

# Delayed Oral Estradiol Combined with Leuprolide Increases Endometriosis-Related Pain

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## ABSTRACT

**Objectives:** To determine if low-dose estrogen replacement can be added to GnRH agonist therapy after three months to reduce hypoestrogenic symptoms while allowing continued relief of pain in patients with endometriosis.

**Materials and Methods:** Thirteen women with endometriosis and pain were treated with six months of leuprolide acetate in a prospective, randomized double-blind placebo controlled study. After three months of therapy, six subjects initiated oral estradiol 1 mg daily, and seven received an identical placebo.

**Results:** Dysmenorrhea improved in both groups, and dyspareunia significantly improved in the GnRH agonist plus placebo group. The mean pain scores of the oral estrogen group tended to be higher than the placebo group, and hot flushes tended to be less severe with estrogen treatment. However, differences observed between the study and placebo groups did not reach statistical significance.

**Conclusion:** In a prospective, randomized study, low-dose estrogen replacement increases endometriosis-related pain during GnRH agonist therapy. The study was terminated after the first 13 subjects due to the concerning trend toward recurrent symptoms in women who received oral estradiol during GnRH agonist therapy for endometriosis-related pain. With the trend toward increasing pain with estrogen add-back therapy, a larger study would not seem to be justifiable.

**Keywords:** Endometriosis, Pelvic pain, Estradiol, Estrogen, Leuprolide, GnRH agonist.

## INTRODUCTION

GnRH agonist therapy has been proven to be beneficial to women with endometriosis-related chronic pelvic pain,<sup>1,2</sup> probably due to a reduction in endometriosis when estrogen levels are suppressed.<sup>3</sup> Unfortunately, long-term usage of GnRH agonists is limited due to problems associated with the hypoestrogenic state, including hot flushes, headaches, vaginal dryness and osteoporosis. The level of estrogen that causes progression of endometriosis is not known. At a low level, estrogen may protect against osteoporosis without stimulating the disease, whereas a higher level may promote progressive symptoms.<sup>4</sup>

Combined estrogen and progestin hormone add-back regimens during GnRH agonist therapy of endometriosis reduces hypoestrogenic side effects without compromising efficacy.<sup>5-7</sup> In addition, estrogen can be added after hysterectomy without increasing endometriosis-related pain.<sup>8,9</sup> We hypothesized that low-dose estrogen could be added to reduce hypoestrogenic side effects during GnRH agonist therapy without affecting pain relief. To test this hypothesis, we initiated a prospective, randomized, double-blinded placebo controlled study of delayed oral estrogen add-back therapy versus placebo during leuprolide acetate treatment for endometriosis-related pain.

## MATERIALS AND METHODS

Women with persistent or recurrent chronic pelvic pain after laparoscopic diagnosis and treatment of endometriosis were eligible for this placebo controlled, prospective, randomized, double-blinded study. Thirteen subjects were enrolled after providing institutional review board approved consent. Demographic data is shown in **Table 1** and indicates a similar makeup between the two groups. All were treated with leuprolide acetate (TAP Pharmaceuticals, Deerfield, IL) 3.75 mg intramuscularly for six months. Subjects were randomly assigned into treatment or placebo groups by the hospital's investigational drug service, and all medications were prescribed through this department. Time period one was considered to be pretherapy visits. GnRH agonist therapy was initiated on cycle day 1 to 3. Months 1,

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**Table 1.**  
Demographic Profile

	Estrogen	Placebo
Age (years)	28.3 (+/- 5.0)	32.4 (+/- 5.2)
Weight (pounds)	156 (+/- 41)	163 (+/- 34)
Height (inches)	64 (+/- 4)	66 (+/- 3)
Smoker	4/7	3/6
Prior pregnancy	7/7	4/6

2 and 3 were considered to be time period two, and all patients received leuprolide with no supplement. During time period three, months 4, 5 and 6 of leuprolide therapy, patients received the study medication: oral estradiol 1 mg daily (Estrace, MeadJohnson Laboratories, Princeton, NJ) or an identical-appearing placebo to be taken daily. All subjects agreed to use barrier contraception throughout the study.

Daily pain and medication diaries including dysmenorrhea, headaches and hot flush scores were kept by the patient. Patients were seen for clinic visits prior to initiating therapy, then every four weeks until the completion of therapy. Dysmenorrhea, pelvic pain, dyspareunia, hot flushes and headaches were assessed by verbal questioning of the patient at each visit. Pelvic induration and pelvic tenderness were scored by physical examination at each visit and three months following therapy. Pelvic tenderness, induration, headaches, and hot flushes were given a score of 0-3, with 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms. Pelvic pain, dyspareunia and dysmenorrhea were given a score of 0-10 on a linear scale, with 0 indicating no symptoms and 10 representing the most severe symptoms. Estradiol levels were obtained at months 4, 5 and 6.

