

# Optimize the medical treatment of endometriosis—Use all available medications

In my referral practice, the most common problem I see in the medical management of endometriosis is a reluctance to prescribe approved hormonal medications from all available drug classes



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## **CASE Endometriosis pain increases despite hormonal treatment**

A 25-year-old woman (G0) with severe dysmenorrhea had a laparoscopy showing endometriosis in the cul-de-sac and a peritoneal window near the left uterosacral ligament. Biopsy of a cul-de-sac lesion showed endometriosis on histopathology. The patient was treated with a continuous low-dose estrogen-progestin contraceptive. Initially, the treatment helped relieve her pain symptoms. Over the next year, while on that treatment, her pain gradually increased in severity until it was disabling. At an office visit, the primary clinician renewed the estrogen-progestin contraceptive for another year, even though it was not relieving the patient's pain. The patient sought a second opinion.

## **We are the experts in the management of pelvic pain caused by endometriosis**

Women's health clinicians are the specialists best trained to care for patients with severe pain caused by endometriosis. Low-dose continuous

estrogen-progestin contraceptives are commonly prescribed as a first-line hormonal treatment for pain caused by endometriosis. My observation is that estrogen-progestin contraceptives are often effective when initially prescribed, but with continued use over years, pain often recurs. Estrogen is known to stimulate endometriosis disease activity. Progestins at high doses suppress endometriosis disease activity. However, endometriosis implants often manifest decreased responsiveness to progestins, permitting the estrogen in the combination contraceptive to exert its disease-stimulating effect.<sup>1,2</sup> I frequently see women with pelvic pain caused by endometriosis, who initially had a significant decrease in pain with continuous estrogen-progestin contraceptive treatment but who develop increasing pain with continued use of the medication. In this clinical situation, it is useful to consider stopping the estrogen-progestin therapy and to prescribe a hormone with a different mechanism of action (TABLE, page 10).

## **Progestin-only medications**

Progestin-only medications are often effective in the treatment of pain caused by endometriosis. High-dose progestin-only medications suppress pituitary secretion of luteinizing hormone (LH) and follicle-stimulating

**High-dose progestin-only medications**  
suppress pituitary secretion of LH and FSH thereby  
**suppressing ovarian synthesis of estrogen**

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**TABLE** Hormone medication options currently available to treat pelvic pain caused by endometriosis

Medication <sup>a</sup>	Route of administration	Dose	Relative cost <sup>b</sup>
<b>Progestins</b>			
<i>Norethindrone acetate</i>	Oral	5 mg daily	\$
Medroxyprogesterone acetate	Oral	20 to 40 mg daily	\$
Depot-medroxyprogesterone acetate	Intramuscular	150 mg every 3 months	\$
<i>Depot-medroxyprogesterone acetate</i>	Subcutaneous	104 mg every 3 months	\$\$
Levonorgestrel (LNG) intrauterine device	Intrauterine device	52-mg device releasing about 20 µg of LNG daily	Cost depends on number of months of use
<b>GnRH analogues</b>			
<i>Nafarelin acetate</i>	Intranasal	One spray twice daily	\$\$\$\$\$
<i>Depot-leuprolide acetate</i>	Intramuscular	3.75 mg monthly	\$\$\$\$\$
<i>Goserelin</i>	Subcutaneous implant	3.6 mg monthly	\$\$\$\$
<i>Elagolix</i>	Oral	150 mg daily or 200 mg twice daily	\$\$\$\$
<b>Androgen</b>			
<i>Danazol</i>	Oral	200 mg twice daily	\$\$\$

<sup>a</sup>Italicized medications are US Food and Drug Administration approved to treat endometriosis.

