

a report by

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Endometriosis—Medical versus Surgical Management

The vast majority of women who see a physician because of endometriosis-related symptoms—dysmenorrhea, pelvic pain, and/or infertility—are seen by a gynecologist. For several reasons, these women usually end up on the operating table undergoing laparoscopy or laparotomy: at present this is the only way to diagnose the disease; these women frequently have lesions that require surgical resection; and gynecologists, especially in the US, are essentially pelvic surgeons. Thus, surgical management is typically the initial approach to the management of endometriosis, which, once diagnosed, often requires recurring surgical therapy. Some gynecologists are even of the opinion that surgical resection is the only effective therapy for this disease. Nevertheless, numerous studies have shown that medical treatment can also be effective and is less likely to compromise ovarian function and future fertility. There are several medical strategies that can be pursued to control endometriosis and its symptoms.

It is well recognized that endometriotic tissue responds to ovarian hormones with proliferation and undergoes cyclic changes similar to those of the uterine endometrium. Cyclic bleeding and endometrial shedding into the peritoneal cavity result in inflammatory changes, development of new lesions, and formation of endometriomas; together, these events are responsible for the symptoms and progression of the disease. Suppression of ovarian hormones or modification of the endocrine milieu to induce amenorrhea is the basis for most medical treatment methods in endometriosis. Estrogen/progestogen components in birth control pills suppress ovarian folliculogenesis and steroid secretion, and can be used continuously rather than cyclically to induce amenorrhea of so-called pseudopregnancy for the management of endometriosis. Progestogens alone have a similar though less consistent effect. However, the suppressive effect of estrogens/progestogens on ovarian steroids needs to be considered in the context of their direct stimulatory effect on the endometriotic tissue. In most women with endometriosis, dysmenorrhea is the major complaint. In such cases, physicians have been using combination-type oral contraceptives (COCs) to induce amenorrhea for three to four months and to decrease the number and length of annual bleeding episodes.^{1,2} Recently, several COCs have been approved by the US Food and Drug Administration (FDA) for extended-cycle contraception and can be used (off-label) in women with endometriosis. While common, this approach is often sub-optimal in providing symptom relief.

Danazol was the first compound that could effectively suppress ovarian function without a direct effect on the endometrium. However, its androgenic side effects made it less attractive to patients and physicians. With transvaginal administration, danazol is free of systemic side effects, yet can control symptoms of the disease. At least two pharmaceutical companies have danazol vaginal delivery systems in clinical trials.^{3,4} Medications

delivered transvaginally or from intrauterine delivery systems are believed to concentrate in the pelvic circulation, which may increase their local effects on endometriosis and possibly decrease undesirable systemic side effects. Several compounds are currently being investigated for this purpose. A levonorgestrel-containing intrauterine device (IUD), currently on the market, has been shown to decrease the symptoms and lesions of endometriosis.⁵ Similarly, a danazol-releasing IUD has also been found to be effective, albeit in uncontrolled, open-label studies.⁶ Another method to decrease estrogen biosynthesis involves systemic administration of aromatase inhibitors. These suppress both ovarian and peripheral estrogen production. Two compounds have been found to be clinically effective, but as yet have not been approved by the FDA for the management of endometriosis.⁷ These compounds may be especially advantageous in rare cases of rapidly progressing autonomous endometriosis in post-menopausal women or after bilateral oophorectomy, when ovarian function is no longer present.

One of the interesting properties of danazol is its effect on the immune system. *In vitro* and *in vivo* studies have shown that danazol has a suppressive effect on both humoral and cell-mediated immunity, properties that make it useful in several immunological diseases. Abnormal activation of the immune system—evidenced by increased production of pro-inflammatory cytokines, increased local inflammatory reaction, and the presence in the circulation of abnormal autoantibodies—has been shown in endometriosis.⁸ Danazol lowers cytokine production by monocytes/macrophages both *in vitro* and *in vivo*, decreases inflammatory reactions, and suppresses abnormal autoantibodies. It also increases apoptosis of endometriotic cells. These properties of the drug are considered to play a role in its beneficial effect on the disease.⁹ With that in mind, several new investigational agents have been developed that are capable of suppressing inflammatory cytokines, stimulating endometrial cell apoptosis, suppressing neoangiogenesis, or decreasing the inflammatory reaction characteristic of endometriosis. These compounds have been found effective in experimental endometriosis in laboratory rodents and monkeys, but convincing clinical studies are yet to come.

