

This supplement is based on a symposium held at the American Society for Reproductive Medicine Annual Meeting in Orlando, Florida, on Monday, October 17, 2011.

It was supported by an independent educational grant from Abbott Laboratories.

To access the free ASRM eLearn™ course, "Long-term management of symptoms of endometriosis," and obtain 1.0 AMA PRA Category 1 Credit™, go to: www.asrm.org/eLearn.

Long-term management of symptoms of endometriosis

SUPPLEMENT FACULTY



Robert S. Schenken, MD (Chair)
Professor and Chairman
Department of Obstetrics and Gynecology
Humana Foundation Distinguished Chair
in Obstetrics and Gynecology
The University of Texas Health Science
Center at San Antonio
San Antonio, Texas



Serdar E. Bulun, MD
Professor and Chief
Division of Obstetrics and Gynecology—
Reproductive Biology Research
George H. Gardner, MD, Professor
of Clinical Gynecology
Northwestern University
Feinberg School of Medicine
Chicago, Illinois



John F. Steege, MD
Professor
Department of Obstetrics and Gynecology
Director, Division of Advanced
Laparoscopy and Pelvic Pain
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

DISCLOSURES

Robert S. Schenken, MD, reports nothing to disclose.

Serdar E. Bulun, MD, reports that he has served as a consultant to MSD, Bayer, Repros, Meditrina, and Orphagen.

John F. Steege, MD, reports nothing to disclose.

There may be discussion of off-label or otherwise non-FDA-approved uses of products and/or devices in this supplement.

Endometriosis and pain: Cause or bystander?

Presented by John F. Steege, MD

The Practice Committee of the American Society for Reproductive Medicine (ASRM) states, "Endometriosis should be viewed as a chronic disease that requires a life-long pain management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures."¹ The process of achieving this management goal begins with an up-to-date perspective on endometriosis-related pain and an accurate appraisal of an individual's condition.

Rethinking the assessment of endometriosis

The correlation between the amount of endometriosis and degree of pain is low. Not all women with endometriosis have pain. And many women who have undergone laparoscopic surgery for pain relief will experience recurrent pain even though the amount of disease is much reduced. Very likely, endometriosis differs biologically among women, and evidence increasingly suggests that adjacent organ systems share neural networks. The challenge for clinicians is to think beyond the role of endometrial implants and take into account the multiple factors that can influence pain perception.

Innervation increases. The neural network is far more complex and changeable than once thought, altering in response to pain and thereby contributing to symptom chronicity. Various studies have shown that the number of nerve fibers is increased in the endometrium and myometrium of women with endometriosis, in the lower neuron segment of women with pelvic pain from multiple causes, and in the vulvar vestibule in patients with vestibulitis. Irritable bowel syndrome, interstitial cystitis, levator spasm, and vulvar vestibulitis are all more prevalent in women with endometriosis.

In women undergoing trachelectomy or hysterectomy for pain

relief, the unmyelinated C-fiber nerve density has been twice as high compared with pain-free controls.² One study has also shown that increased nerve fiber density in the endometrium and the myometrium can be diminished with oral contraceptives.³

Many factors affect pain threshold and tolerance. Menstruation lowers pain threshold and tolerance. In menopause, women taking estrogen are more sensitive to pain than those who are not taking estrogen. Among women having laparoscopic treatment of endometriosis, those exhibiting greater sensitivity to somatic pain (pressure on the thumb) experienced less pain relief after surgery (S. As-Sanie, MD, MPH, University of Michigan, unpublished data). Catastrophization is a mindset in which one looks at life's glass as half empty rather than half full. Such patients in pain see their world as collapsing and themselves as helpless. Higher scores on catastrophization testing have been associated with poorer outcomes after laparoscopic treatment of endometriosis. A study at the University of North Carolina, for example, found that in a cohort of 74 patients followed for a year after surgery, the single most important component affecting outcome variance was catastrophization.