<sup>b</sup>Relative cost: \$ = < \$50 per month; \$\$ = \$50 to \$150 per month; \$\$\$ = > \$150 and < \$250 per month; \$\$\$\$ = ≥ 250 and < 1,000 per month; \$\$\$\$\$ = > \$1,000 per month.

hormone (FSH), thereby suppressing ovarian synthesis of estrogen, resulting in low circulating levels of estrogen. This removes the estrogen stimulus that exacerbates endometriosis disease activity. High-dose progestins also directly suppress cellular activity in endometriosis implants. High-dose progestins often overcome the relative resistance of endometriosis lesions to progestin suppression of disease activity. Hence, high-dose progestin-only medications have two mechanisms of action: suppression of estrogen synthesis through pituitary suppression of LH and FSH, and direct inhibition of cellular activity in the endometriosis lesions. High-dose progestin-only treatments include:

- oral norethindrone acetate 5 mg daily
- oral medroxyprogesterone acetate (MPA) 20 to 40 mg daily

- subcutaneous, or depot MPA
- levonorgestrel-releasing intrauterine device (LNG-IUD).

In my practice, I frequently use oral norethindrone acetate 5 mg daily to treat pelvic pain caused by endometriosis. In one randomized trial, 90 women with pelvic pain and rectovaginal endometriosis were randomly assigned to treatment with norethindrone acetate 2.5 mg daily or an estrogen-progestin contraceptive. After 12 months of treatment, satisfaction with treatment was reported by 73% and 62% of the women in the norethindrone acetate and estrogen-progestin groups, respectively.<sup>3</sup> The most common adverse effects reported by women taking norethindrone acetate were weight gain (27%) and decreased libido (9%).

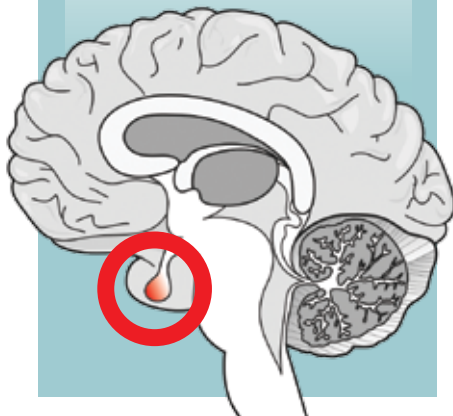
Oral MPA at doses of 30 mg to 100 mg daily has been reported to be

effective for the treatment of pelvic pain caused by endometriosis. MPA treatment can induce atrophy and pseudodecidualization in endometrium and endometriosis implants. In my practice I typically prescribe doses in the range of 20 mg to 40 mg daily. With oral MPA treatment, continued uterine bleeding may occur in up to 30% of women, somewhat limiting its efficacy.<sup>4-7</sup>

Subcutaneous and depot MPA have been reported to be effective in the treatment of pelvic pain caused by endometriosis.<sup>4,8</sup> In some resource-limited countries, depot MPA may be the most available progestin for the treatment of pelvic pain caused by endometriosis.

The LNG-IUD, inserted after surgery for endometriosis, has been reported to result in decreased pelvic pain in studies with a modest number of participants.<sup>9-11</sup>

**GnRH analogues reduce pelvic pain caused by endometriosis by suppressing pituitary secretion of LH and FSH**



**GnRH analogue medications**

Gonadotropin-releasing hormone (GnRH) analogues, including both GnRH agonists (nafarelin, leuprolide, and goserelin) and GnRH antagonists (elagolix) reduce pelvic pain caused by endometriosis by suppressing pituitary secretion of LH and FSH, thereby reducing ovarian synthesis of estradiol. In the absence of estradiol stimulation, cellular activity in endometriosis lesions decreases and pain symptoms improve. In my practice, I frequently use either nafarelin<sup>12</sup> or leuprolide acetate depot plus norethindrone add-back.<sup>13</sup> I generally avoid the use of leuprolide depot monotherapy because in many women it causes severe vasomotor symptoms.