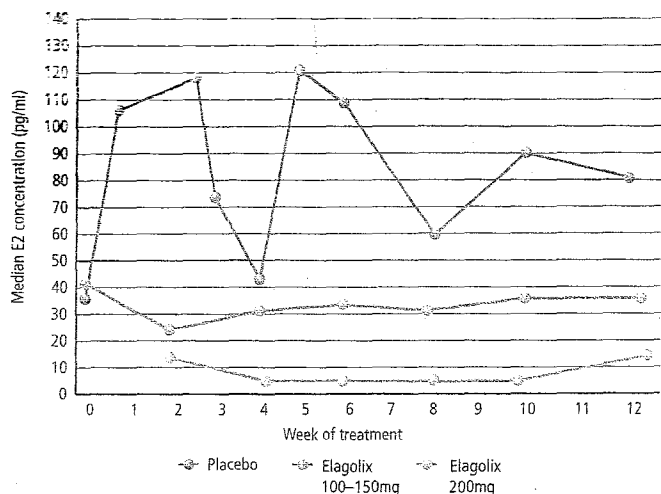


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Menstrual and Uterine Disorders

Figure 1: Serum Estradiol Levels During Treatment with Elagolix or Placebo



Modified from O'Brien et al., 2008.¹⁹

Table 1: Adverse Events During Treatment with Elagolix 50--200mg/day or Placebo

Adverse Event	Elagolix (n=136) n (%)	Placebo (n=68) n (%)
Hot flashes	67 (49.3)	29 (42.6)
Headache	44 (32.4)	15 (22.1)
Nausea	23 (16.9)	5 (7.4)
Dizziness	15 (11.0)	2 (2.9)
Nasopharyngitis	15 (11.0)	6 (8.8)
Back pain	11 (8.1)	3 (4.4)
Urinary tract infection	10 (7.4)	3 (4.4)
Vomiting	9 (6.6)	3 (4.4)
Pharyngolaryngeal pain	8 (5.9)	3 (4.4)
Upper respiratory tract infection	8 (5.9)	5 (7.4)

Adapted from O'Brien et al., 2008.¹⁹

Gonadotropin-releasing Hormone Agonists

Several gonadotropin-releasing hormone (GnRH) agonists—introduced about the same time in the early 1980s—profoundly suppress ovarian function and induce endometrial atrophy and amenorrhea. After the initial stimulatory (flare-up) effect on the pituitary, continuous delivery of agonists results in gradual desensitization of gonadotropic cells and reduction in the number of GnRH receptors on the cell membrane (downregulation). This is followed by a decrease in secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and suppression of ovarian function. Agonists are currently available only for parenteral use as depot intramuscular (IM) injections, subcutaneous depot implants, subcutaneous injections, or intranasal sprays. The daily release dose of agonist is adjusted in such a way that complete pituitary suppression is induced. FSH and LH levels are undetectable and estradiol remains <20pg/ml. This profound ovarian suppression results in amenorrhea, symptomatic improvement, and regression of endometriotic lesions. However, at the same time the majority of women develop menopausal symptoms, hypoestrogenic changes, and bone loss. Thus, the pelvic pain symptoms of endometriosis are traded for menopausal symptoms and depressive mood symptoms, which many women find unacceptable.¹⁰ In order to reduce the severity of menopausal

symptoms and to prevent bone loss, various estrogen/progestogen add-back regimens have been recommended.^{11,12} Complete ovarian suppression with the agonist along with the add-back of estrogen and/or progestogen can effectively control endometriosis and its symptoms and blunt hypoestrogenic side effects. It has been theorized by Barbieri¹³ that estradiol levels between 30 and 50pg/ml are effective in inducing endometrial atrophy and that initiation of bone loss requires much lower levels. Thus, a therapeutic window of estradiol levels adequate for suppression of endometriosis without untoward side effects may be attainable. From the practical standpoint, however, this means that the patient needs to take two medications: one to completely suppress ovarian function and the other to bring ovarian hormones to a desirable range. Undesirable side effects of agonists combined with frequent exacerbation of the disease and its symptoms during the initial flare-up effect, as well as inconsistent suppressive effect in some patients with conditions such as polycystic ovaries (PCO), mean agonists are not a suitable treatment in many women.¹¹

