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# Effect of Letrozole on endometriosis-related pelvic pain

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## Abstract

**Background**: To determine the role of Letrozole, an aromatase inhibitor, in the treatment of endometriotic pain.

**Methods:** In this prospective, randomized, controlled clinical trial in minimally invasive surgery research center, 51 women with pelvic endometriosis and endometriotic pain (dyspareunia, dysmenorrhea, pelvic pain) score of 5 or more (for at least one of these endometriotic pain), after laparoscopic diagnosis and conservative laparoscopic surgery were treated with either Letrozole plus OCP (n=25) or only OCP (n=26) for 4 months continuously.

**Results:** Using VAS test, the score of dyspareunia, dysmenorrhea and pelvic pain 4 months after the laparoscopic surgery declined significantly in both groups but the difference between results of the two groups was not significant.

**Conclusion:** Both treatment modalities showed comparable effectiveness in the treatment of pains related to endometriosis and in comparison with OCP, Letrozole did not affect the outcome.

**Keywords:** Aromatase inhibitor, Endometriosis, Letrozole, Pelvic pain.

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## Introduction

Presence of endometrial glandular and stromal cells outside the uterine cavity is called endometriosis which can be diagnosed by visual inspection of the pelvis during laparoscopy. The most common manifestations of endometriosis are dyspareunia, dysmenorrhea, pelvic pain and infertility that can have important effects on the quality of life (1,2). Endometriosis is an estrogen dependent disease (3,4) and estradiol supports growth and inflammation process in endometriotic lesions (2,5). Almost all treatments for endometriosis (GNRH agonists, progestins, danazol, OCP) have an effect on endometriosis by decreasing ovarian estrogen levels or antagonize estrogen.

In women, another estrogen source is androgen change into estrogen in peripheral tissues by aromatase P 450 enzyme (1,6). Aromatase is a key enzyme in the synthesis of estrogens. Aromatization is the last step in estradiol biosynthesis (3). Aromatase mediates the conversion of androstendione and testosterone to estrogens. Perhaps inhibition of aromatase enzyme and decreasing the peripheral conversion of androgens to estrogen could have a therapeutic effect as inhibition of endometriotic foci. Letrozole

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is a drug that can inhibit aromatase enzyme and in some studies on animal models (rats, mice and baboons) it has led to the reduction in the size of endometriotic implants (7-10). Letrozole is a drug that inhibits the aromatase enzyme by competitively binding to the cytochrome P 450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. Elevated levels of aromatase have been found in endometriotic lesions (11). Therefore, aromatase inhibitors maybe effective in treating endometriosis related pelvic pain.

## Methods

This study was conducted as a randomized controlled trial to assess the effect of Letrozole on pain due endometriosis. As Letrozole can activate ovulation and is also a teratogen (12), during its use the patient must take contraception. We prescribed Letrozole in combination with OCP in one group and in the control group we prescribed OCP only. Our sample was composed of the patients with at least one kind of endometriotic pain (dyspareunia, dysmenorrhea, pelvic pain) who were diagnosed as endometriotic by laparoscopy. Laparoscopy was performed under general anesthesia using the triple puncture technique. On laparoscopy, the surgeon tried to excise or ablate all the endometriotic implants and adhesiolysis was also performed. The day before laparoscopy, a data collection form was filled by a physician. The severity of dyspareunia, dysmenorrhea and pelvic pain was estimated by Visual Analogue Scale test (VAS test). Scale 0 was no pain and 10 was the most severe pain ever experienced. Those patients who had the score of 5 or more before the operation for one of their painful symptoms (dyspareunia, dysmenorrhea, pelvic pain) were included in our study. After operation, the severity of endometriosis was written in the data collection form as revised American Society for Reproductive Medicine classification (ASRM) scores for endometriosis (1,13).