Dampening of pain perception occurs with suppression of the hypothalamic-pituitary-ovarian (HPO) axis, as happens with gonadotropin-releasing hormone (GnRH) analogs, regardless of whether endometriosis is truly diminishing.

Implications for practice

The standard bi-manual examination confuses pain signals from the pelvic floor, abdominal wall, bladder, and other viscera. A pain-oriented assessment is mandatory, relying on a rectal-vaginal exam with the index finger, carefully mapping areas that are tender, then considering the size, shape, and mobility of structures.

GnRH trials have little bearing on diagnosis. Following a presumptive diagnosis of endometriosis based on findings in a patient's history and physical examination, many practitioners give a therapeutic trial of a GnRH agonist. If the patient's pelvic pain remits, confirmation of the diagnosis is assumed and

treatment continues, even though this assumption is unwarranted. In a randomized controlled trial, women with and without endometriosis who had pelvic pain experienced equivalent pain relief from depot leuprolide (82% and 73%, respectively).⁴ In 2006, the Practice Committee of the ASRM recommended that diagnostic laparoscopy confirming endometriosis precede medical treatment, to avoid unnecessary short- and long-term exposure to the adverse effects of GnRH.⁵

Earlier surgical intervention recommended. If endometriosis is discovered at the time of diagnostic laparoscopy, immediate surgical intervention is indicated.^{6,7} Administering GnRH may be useful as postoperative adjunctive therapy, but it is not a substitute for surgery.

Repeat laparoscopies are generally unhelpful. Repeating laparoscopic procedures is common, despite the fact that the number of implants has continually decreased. The more likely explanations for initial pain relief that dwindles with time may be a placebo effect from the procedure or a lingering effect of anesthesia. With recurrence or continuation of pain following laparoscopy, consider alternative diagnoses before resorting to organ removal.

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril.* 2008;90(5 suppl):S260-S269.
2. Atwal G, du Plessis D, Armstrong G, et al. Uterine innervation after hysterectomy for chronic pelvic pain with, and without, endometriosis. *Am J Obstet Gynecol.* 2005;193:1650-1655.
3. Tokushige N, al-Jefout M, Salih H, Fraser IS. Endometrial nerve fibres in endometriosis. *Iran J Repro Med.* 2007;5:81-88.
4. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Pelvic Pain Study Group. Obstet Gynecol.* 1999;93:51-58.
5. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril.* 2006;86(suppl 1):S18-S27.
6. Sutton CJ, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil Steril.* 1994;62:696-700.
7. Abbott J, Hawe J, Hunter D, et al. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril.* 2004;82:878-874.

Surgery vs medical therapy for endometriosis: Risks and benefits

Presented by Robert S. Schenken, MD

Endometriosis is managed with surgical procedures, medical therapies, and various combinations of both.

Surgical options for endometriosis

When resecting, fulgurating, or ablating endometriotic lesions, removing adhesions, and repairing tubal damage, most procedures are done laparoscopically. However, severe or advanced endometriosis, especially with bowel involvement, may require laparotomy. Two controversial approaches are laparoscopic

uterosacral nerve ablation (LUNA) and presacral neurectomies.

Clinical data on symptom relief

Laparoscopic excision has been shown to provide significantly greater pain relief than placebo laparoscopy (80% vs 32%).¹ In comparing laser laparoscopy and LUNA with exploratory-only laparoscopy, a randomized controlled trial showed that pain relief at 6 months was dramatic in the treatment group and only modest in the comparison group. The difference was even greater at 12 months.² In another trial, however, women who had pelvic

pain with or without evidence of endometriosis were randomized to receive laparoscopic surgery with or without LUNA and were evaluated at 3 and 12 months. Adding LUNA to laparoscopic surgery did not significantly reduce pain, dysmenorrhea, dyspareunia, or dyschezia.³ Various meta-analyses of LUNA have confirmed that the procedure performed in conjunction with laparoscopic treatment does not improve pain relief.^{2,4,5}

A randomized controlled trial comparing presacral neurectomy with laparoscopic surgery showed that women in both groups had significantly reduced frequency and severity of pelvic pain, dysmenorrhea, and dyspareunia at 6 and 12 months.⁶ At 12 months, severity of symptoms was less in the presacral neurectomy group compared with the laparoscopy group.

