹: DMPA, 150 mg IM, monthly, and DMPA, 150 mg IM, every 3 months produced similar relief of pelvic pain.

Oral medroxyprogesterone acetate, prescribed at high dosages, is also effective for pelvic pain caused by endometriosis. In a pilot study (n = 21), oral MPA, 50 mg/d for 4 months, alleviated dysmenorrhea,

Welcome, Dr. Jennifer Gunter!



The Editors of OBG MANAGEMENT have appointed **Jennifer Gunter, MD**, to the publication's roster of Contributing Editors as an advisor

on electronic communications, the Web, and social media.

Dr. Gunter is in ObGyn practice in San Francisco. She is the author of *The Premie Primer: A Complete Guide for Parents of Premature Babies—from Birth through the Toddler Years and Beyond* (Da Capo Press, 2010) and of recent articles in OBG MANAGEMENT. She blogs at <http://www.drjengunter.com>

dyspareunia, pelvic pain, dyschezia, and pelvic tenderness and decreased pelvic nodularity. Sixty percent of subjects reported weight gain—1.5 kg, on average.¹²

Progestin-releasing devices: Mirena and Implanon

Many pilot studies have reported that the levonorgestrel-releasing intrauterine system (LNG-IUS) is effective for pelvic pain caused by endometriosis.¹³⁻¹⁷ For example:

Research. In a small clinical trial, 30 women who had pelvic pain and endometriosis were randomized to receive an LNG-IUS (Mirena) or DMPA, 150 mg IM, every 3 months for 3 years.¹³ Both therapies were effective at reducing pelvic pain.

At the conclusion of the study, more women opted to retain the LNG-IUS (87%) than to continue DMPA injection (47%). Bone density was maintained in women who had the LNG-IUS placed but slightly diminished in women receiving DMPA.

In a pilot study of an etonogestrel releasing implant (Implanon), 41 women who had pelvic pain and endometriosis were randomized to receive the implant or DMPA, 150 mg IM, every 3 months for 1 year.¹⁸ Both therapies were similarly effective at reducing pelvic pain.

Notably, irregular uterine bleeding is a common problem when the etonogestrel-releasing implant is used to treat endometriosis. Achieving amenorrhea or oligomenorrhea is an important goal for women who suffer from pelvic pain caused by endometriosis.

My recommendation

Most ObGyns see patients who are suffering from difficult-to-treat pelvic pain caused by endometriosis. Many of these patients have not had

a trial of a progestin, such as NEA, DMPA, or the LNG-IUS that I use in my practice.

Progestins are, as I've described, effective for pelvic pain. They are also relatively inexpensive and have a side-effect profile that most patients find acceptable. I recommend that you try a progestin for your patients who have refractory pelvic pain. ☺

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Correction Reimbursement Adviser, November 2011

The date of the changeover to the 10th revision of International Classification of Diseases (ICD-10-CM) codes is incorrectly stated on page 51. The date should be October 1, 2013.

The corrected version of this article appears at http://www.obgmanagement.com/article_pages.asp?AID=10041&UID=

—The Editors