With the acceptance of ethic committee of Tehran University of Medical Sciences and obtaining informed consent in cases of Letrozole prescription, we prescribed OCP (Levonorgestrel 0.15 mg plus Ethinyl Estradiol 0.03 mg, Iran Hormon, Tehran, Iran) daily for 4 months continuously in control group and OCP in combination with oral Letrozole (Femara, 2.5 mg-Novartis-Switzerland) daily for 4 months continuously in another group. Both groups took vitamin D 400IU plus Calcium 1 gram (Schiff, USA) daily for 4 months. All of the samples were the patients who had not planned to become pregnant after discharge. We randomized the patients by assigning to the case and control groups alternately in the order of their admission. Patients were evaluated at one and four months after operation and after starting medical treatment by office visits and telephone inquiry for severity of their endometriotic pain and drug compliance. The patients did not have any other medical or systemic diseases. Before initiation of treatment, liver function tests, serum urea, creatinin, lipids and plasma glucose were checked.

We analyzed the data by SPSS 13, using the KS test (One-sample Kolmogorov-Smirnov test) for normality of data distribution, Levene's test for equality of variances and independent samples t-test for equality of means for comparing quantitative normal data between two groups, paired sample t-tests for comparing quantitative normal data between before and after treatment in each group and Pearson Chi-square test for matching and comparing categorical variables between two groups. According to the KS test, we compared the non-normal quantitative data by Mann-Whitney U nonparametric test between two groups and Wilcoxon Signed Ranks test for comparing before and after treatment data in each group.The categorical variables, before and after medical treatment were analyzed by Mc Nemar test.

## Results

In this study we had 25 patients in Letro-

Table 1. comparison of age and severity of pain in two groups before and after treatment

| | Treatment Group | N | Mean | p value |
|---|---|---|---|---|
| Age | Letrozole | 25 | 31.0000 | 0.018 |
| | OCP | 26 | 27.5385 | 0.019 |
| Dysmenorhea score before treatment | Letrozole | 25 | 7.2000 | 0.599 |
| | OCP | 26 | 7.5000 | 0.600 |
| Dypareunia score before treatment | Letrozole | 15 | 4.8000 | 0.490 |
| | OCP | 14 | 5.5714 | 0.491 |
| Noncyclic pelvic pain score before treatment | Letrozole | 25 | 6.3200 | 0.460 |
| | OCP | 26 | 5.8077 | 0.461 |
| Dysmenorhea score 4 month after treatment | Letrozole | 25 | 1.1200 | 0.050 |
| | OCP | 26 | 1.3846 | 0.049 |
| Dypareunia score 4 month after treatment | Letrozole | 14 | 1.8571 | 0.631 |
| | OCP | 14 | 2.0000 | 0.631 |
| Noncyclic pelvic pain score 4 month after treatment | Letrozole | 24 | 1.9583 | 0.055 |
| | OCP | 26 | 2.5000 | 0.058 |

zole plus OCP group (L group) and 26 patients in OCP group (O group). The age range was 20 - 43 years old. 10 patients from L group and 12 patients from O group were single and had not sexual contact. The patients in the L group were matched with O group for marital status, severity of endometriosis and severity of pelvic pain so that there had been no significant differences (Table 1).

All the patients reported improvement in the pain score within one month and four months of initiation of medical treatment. The pain scores continued to decrease during the course of the treatment. All of the patients developed amenorrhea after initiation of therapy and none of them had bone pain.

There was no significant difference in severity of dyspareunia, dysmenorrhea and pelvic pain between the two groups before and after treatment, but after treatment the severity of the 3 mentioned symptoms was significantly reduced in both groups in comparison with their pretreatment status (Table 1,5).

None of the patients developed any side-effects of Letrozole or OCP and all continued the prescribed medication for 4 months.