Peptide Gonadotropin-releasing Hormone Antagonists

Peptide GnRH antagonists structurally resemble native GnRH and GnRH agonists. Unlike agonists, antagonists competitively block GnRH receptors and produce an immediate suppressive effect on the pituitary. After administration of GnRH antagonists, serum levels of FSH and LH decrease within hours. However, the pituitary maintains its responsiveness to the GnRH stimulus after pre-treatment with an antagonist. Early GnRH antagonists had troublesome side effects. They stimulated histamine release from mast cells, resulting in injection-site reactions and, in some instances, allergic/anaphylactic systemic reactions. Second-generation peptide GnRH antagonists are relatively free of this effect and are currently approved for indications other than endometriosis. The difference in pharmacological mechanisms between agonists and antagonists offers theoretical advantages in the management of endometriosis. The immediate suppressive effect should prevent the initial flare-up seen with agonists and should result in more immediate symptomatic improvement and perhaps a shorter course of treatment. After cessation of treatment with antagonists, the return of normal menstrual function and fertility should also be more rapid.

In 1999, as part of a multicenter trial, we investigated the safety and efficacy of the peptide antagonist abarelix depot against lupron depot in women with endometriosis and pelvic pain. The results of this randomized phase II clinical trial were quite promising:¹⁵ pituitary-ovarian suppression was immediate and, unlike lupron, abarelix did not induce hormonal flare-up or exacerbation of endometriosis symptoms. However, because of a complete suppression of ovarian function, the side effects of abarelix were comparable to those of lupron. Injection-site reactions secondary to histamine release were infrequent. Abarelix has not been approved for clinical use and is not on the market. Cetrorelix, another peptide GnRH antagonist, is approved for suppression of LH surge in women undergoing *in vitro* fertilization (IVF). Used in clinical trials in women with endometriosis, cetrorelix was found to be effective in controlling pelvic pain and in inducing regression of endometriosis on post-treatment laparoscopy.¹⁶ The effect was immediate, without flare-up, and the course of treatment was shorter than that with GnRH agonists.

Non-peptide Gonadotropin-releasing Hormone Antagonist—Elagolix (NB1-56418)

Peptide GnRH analogs, both agonists and antagonists, require parenteral administration, often in the form of long-acting depots of these drugs; this

Table 2: Effect of Elagolix on Pelvic Pain Scores

Assessment	Mean Baseline Score	Elagolix				
		Placebo (n=48)	75mg (n=25)	100mg (50mg bid) (n=21)	150mg (n=23)	200mg (100mg bid) (n=24)
CPSS	8	-3.7 and -4.5	-3.8	-4.4	-5.2	-5.9
Peak VAS (mm)	60-70	-14.7 and -33.6	-22.9	-24.4	-38.2	-44.6
Dysmenorrhea score	2	0.9	-1.1	-1.3	-1.6	-1.9
No dysmenorrhea at study end (%)	—	22 and 17	35	55	63	81

Mean change during treatment; results of two studies. CPSS = composite pelvic signs and symptoms score; VAS = visual analog scale for pelvic pain. Adapted from O'Brien et al., 2008.¹⁹

is associated with prolonged effect and inability to rapidly terminate the treatment if necessary, as well as other limitations. During the past decade, several non-peptide small-molecule GnRH antagonists have been developed.¹⁷ They are orally active, which improves patient acceptability and facilitates dosing and the possibility of rapid discontinuation if necessary. Furthermore, individual dose adjustment of these compounds to vary the level of pituitary suppression and therefore allow adjustment of the circulating estradiol levels in the therapeutic window may be possible. This may facilitate long-term treatment without the need for add-back therapy.

Neurocrine Biosciences, Inc. has reported on two such compounds, one of which—elagolix (NBI-56418)—is being evaluated in endometriosis.^{18,19} Elagolix is a small non-peptide molecule that binds reversibly with high affinity to the human GnRH receptor. The histamine release from rat peritoneal mast cells stimulated *in vitro* by elagolix is well below that seen with peptide antagonists and similar to that seen with vehicle.