Type of intervention and recurrence rates

No evidence suggests that any surgical approach (ie, ablation vs resection) is superior to another in reducing recurrence rates. In one study, the cumulative 5-year recurrence rate was 19%.⁷ Other studies suggest the rate may be much higher. Conservative surgery is preferred, especially for women interested in bearing children. But with advanced stages of disease, hysterectomy may be necessary.

One retrospective study reviewed reoperation rates for up to 7 years following excision or hysterectomy with and without oophorectomy. Excision yielded good short-term results, but long-term results were better with hysterectomy, particularly when the ovaries were removed.⁸ In another study, hysterectomy with ovarian tissue preservation also resulted in a slightly higher incidence of recurrent pain and reoperation. There appeared to be no correlation with the use of estrogen replacement therapy (ERT) after surgery.⁹

Timing of ERT following surgery

Some clinicians advocate delaying ERT until several weeks or months following hysterectomy and oophorectomy, to allow further suppression of endometriosis. The literature, however, shows no benefit in this practice. In one study, 7% of women who started ERT immediately following surgery had recurrent pain, compared with 20% for whom ERT was delayed more than 6 weeks.¹⁰

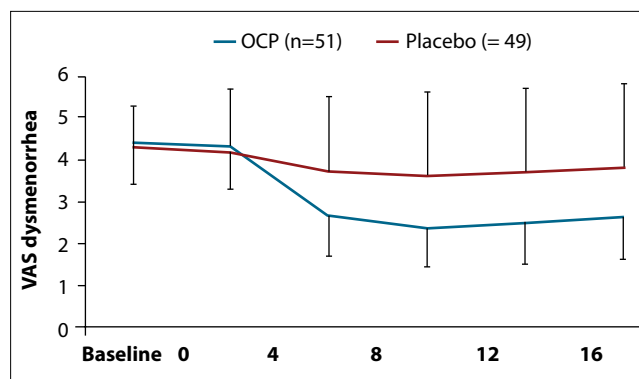
Medical management options

Oral contraceptives (OCs). Women with endometriosis and dysmenorrhea experience greater pain relief with OCs than with placebo (FIGURE).¹¹ In a trial comparing continuous OCs and leuprolide plus norethindrone for 48 weeks, both treatments significantly decreased scores on pain inventories, the Beck Depression Inventory, and the Index of Sexual Satisfaction.¹² OCs significantly reduce dysmenorrhea and pelvic pain associated with endometriosis, but they are less effective than the gonadotropin-releasing hormone (GnRH) analog, goserelin, in reducing dyspareunia.¹³ Patients who don't respond well to cyclic oral contraceptives may do better with continuous OCs.

GnRH analogs have reduced dysmenorrhea and pelvic pain, and to a lesser extent dyspareunia.¹⁴ However, recurrence rates

FIGURE

Cyclic OCs vs placebo for endometriosis and dysmenorrhea



Dysmenorrhea associated with endometriosis decreased significantly in patients randomly selected to receive a low-dose oral contraceptive (OCs) compared with those who received placebo.

VAS, visual analog scale.

Adapted from Harada T, et al,¹¹ with permission.

as high as 70% have been seen following treatment cessation.¹⁵ Add-back hormonal therapy is commonly used, either at the outset of GnRH treatment or after vasomotor symptoms occur. It does not decrease the efficacy of GnRH analogs and it helps diminish vasomotor symptoms and bone loss in the short term. Even several years of add-back therapy, however, will not prevent a significant loss of bone mineral density.¹⁶

Progestins. A number of studies confirm the efficacy of progestin in reducing pelvic pain. And a significantly high percentage of patients remain pain free after progestin therapy. The levonorgestrel-releasing intrauterine system (LNG IUS) has shown efficacy similar to that of depot leuprolide for endometriosis-associated pelvic pain.¹⁷

Danazol. Many studies demonstrate the efficacy of danazol.^{18,19} New data should soon be available regarding vaginal danazol, which may relieve symptoms of endometriosis while decreasing androgenic effects.