Table 2. severity of pelvic pain in two groups before treatment

| | | | Treatment Group | | Total |
|---|---|---|---|---|---|
| | | | Letrozole | OCP | |
| Noncyclic pelvic pain score before treatment | 1.00 | Count | 2 | 2 | 4 |
| | | percent | 50.0% | 50.0% | 100.0% |
| | 2.00 | Count | 1 | 0 | 1 |
| | | percent | 100.0% | .0% | 100.0% |
| | 3.00 | Count | 0 | 3 | 3 |
| | | percent | .0% | 100.0% | 100.0% |
| | 4.00 | Count | 0 | 1 | 1 |
| | | percent | .0% | 100.0% | 100.0% |
| | 5.00 | Count | 7 | 5 | 12 |
| | | percent | 58.3% | 41.7% | 100.0% |
| | 6.00 | Count | 5 | 3 | 8 |
| | | percent | 62.5% | 37.5% | 100.0% |
| | 7.00 | Count | 0 | 6 | 6 |
| | | percent | .0% | 100.0% | 100.0% |
| | 8.00 | Count | 5 | 4 | 9 |
| | | percent | 55.6% | 44.4% | 100.0% |
| | 9.00 | Count | 1 | 1 | 2 |
| | | percent | 50.0% | 50.0% | 100.0% |
| | 10.00 | Count | 4 | 1 | 5 |
| | | percent | 80.0% | 20.0% | 100.0% |
| Total | | Count | 25 | 26 | 51 |
| | | percent | 49.0% | 51.0% | 100.0% |

Table 3. severity of dyspareunia in two groups before treatment

| | | | Treatment Group | | Total |
|---|---|---|---|---|---|
| | | | Letrozole | OCP | |
| Dyspareunia score before treatment | 1.00 | Count | 4 | 2 | 6 |
| | | percent | 66.7% | 33.3% | 100.0% |
| | 2.00 | Count | 0 | 1 | 1 |
| | | percent | .0% | 100.0% | 100.0% |
| | 3.00 | Count | 0 | 1 | 1 |
| | | percent | .0% | 100.0% | 100.0% |
| | 4.00 | Count | 3 | 0 | 3 |
| | | percent | 100.0% | .0% | 100.0% |
| | 5.00 | Count | 2 | 4 | 6 |
| | | percent | 33.3% | 66.7% | 100.0% |
| | 6.00 | Count | 1 | 0 | 1 |
| | | percent | 100.0% | .0% | 100.0% |
| | 7.00 | Count | 3 | 0 | 3 |
| | | percent | 100.0% | .0% | 100.0% |
| | 8.00 | Count | 0 | 4 | 4 |
| | | percent | .0% | 100.0% | 100.0% |
| | 9.00 | Count | 1 | 1 | 2 |
| | | percent | 50.0% | 50.0% | 100.0% |
| | 10.00 | Count | 1 | 1 | 2 |
| | | percent | 50.0% | 50.0% | 100.0% |
| Total | | Count | 15 | 14 | 29 |
| | | percent | 51.7% | 48.3% | 100.0% |

Table 4. severity of dysmenorrhea in two groups before treatment

| | | | Treatment Group | | Total |
|---|---|---|---|---|---|
| | | | Letrozole | OCP | |
| Dysmenorrhea score before treatment | 1.00 | Count | 0 | 1 | 1 |
| | | percent | .0% | 100.0% | 100.0% |
| | 3.00 | Count | 2 | 0 | 2 |
| | | percent | 100.0% | .0% | 100.0% |
| | 4.00 | Count | 1 | 0 | 1 |
| | | percent | 100.0% | .0% | 100.0% |
| | 5.00 | Count | 2 | 2 | 4 |
| | | percent | 50.0% | 50.0% | 100.0% |
| | 6.00 | Count | 5 | 2 | 7 |
| | | percent | 71.4% | 28.6% | 100.0% |
| | 7.00 | Count | 2 | 5 | 7 |
| | | percent | 28.6% | 71.4% | 100.0% |
| | 8.00 | Count | 6 | 10 | 16 |
| | | percent | 37.5% | 62.5% | 100.0% |
| | 9.00 | Count | 2 | 3 | 5 |
| | | percent | 40.0% | 60.0% | 100.0% |
| | 10.00 | Count | 5 | 3 | 8 |
| | | percent | 62.5% | 37.5% | 100.0% |
| Total | | Count | 25 | 26 | 51 |
| | | percent | 49.0% | 51.0% | 100.0% |

## Discussion

The major finding of this prospective, randomized trial of Letrozole plus OCP versus OCP in the treatment of endometriotic pelvic pain after ablative surgery was that there was no significant difference in outcome between the two groups and the results of both treatment modalities were similar.