Exclusion criteria for the study included a history of prior GnRH agonist therapy, history of an emotional disorder, pregnancy or lactation. Further exclusions were osteoporosis, known or suspected breast cancer, present or past endometrial hyperplasia or carcinoma, a history of thrombosis, thrombophlebitis, or thromboembolism and undiagnosed abnormal genital bleeding. Usage of oral contraceptives or other treatment outside the protocol was not permitted.

The serum estradiol level was measured at visits 4, 5 and

6 by the COAT-A-Count® (Diagnostic Products Corporation, Los Angeles, CA) alternate "IVF" procedure, intra-assay CV <5.6%, interassay CV <5.5%.

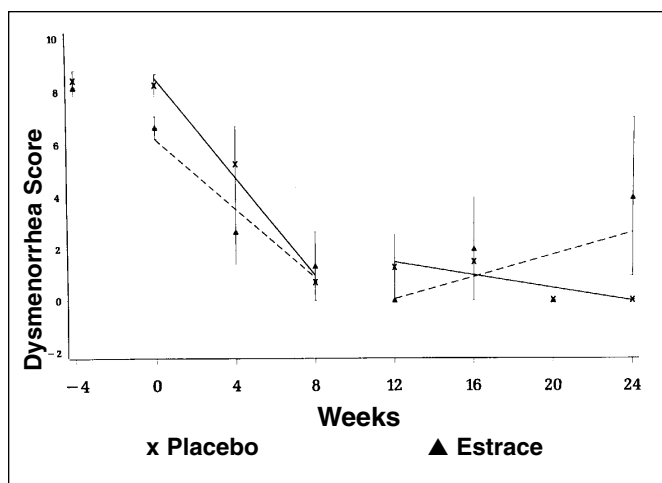
### Statistical Analysis

For the purpose of analysis, the monthly visits were described as weeks (ie, pre-therapy visit is represented by week -4, baseline is represented by week 0, and month 1 of treatment is represented by week 4). All analyses were conducted using SAS/STAT Software, version 6.11.<sup>10</sup> The demographic parameters were compared using an independent samples t-test for each continuous variable and a Fisher's exact test for comparisons of proportions. Means at each time point for each treatment group were estimated for each dependent variable. Longitudinal mixed effects analyses were applied to the four continuous dependent variables of pelvic pain, dysmenorrhea, dyspareunia, and estradiol.<sup>11</sup> According to a mixed effects model, regression lines were fit through each of the period two data and the period three data for the placebo group and the oral estradiol group separately. Hypothesis tests were used to determine whether slopes differed significantly from zero, and contrasts were used to test whether the period three oral estradiol slope was significantly different from the period three placebo group slope.

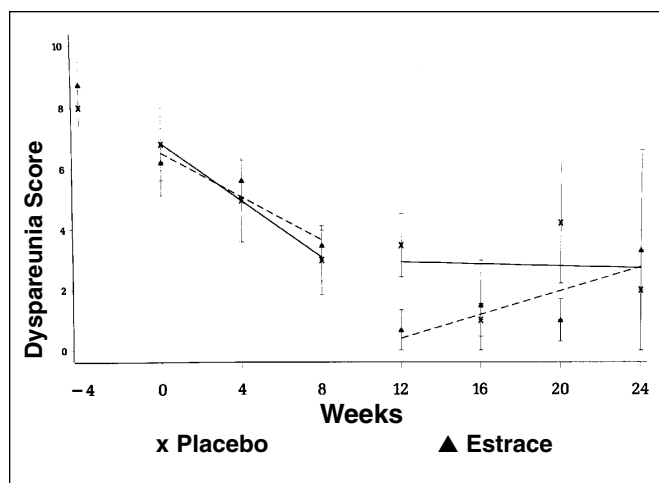
A generalized estimating equation approach for analyzing repeated ordinal and categorical values was applied to the four ordinal variables of hot flushes, pelvic tenderness, headache and induration. Because of problems with available software, this approach was found to be limited. Instead, logistic regression analysis with the assumption of independence was used to analyze the ordinal variables.<sup>12</sup>

### RESULTS

Seven women were randomized to oral estradiol and six to placebo. Demographic data is shown in **Table 1** and indicates a similar makeup between the two groups for each parameter listed,  $p>0.05$ . Plots of the means and standard errors for the endometriosis-related symptom variables of pelvic pain, dysmenorrhea, dyspareunia, induration and pelvic tenderness were assessed. A statistically significant difference was seen between the period two and period three placebo dysmenorrhea slopes, as well as between the period two and period three estrogen therapy dysmenorrhea slopes (**Figure 1**),



**Figure 1.** Plots of the means and standard errors for dysmenorrhea. Week -4 indicates the pretreatment visit (time period one). Week 0 indicates the start of leuprolide therapy (time period two). Week 12 is the start of oral estradiol or placebo in addition to leuprolide (time period three).