At standard doses, nafarelin therapy generally results in serum estradiol levels in the range of 20 to 30 pg/mL, a “sweet spot” associated with modest vasomotor symptoms and reduced cellular activity in endometriosis implants.<sup>12,14</sup> In many women who become amenorrheic

on nafarelin two sprays daily, the dose can be reduced with maintenance of pain control and ovarian suppression.<sup>15</sup> Leuprolide acetate depot monotherapy results in serum estradiol levels in the range of 5 to 10 pg/mL, causing severe vasomotor symptoms and reduction in cellular activity in endometriosis lesions. To reduce the adverse effects of leuprolide acetate depot monotherapy, I generally initiate concomitant add-back therapy with norethindrone acetate.<sup>13</sup> A little recognized pharmacokinetic observation is that a very small amount of norethindrone acetate, generally less than 1%, is metabolized to ethinyl estradiol.<sup>16</sup>

The oral GnRH antagonist, elagolix, 150 mg daily for up to 24 months or 200 mg twice daily for 6 months, was approved by the US Food and Drug Administration (FDA) in July 2018. It is now available in pharmacies. Elagolix treatment results in significant reduction in pain caused by endometriosis, but only moderately bothersome vasomotor symptoms.<sup>17,18</sup> Elagolix likely will become a widely used medication because of the simplicity of oral administration, efficacy against endometriosis, and acceptable adverse-effect profile. A major disadvantage of the GnRH analogue-class of medications is that they are more expensive than the progestin medications mentioned above. Among the GnRH analogue class of medications, elagolix and goserelin are the least expensive.

**Androgens**

Estrogen stimulates cellular activity in endometriosis lesions. Androgen and high-dose progestins inhibit cellular activity in endometriosis lesions. Danazol, an attenuated androgen and a progestin is effective

in treating pelvic pain caused by endometriosis.<sup>19,20</sup> However, many women decline to use danazol because it is often associated with weight gain. As an androgen, danazol can permanently change a woman’s voice pitch and should not be used by professional singers or speech therapists.

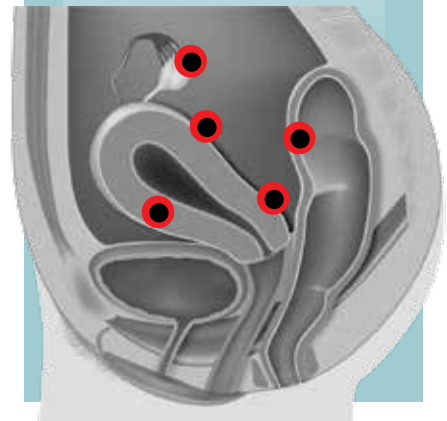
**Aromatase Inhibitors**

Estrogen is a critically important stimulus of cell activity in endometriosis lesions. Aromatase inhibitors, which block the synthesis of estrogen, have been explored in the treatment of endometriosis that has proven to be resistant to other therapies. Although the combination of an aromatase inhibitor plus a high-dose progestin or GnRH analogue may be effective, more data are needed before widely using the aromatase inhibitors in clinical practice.<sup>21</sup>

**Don’t get stuck in a rut**

When treating pelvic pain caused by endometriosis, if the patient’s

**Androgen and high-dose progestins inhibit cellular activity in endometriosis lesions**



**Aromatase inhibitors, which block the synthesis of estrogen, have been explored in the treatment of endometriosis that has proven to be resistant to other therapies**

hormone regimen is not working, prescribe a medication from another class of hormones. In the case presented above, a woman with pelvic pain and surgically proven endometriosis reported inadequate control of her pain symptoms with a continuous estrogen-progestin medication. Her physician prescribed another year of the same estrogen-progestin medication. Instead of renewing the medication, the physician could have offered the patient a hormone medication from another drug class: 1) progestin only, 2) GnRH analogue, or 3) danazol. By using every avail-

able hormonal agent, physicians will improve the treatment of pelvic pain caused by endometriosis. Millions of women in our country have pelvic pain caused by endometriosis. They are counting on us, women's health specialists, to effectively treat their disease. ●



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