Anastrazole and oral contraceptives: a novel treatment for endometriosis

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Objective: To establish the use of aromatase inhibitors as a therapeutic option for endometriosis.
Design: Prospective open-label Food and Drug Administration phase 2 trial with Institutional Review Board approval.
Setting: Outpatient tertiary care centers.
Patient(s): Fifteen premenopausal patients with documented refractory endometriosis and chronic pelvic pain.
Intervention(s): After a 1-month washout of endometriosis hormone therapies, women took 1 mg anastrazole (Arimidex; AstraZeneca, Wilmington, DE) and one tablet of 20 μg ethinyl estradiol/0.1 mg levonorgestrel (Alesse; Wyeth, Madison, NJ) daily for 6 months.
Main Outcome Measure(s): An analog pain scale recorded pelvic pain in daily diaries and surveys at baseline and after each treatment month. Side effects, blood counts, liver and renal function tests, cholesterol levels, and bone density were monitored.
Result(s): Fourteen of 15 patients achieved significant pain reduction. Median pain scores decreased 55% after 6 months, while mean pain scores decreased 40%. Pain reduction comparing each treatment month to baseline achieved statistical significance. Average pain scores began dropping after only 1 treatment month and continued decreasing each additional month. No organ system experienced adverse effects. Estradiol levels were suppressed during treatment. Side effects were mild and improved over time.
Conclusion(s): Fourteen of 15 patients with refractory endometriosis achieved significant pain relief using anastrazole and 20 μg ethinyl estradiol/0.1 mg levonorgestrel with minimal side effects. This treatment for endometriosis is a promising new modality that warrants further investigation. (Fertil Steril® 2005;84: 300–4. ©2005 by American Society for Reproductive Medicine.)

Key Words: Anastrazole (Arimidex), aromatase inhibitors, endometriosis, pelvic pain

Endometriosis affects approximately 7%–10% of all women, 71%–87% of women with chronic pelvic pain, and 38% of all infertile women. Chronic pelvic pain, dysmenorrhea, and dyspareunia are the hallmark symptoms experienced by affected women (1). There are several medical treatments available including oral contraceptives, Depo-Provera, oral progestins, danazol, and GnRH agonists. These treatments attempt to create a hypoestrogenic state since estrogen is believed to be a contributing factor to endometriosis (2). Masculinizing side effects have essentially rendered danazol a treatment of the past (3). Menopausal side effects, including osteoporosis, that are associated with GnRH agonists make them only short-term solutions for the treatment of endometriosis (4).

Many patients have pain associated with endometriosis that is refractory to all currently available medical treatments. Laparoscopy and fulguration or excision of endometriosis can often provide some relief; however, it often recurs. Currently, when no other medical options remain and minimally invasive surgery has failed, women resort to a total hysterectomy with or without bilateral salpingo-oophorectomy. Even after this invasive procedure, their pain may not be relieved (3, 5). As a result of our limited arsenal of treatments, research has focused on other components of the biochemical pathway that are proposed to explain endometriosis in the hopes of discovering new treatments.

Endometriosis occurs primarily in reproductive-age women and often resolves after menopause or bilateral oo-

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TABLE 1

Prior failed treatments for each patient.

Patient	SM	JN	JZ	VS	WJ	MA	RC	MM	RS	RV	JM	KM	EL	MAn	KB	AR	SG	KG
Oral contraceptives		X	X		X		X	X		X	X	X		X	X	X	X	X
P	X	X				X		X		X	X			X	X	X	X	X
Danazol									X	X	X		X		X	X	X	
Lupron	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laparoscopy (n)	1	3	2	1	1	3	1	1	4	2	2	1	3	1	5	1	5	2

Amsterdam. Anastrazole treats endometriosis. Fertil Steril 2005.

phorectomy. Therefore, endometriosis is considered to be an estrogen-dependent disease process (2, 6). Aromatase P450 converts androstenedione to estrone. This step precedes the conversion to E_2, the more biologically active form of estrogen (7).

Recent studies show that patients with endometriosis have high levels of aromatase P450 expression in eutopic endometrial tissue. However, aromatase is not expressed in the endometrial tissue of women without endometriosis (8). Functioning endometrial tissue is also found outside of the uterus in patients with endometriosis. These ectopic implants are also found to express high levels of aromatase. Therefore, it may be this aberrant intrauterine and ectopic expression of aromatase, and thereby estrogen, that is responsible for the signs and symptoms of endometriosis (9). We hypothesize that current treatments only address the estrogen produced at the level of the ovary and not that produced locally in endometrial tissue or ectopic implants (3, 10). An aromatase inhibitor's unique ability to work at both the level of the ovary and locally in the tissue itself will allow it to be a more potent treatment for endometriosis.

Aromatase inhibitors, such as anastrazole (Arimidex; AstraZeneca, Wilmington, DE), are currently used in postmenopausal women to treat hormone receptor–positive breast cancer refractory to tamoxifen (11). The principle side effects experienced by these patients include weakness, nausea, headaches, and hot flashes. When compared with tamoxifen for the treatment of these tumors, anastrazole has similar efficacy with an increase in survival time and fewer episodes of vaginal bleeding or thromboembolism (12). Aromatase inhibitor use in postmenopausal women decreases the level of circulating estrogen to 1%–10% of the pretreatment level (13).

We speculate that aromatase inhibitors will effectively down-regulate aromatase expression in premenopausal patients with endometriosis in a similar fashion to that seen in postmenopausal women treated for breast cancer. It is theorized that diminished levels of aromatase will lead to a decline in pelvic pain and estrogen expression. In addition, we expect the side effects of this treatment to be better tolerated than those associated with other current medical regimens for endometriosis. To date, one trial using letrozole and norethindrone acetate (14) and one case study using anastrazole have reported successful treatment with an aromatase inhibitor of a patient with endometriosis refractory to all current medical and surgical treatments (7). The objective of this study was to evaluate the efficacy of anastrazole (Arimidex) in the treatment of pelvic pain associated with endometriosis.

MATERIALS AND METHODS

Age ranged from 23 to 46 years old. All patients were treated with at least two treatments in the past. A list of prior treatments for each patient is given in Table 1. Two sites (Indianapolis and Chicago) were involved in conducting this trial.

This study was conducted as a prospective, multicenter, open-label Food and Drug Administration phase 2 trial. Institutional Review Board approval was obtained independently at Indiana University School of Medicine and the University of Illinois School of Medicine. To participate in this study, each patient was required to be on a nonhormonal form of birth control, be premenopausal, have endometriosis documented by laparoscopy or laparotomy, have experienced at least 6 months of pelvic pain, and have failed multiple other medical treatments for endometriosis.

Patients were excluded if they had a prior hysterectomy, were breast-feeding, were pregnant or planning a future pregnancy, or were osteopenic. In addition, patients with the following medical conditions were also excluded: myocardial infarction, stroke, chest pain, unexplained vaginal bleeding, breast nodules, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, epilepsy, kidney disease, clotting disorders, gallbladder disease, and cancer of the breast, uterus, cervix, vagina, or liver.

Eighteen premenopausal patients with documented endometriosis and chronic pelvic pain refractory to multiple medical and surgical treatments were enrolled in the study. After a washout period of at least 1 month from all forms of hormonal treatment for endometriosis, each patient was started on a daily regimen of 1 mg anastrazole and continuous one tablet 20 μg ethinyl estradiol/0.1 mg levonorgestrel (Alesse; Wyeth, Madison, WI) to be taken for 6 months. The