**Figure 2.** Plots of the means and standard errors for dyspareunia. Week 4 indicates the pretreatment visit (time period one). Week 0 indicates the start of leuprolide therapy (time period two). Week 12 is the start of oral estradiol or placebo in addition to leuprolide (time period three).

$p < 0.05$ . For the placebo group, the dysmenorrhea scores decreased at a slower rate during period three than in period two. For the oral estradiol group, the dysmenorrhea score increased during period two and decreased during period three. Additionally, dyspareunia was significantly different in the placebo group when the period two slope was compared to the period three slope (Figure 2).

The differences observed between the oral estrogen study and placebo groups were not statistically significant, although the mean pain scores of the oral estrogen group during period three are usually higher than those of the placebo group. This result indicates the oral estradiol add-back is likely causing an increase in endometriosis-related symptoms in the oral estradiol group. Because some subjects tended to experience increased pain, the blind was broken, and the data was analyzed after these first 13 patients had completed the study. Subsequently, the study was terminated and no further patients were enrolled. No adjustments were made to significance levels of hypothesis tests since this study was stopped due to safety concerns.

The GnRH agonist side effects were evaluated. As expected, hot flush and headache mean scores during time period three are usually lower for the estradiol

group than for the placebo group, although these differences were not statistically significant. This trend toward fewer hypoestrogenic side effects with estrogen indicates that the estradiol add-back appears to be effective in reducing the GnRH agonist related hot flushes.

## DISCUSSION

The trend toward increased pain with low-dose estrogen therapy is surprising. Estrogen replacement therapy after menopause reduces menopausal symptoms and lowers the risk of osteoporosis.<sup>13</sup> Estrogen replacement therapy has been successfully used for patients with endometriosis after hysterectomy and bilateral oophorectomy.<sup>5,6</sup> Recurrent endometriosis-related symptoms are uncommon when estrogen replacement therapy is initiated after surgery.<sup>9</sup> Approximately 90% of patients will tolerate estrogen replacement therapy in this situation without recurrent pain.<sup>14</sup> In this study, we hoped that we could achieve suppression of endometriosis by three months of therapy, without recurrence of pain when estrogen was eventually added back at low levels.

The study was terminated after the first 13 subjects due to the concerning trend toward recurrent symptoms in women who received oral estradiol during leuprolide acetate therapy for endometriosis related pain. As a

result, a statistically significant difference could not be found between the placebo group and the treatment group during time period three when pelvic pain, dysmenorrhea, dyspareunia, induration, hot flushes and headaches were compared. Although the progression of symptoms suggesting deterioration with oral estrogen cannot be supported by statistical significance, this study was designed as an exploratory study.

The lack of a statistically significant difference in this study should be interpreted with caution. Given the small sample size, the ability to find significant differences between the estradiol group and the placebo group is low. The power to find a significant difference with the observed differences between the slopes of the placebo group and the estradiol group in this study ranges from 0.03 for hot flushes to 0.27 for induration. Since an acceptable power is generally 0.80, a larger sample size should demonstrate a difference, if there is one. Our intention in this study was to reduce hypoestrogenic symptoms with estrogen without compromising efficacy of GnRH agonist therapy. Clearly, this study did not meet this goal, since pain tended to increase with estrogen. However, an expanded study to prove that estrogen treatment is harmful would be unethical.

Delaying the start of estrogen replacement therapy did not appear to be beneficial in our study. The delay was incorporated in the protocol to allow for regression of endometriosis and pain before adding estrogen. Effective relief of endometriosis-related pain occurs by the third month of GnRH agonist therapy.<sup>15</sup> In theory, estrogen could be added after the maximal benefit had been achieved in order to minimize the hypoestrogenic side effects and could be continued for a prolonged interval. However, delayed add-back of progestin was not found to be advantageous in one study.<sup>16</sup> Based upon the observations in our study, it is doubtful that the immediate addition of estrogen would have resulted in a more acceptable regimen.

Since endometriosis is an estrogen-dependent condition, physicians have been reluctant to prescribe even low-dose estrogen for patients during GnRH agonist therapy for endometriosis. Recent studies have confirmed the safety of combined estrogen plus progestin add-back during GnRH agonist therapy for endometriosis. However, based upon the results of our study, estrogen add-back therapy without progestin cannot be advised.

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