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The role of progestins in treating the pain of endometriosis

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Abstract. Progestins, synthetic progestational agents, have been used in the management of symptomatic endometriosis both as primary therapy and as an adjunct to surgical resection. A variety of oral agents have been employed in this regard with investigators demonstrating differing degrees of benefit. Unfortunately, due to the lack of large-scale, appropriately controlled, randomized trials, or dose-ranging studies, no single agent can be demonstrated to be truly efficacious. The lack of a standardized instrument to evaluate painful symptoms makes comparative analysis more difficult. Injectable administration of long-acting depot medroxyprogesterone acetate preparations intramuscularly or subcutaneously has been investigated in three randomized trials. The lower dose subcutaneous injection holds promise with an apparent reduction in side effects. Issues of reversible bone mineral density loss, breakthrough bleeding, and return of menses have not been completely resolved. Selective progesterone receptor modulators represent an intriguing alternative. These orally administered agents have been shown in preliminary investigations to be not only efficacious in reducing symptoms but also associated with minimal side effects. Further investigation of these agents is clearly required.

Progestins represent a class of compounds that exert progesterone-like effects on appropriate target tissues. A variety of progestational agents administered through oral, injectable, and intrauterine means have been employed with varying degrees of success in the management of symptomatic endometriosis. Unfortunately, there exists a relative paucity of well-designed prospective, randomized trials on which definitive management decisions can be based.

Mechanisms of action

The theoretic basis for hormonal therapy of endometriosis has been the long-held assumption that endometriotic implants and the endometrium should respond in a similar fashion to sex steroid hormone manipulation. Theoretically, progestins should induce a decidual reaction, result in endometrial atrophy, and impact estrogen receptors.[1] These agents have been shown to act on eutopic endometrium by inhibiting estrogen-induced mitosis and induction of a variety of endometrial enzymes that may oppose the stimulatory effect of estrogens.[1] Progestins administered in pharmacologic doses have been shown to inhibit directly endometrial stromal cell proliferation in vitro.[2] More recently, Bruner et al demonstrated that progesterone appears to affect the expression of endometrial matrix metalloproteinases, which may play a significant role in the establishment of endometriotic implants.[3] In addition, progestins have been shown to have an inhibitory effect on angiogenesis by suppressing plasminogen activator activity.[4]

However, there is conflicting evidence as to whether eutopic and ectopic endometrium truly respond similarly to progestational agents. In a large series evaluating 443 im-

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Table 1 Oral progestins investigated as monotherapy for symptomatic endometriosis

Cyproterone acetate
Dienogest
Dydrogesterone
Gestrinone
Lynestrenol
Medroxyprogesterone acetate
Megestrol acetate
Norethindrone/norethisterone acetate

plants in 196 patients, Metzger and colleagues demonstrated that histologic concordance between endometrium and endometriotic implants could be demonstrated in only 13% of samples.[5] Others have shown that the concentration of steroid receptors was significantly lower in endometriotic implants than in eutopic endometrium and that cyclic patterns could not be demonstrated in hormone-dependent secretory products of such lesions in culture.[6–9] Osteen et al have reported that endometrial tissue from women with endometriosis demonstrated a partial loss of sensitivity to progesterone in comparison with tissue from women without the disease.[10] The authors proposed that this phenomenon could result in the altered expression of matrix metalloproteinases associated with this disease.

Oral progestins

A variety of oral progestins have been employed in the medical management of endometriosis (Table 1). Some of these agents have been administered as part of combination oral contraceptive regimens and will be reviewed elsewhere. No studies have evaluated micronized progesterone for the treatment of endometriosis. It is important to understand that the potency and degree of interaction of progestins with progesterone receptors vary widely. As a result, the doses needed to induce appropriate secretory change in normal endometrium also vary[11] (Table 2). There are no dose-ranging studies that evaluate the minimum dose necessary to induce regression of endometriotic implants for any of these agents.

The majority of trials employing oral progestins are observational in nature and include relatively small samples.[12] The duration of therapy and follow-up is widely disparate. Inclusion criteria typically consist of patients with pelvic pain but varying stages of endometriosis. The lack of any uniform instrument for the evaluation of pain makes comparison of outcomes among trials challenging at best.

Medroxyprogesterone acetate (MPA) has been employed in several observational trials. After completion of a 3-month trial employing a 30-mg oral daily dose, Moghissi and Boyce reported an absence of symptoms in all 24 patients.[13] Roland et al reported similar findings in a 3-month trial in which a lower 10-mg daily dose was employed.[14] Luciano and colleagues reported upon the only laparoscopically controlled trial involving oral MPA in which 50 mg daily was administered for 6 months to 28 women with pelvic pain.[15] Dysmenorrhea, deep dyspareunia, and nonmenstrual pain persisted in 12%, 17%, and 12% of patients, respectively. Disease regression was noted, but no long-term follow-up was provided. Telimaa et al evaluated the effects of MPA 100 mg daily in a 6-month prospective, randomized trial after surgical excision of endometriosis. A greater degree of postoperative pain relief and reduction of disease at follow-up laparoscopy was noted in comparison with placebo, a result that was similar to that achieved with postoperative danazol 600 mg daily.[16]

Although the minimal effective dose of oral MPA for the treatment of endometriosis has not been established, it is interesting to note that when MPA 10 to 20 mg daily was administered as an "add-back" to a gonadotropin-releasing hormone (GnRH) agonist in a 6-month trial, the extent of symptom relief and laparoscopic evidence of disease improvement were dramatically less than that achieved by historic controls given the agonist alone.[17]

The efficacy of the synthetic progestin megestrol acetate was evaluated in a single retrospective trial.[18] Twenty-nine patients with symptomatic endometriosis were given a 40-mg daily dose. Unfortunately, the duration of therapy was not standardized. Twenty-one patients continued therapy for at least 2 months, and among the 18 who reported symptom improvement, the mean duration of therapy was 7.7 months. No long-term follow-up was provided.

In a prospective, randomized, placebo-controlled, double-blind trial, Overton and colleagues assessed the effect of the progestin dydrogesterone, an agent not available in the United States, administered during the luteal phase in two daily doses (40 and 60 mg) for 6 months.[19] Unfortunately, of the 62 patients evaluated, only 12 were initially seen for pain, whereas the other 50 had a primary diagnosis of

Table 2 Oral progestins: Relative potency in inducing endometrial secretory change

	Progesterone	MPA	Levonorgestrel	Norethindrone
Relative potency	0.002	0.09	8	1
Dose needed to produce endometrial secretory change (mg/day)	200	5	0.075	0.35

MPA = medroxyprogesterone acetate.
Modified from reference 11.