How available therapies compare overall. A Cochrane database review showed no clear evidence that any medical therapy is superior to another for endometriosis and pelvic pain, with the exception that GnRH analogs may be more effective against dyspareunia.²⁰

Combining surgical and medical treatments

A single randomized study has evaluated preoperative medical therapy with a GnRH analog for endometrioma.²¹ It showed no advantages in reducing the time for total operation, cyst excision, capsule stripping, or coagulation, or in lessening disease recurrence rates.

Postsurgical use of continuous OCs reduces recurrent dysmenorrhea associated with endometriosis up to 24 months.²²

In a randomized, controlled double-blind study, nafarelin

reduced pain scores at 6 months to a greater degree than placebo. Differences between the groups disappeared at 12 months of follow-up.²³ However, the nafarelin group had a far lower percentage of patients requiring alternative pain treatment.

The LNG IUS also significantly decreases dysmenorrhea postoperatively compared with placebo.²⁴ But it has little effect on dyspareunia and pelvic pain.

Another randomized trial looked at the LNG IUS vs goserelin following laparoscopic surgery for severe endometriosis.²⁵ As assessed by the visual analog scale, pain decreased in both groups significantly at 1 month. It increased slowly, but was still lower at 12 months of follow-up.

REFERENCES

1. Abbott J, Hawe J, Hunter D, et al. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril.* 2004;82:878-884.
2. Sutton CJ, Pooley AS, Ewen SP, et al. Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. *Fertil Steril.* 1997;68:1070-1074.
3. Johnson NP, Farquhar CM, Crossley S, et al. A double-blind randomised controlled trial of laparoscopic uterine nerve ablation for women with chronic pelvic pain. *BJOG.* 2004;111:950-959.
4. Yen YK, Liu WM, Yuan CC, et al. Addition of laparoscopic uterine nerve ablation to laparoscopic bipolar coagulation of uterine vessels for women with uterine myomas and dysmenorrhea. *J Am Assoc Gynecol Laparosc.* 2001;8:573-578.
5. Vercellini P, Aimi G, Busacca M, et al. Laparoscopic uterosacral ligament resection for dysmenorrhea associated with endometriosis: results of a randomized, controlled trial. *Fertil Steril.* 2003;80:310-319.
6. Zullo F, Palomba S, Zupi E, et al. Effectiveness of presacral neurectomy in women with severe dysmenorrhea caused by endometriosis who were treated with laparoscopic conservative surgery: a 1-year prospective randomized double-blind controlled trial. *Am J Obstet Gynecol.* 2003;189:5-10.
7. Redwine DB. Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis reoperation and persistent or recurrent disease. *Fertil Steril.* 1991;56:628-634.
8. Shakiba K, Bena JF, McGill KM, et al. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstet Gynecol.* 2008;111:1285-1292.
9. Namnoum AB, Hickman TM, Goodman SB, et al. Incidence of symptom recurrence after hysterectomy for endometriosis. *Fertil Steril.* 1995;64:898-902.
10. Hickman TN, Namnoum AB, Hinton EL, et al. Timing of estrogen replacement therapy following hysterectomy with oophorectomy for endometriosis. *Obstet Gynecol.* 1998;91:673-677.
11. Harada T, Momoeda M, Taketani Y, et al. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. *Fertil Steril.* 2008;90:1583-1588.
12. Guzick DS, Huang LS, Broadman BA, et al. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. *Fertil Steril.* 2011;95:1568-1573.
13. Vercellini P, Trespidi L, Colombo A, et al. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. *Fertil Steril.* 1993;60:75-79.
14. Dlugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. *Lupron Study Group. Fertil Steril.* 1990;54:419-427.
15. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. *Fertil Steril.* 1993;59:511-515.
16. Pierce SJ, Gasvani MR, Farquharson RG. Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. *Fertil Steril.* 2000;74:964-968.
17. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod.* 2005;20:1993-1998.
18. Buttram VC Jr, Reiter RC, Ward S. Treatment of endometriosis with danazol: report of a 6-year prospective study. *Fertil Steril.* 1985;43:353-360.
19. Barbieri RL, Evans S, Kistner RW. Danazol in the treatment of endometriosis: analysis of 100 cases with a 4-year follow-up. *Fertil Steril.* 1982;37:737-746.
20. Brown J, Pan A, Hart RJ. Gonadotropin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database System Rev.* 2010:CD008475.
21. Muzii L, Marana R, Caruana P, et al. The impact of preoperative gonadotropin-releasing hormone agonist treatment on laparoscopic excision of ovarian endometriotic cysts. *Fertil Steril.* 1996;65:1235-1237.
22. Vercellini P, Frontino G, De Giorgi O, et al. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. *Fertil Steril.* 2003;80:560-563.
23. Hornstein MD, Hemmings R, Yuzpe AA, et al. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. *Fertil Steril.* 1997;68:860-864.
24. Vercellini P, Frontino G, De Giorgi O, et al. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. *Fertil Steril.* 2003;80:305-309.
25. Bayoglu Tekin Y, Dilbaz B, Altinbas K, et al. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. *Fertil Steril.* 2011;95:492-496.