Elagolix is currently in phase II clinical trials in women with pelvic pain associated with endometriosis. The drug is rapidly absorbed from the gastrointestinal (GI) system, with time to maximum plasma concentration

The difference in pharmacological mechanisms between agonists and antagonists offers theoretical advantages in the management of endometriosis.

(T_{max}) values ranging from 30 minutes to one hour after dosing, followed by a rapid decline in blood levels. Elagolix induces dose-dependent FSH, LH, and estradiol suppression without detectable flare effect. At a dose of 100–150mg/day, serum estradiol concentrations remained between 20 and 50pg/ml, which seems to be the optimal range for the management of endometriosis (see Figure 1).

Elagolix seems to be well tolerated in comparison with placebo. The most common side effects reported more frequently than in placebo groups were headaches, nausea, and dizziness. The reporting of hot flashes with doses ranging from 50 to 200mg was 49.3% compared with 42.6% in the placebo groups. None of the women receiving elagolix reported severe vasomotor or hypoestrogenic symptoms. There was no increase in serum N-telopeptide concentrations, a biomarker for bone resorption. There was improvement in the composite pelvic signs and symptoms

Elagolix induces dose-dependent follicle-stimulating hormone, luteinizing hormone, and estradiol suppression without detectable flare effect.

score (CPSS) and the visual analog scale (VAS) for pelvic pain scores, which was most pronounced at doses of 150mg once daily and 100mg twice daily (see Table 2). The proportion of subjects with at least a one-point reduction in dysmenorrhea and non-menstrual pelvic pain was 92% in the 150mg and 200mg elagolix groups, in contrast to 40–50% in the placebo recipients. Return of regular ovulatory cycles, as evidenced by urinary pregnanediol measurements, was rapid in most patients.

The exploratory phase II studies with elagolix described above have led to additional clinical trials to assess longer-duration treatments of six months, an additional dose (250mg once daily), and dual-energy X-ray absorptiometry (DEXA) scans to assess the impact of treatment on bone mineral density. Results from these trials are expected to be reported in 2008 and 2009. ■

Acknowledgments

The author is grateful to Dr Chris O'Brien from Neurocrine Biosciences, Inc. for providing access to clinical and experimental data on elagolix.

- Sulak PJ, Cressman BE, Waldrop E, et al., *Obstet Gynecol*, 1997;89:179–83.
- Anderson FD, Hait H, *Contraception*, 2003;68:89–96.
- Janicki TI, Dmowski WP, *J Soc Gynecol Investig*, 2004;11(S):161A.
- Razzi S, Luisi S, Calonaci F, et al., *Fertil Steril*, 2007;88:789–94.
- Muzii L, *J Minim Invasive Gynecol*, 2006;13:535–8.
- Cobellis L, Razzi S, Fava A, et al., *Fertil Steril*, 2004;82:239–40.
- Patwardhan S, Nawathe A, Yates D, et al., *BJOG*, 2008;115: 818–22.
- Dmowski WP, Braun D, *Best Practice & Research*, 2004;18:245–63.
- Braun DP, Gebel H, Dmowski WP, *Fertil Steril*, 1994;62:89–95.
- Warnock JK, Bundred JC, Morris DW, *Fertil Steril*, 2000;74:984–6.
- Fernandez H, Lucas C, Hedon B, et al., *Hum Reprod*, 2004;19: 1465–71.
- Surrey ES, Hornstein MD, for the Add-Back Study Group, *Obstet Gynecol*, 2002;99:709–19.
- Barbieri RL, *Am J Obstet Gynecol*, 1992;166:740–45.
- Craft I, Gorgy A, Hill J, Menon D, et al., *Hum Reprod*, 1999;14: 2959–62.
- Martha PM, Gray ME, Campion M, et al., *Fertil Steril*, 1999;71:95.
- Kupker W, Felberbaum RE, Krapp M, et al., *Reprod Biomed Online*, 2002;5:12–16.
- Millar RP, Zhu Y-F, Chen C, et al., *Brit Med Bull*, 2000;56:761–72.
- Struthers RS, Xie Q, Sullivan SK, et al., *Endocrinology*, 2006;148: 857–67.
- O'Brien C, Jimenez R, Grundy J, et al., Presented at the World Congress of Endometriosis, 12 March 2008, Melbourne, Australia.