Treatment options for refractory endometriosis

Presented by Serdar E. Bulun, MD

Among patients who respond to treatment for endometriosis, most will experience recurrent pain within 2 to 5 years after discontinuance. Repeat treatment works for perhaps 50% of patients, although they, too, will experience recurrent pain within 6 months to 2 years. Refractory endometriosis is managed most effectively using a judicious combination of medical and surgical approaches.

Conventional therapies

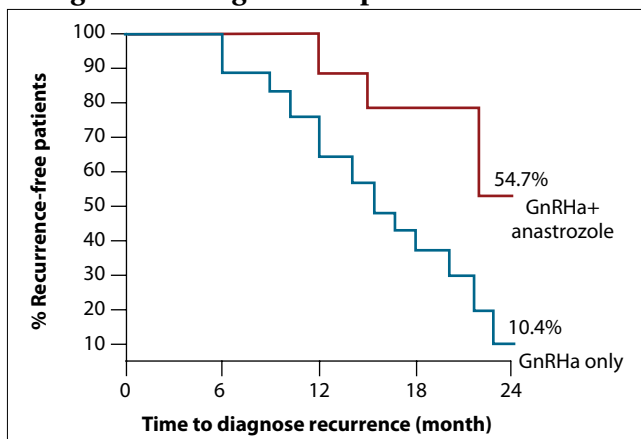
Laparoscopy. An advantage of laparoscopic resection and ablation is the opportunity to assess the extent of disease. Prudent use of en bloc stripping of cul-de-sac peritoneum may reveal

microscopic disease. Data suggest that resection is superior to vaporization or fulguration. Patients with dyspareunia may be candidates for rectovaginal dissection. The expertise of the surgeon makes a tremendous difference in outcomes.

Continuous oral contraceptives (OCs) are usually the first line of treatment. Noncompliance can become an issue if patients have unrealistic expectations for decreased spotting and pain. So, patient education is important. If patients keep a daily pain diary, they may see a difference in a few months, which will encourage compliance.

Progestins. Depot medroxyprogesterone acetate injections and norethindrone acetate in oral formulation have similar efficacy to OCs. Side effects include mood swings or weight gain.

FIGURE

Kaplan-Meier curves for patients (n=80) treated with goserelin vs goserelin plus anastrozole

Women with persistent endometriosis following conservative surgery have experienced significant pain reduction with experimental treatment combining a GnRH agonist and an aromatase inhibitor, compared with women given a GnRH agonist only.

GnRH_a, gonadotropin-releasing hormone agonist.

Adapted from Soysal S, et al,⁴ with permission.

Gonadotropin-releasing hormone (GnRH) agonists. The efficacy of GnRH agonists is similar to that of other hormonal treatments. They are definitely more expensive. Risks include bone loss, depression, and confusion. GnRH antagonists being developed may cause less suppression of the hypothalamic-pituitary-adrenal axis and fewer side effects.

Danazol could be an effective treatment choice. This drug acts through pituitary suppression and through androgen receptors in lesions or the uterus. In addition, it has been shown to be an aromatase inhibitor. Its adverse effects, however, including masculinization, are unacceptable to many women.

Treatments ineffective for refractory endometriosis are endometrial ablation, hysterectomy without oophorectomy, and laparoscopic uterosacral nerve ablation (LUNA). The usefulness of progestin intrauterine devices (IUDs) or presacral neurectomy is unclear.

Experimental treatments

Aromatase inhibitors can provide relief for 90% of women whose pain has been refractory to prior treatment. But pain returns immediately after cessation of therapy. Letrozole 2.5 mg/d or anastrozole 1 mg/d have been used as monotherapy in postmenopausal women, who are without functioning ovaries.¹ In premenopausal women, aromatase inhibitors may have an additional effect on the brain, giving rise to follicular genesis

and cyst formation in the ovaries.² We thus combine an aromatase inhibitor with a pituitary suppressant, such as an OC or a progestin or a GnRH agonist.

The first open-label trial of an aromatase inhibitor in premenopausal women who had not found relief with other treatments was with letrozole given with norethindrone acetate.³ Pain relief was significant, and laparoscopically detectable lesions decreased dramatically. In the first prospective randomized trial of aromatase inhibitors for endometriosis persisting after conservative surgery, the 2 groups received either a GnRH agonist alone or the GnRH agonist plus anastrozole for 6 months (FIGURE).⁴ Over the following 2 years, pain recurrence was significantly less among the combined-therapy group. Early bone loss was more pronounced among patients treated with combination therapy, but bone loss between the groups was roughly equivalent by the end of treatment.

In a recent retrospective study by our group, 16 patients unresponsive to prior treatment received letrozole and a combination OC or norethindrone acetate for 6 months.⁵ The median baseline pain score was 7 on a scale of 0 to 10. By the end of treatment, the median pain score was 1.5. Nine patients were evaluated after discontinuation of therapy, and their pain scores returned to pre-treatment levels. No correlation was detected between length of treatment and overall improvement in pain score.

Progesterone-receptor modulators, such as RU486, have also shown promise in reducing pain associated with endometriosis.

Summing up

Key points regarding treating refractory endometriosis include:

- The most effective management includes a judicious combination of medical and surgical approaches.
- Hysterectomy-oophorectomy is a radical, but not definitive, option.
- Long-term continuous OC therapy, combined with patient education, is a very good option.
- From a risk-benefit perspective, aromatase inhibitors and selective progesterone-receptor modulators are promising new treatments.

REFERENCES

1. Takayama K, Zeitoun K, Gunby RT, et al. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. *Fertil Steril.* 1998;69:709-713.
2. Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? *Fertil Steril.* 2006;85:1307-1318.
3. Ailawadi RK, Jobanputra S, Kataria M, et al. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. *Fertil Steril.* 2004;81:290-296.
4. Soysal S, Soysal ME, Ozer S, et al. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. *Hum Reprod.* 2004;19:160-167.
5. Abushahin F, Goldman KN, Barbieri E, et al. Aromatase inhibition for refractory endometriosis-related chronic pelvic pain. *Fertil Steril.* 2011;96:939-942.