The highest level of aromatase in premenopausal women is in ovary. There are observations of increased expression of aromatase P 450 in endometriotic tissues (11,14-16) and aromatase inhibitors had been successful in regressing endometriotic tissue (17) and decreasing pelvic pain (17-22).

In a retrospective study by Abushahin et al. on 16 patients with endometriosis and chronic pelvic pain Letrozole 2.5 mg plus norethindrone acetate 2.5mg daily for 6 months improved pain symptoms, however

Table 5. Paired Samples Test (pain scores before treatment and 4 months after start of treatment in Letrozole group)

| | Paired Differences | | | | t | sig |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | 95% Confidence Interval of the Difference | | | |
| | | | Lower | Upper | | |
| Dysmenorrhea score before treatment - Dysmenorrhea score 4 month after start of treatment | 6.08000 | 2.03961 | 5.23809 | 6.92191 | 14.905 | .000 |
| Dyspareunia score before treatment - Dyspareunia score 4 month after start of treatment | 3.21429 | 2.32639 | 1.87107 | 4.55750 | 5.170 | .000 |
| Noncyclic pelvic pain score before treatment - Noncyclic pelvic pain score 4 month after start of treatment | 4.37500 | 2.44616 | 3.34208 | 5.40792 | 8.762 | .000 |

Treatment Group = Letrozole

Table 6. Paired Samples Test ( pain scores before treatment and 4 months after start of treatment in OCP group)

| | Paired Differences | | | | t | sig |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | 95% Confidence Interval of the Difference | | | |
| | | | Lower | Upper | | |
| Dysmenorrhea score before treatment -Dysmenorrhea score 4 month after start of treatment | 6.11538 | 1.79615 | 5.38990 | 6.84087 | 17.361 | .000 |
| Dyspareunia score before treatment - Dyspareunia score 4 month after start of treatment | 3.57143 | 3.00549 | 1.83611 | 5.30675 | 4.446 | .001 |
| Noncyclic pelvic pain score before treatment - Noncyclic pelvic pain score 4 month after start of treatment | 3.30769 | 1.91351 | 2.53481 | 4.08058 | 8.814 | .000 |

Treatment Group = OCP

pain recurred after treatment was completed (19). In another study by Verma et al. on 4 premenopausal women with endometriosis prescription of 2.5mg Letrozole plus 2.5mg norethisterone daily for 6 months, the mean pain score fell from 9 prior to the treatment to 4.5 at the end of treatment (4). In a prospective study by Ailawadi et al. on 10 patients with endometriosis and chronic pelvic pain, they prescribed 2.5mg per day Letrozole plus norethinderone for 6 months and after that they did a second-look laparoscopy. On laparoscopy, there was no histologic evidence of endometriosis and pelvic pain score decreased significantly in response to treatment (17). In a study by Amesterdam et al., Anastrozole and OCP continuously for 6 months made reduction of pain in 93% of cases (23). In a study by Seal et al., 5 patients with ovarian endometrioma used letrozole, 2.5mg per day plus OCP for 6 months and they found disappearance of ovarian endometrioma and reduction of pain scores (24).

We did not use Letrozole with progestins because of break through bleeding and that they could not make adequate contraceptive effect (because Letrozole is teratogen and during its use, the patient must have effective contraception. In our study, the results of OCP prescription for endometriotic pain in comparison with Letrozole plus OCP were similar.

## Limitations

1. We prescribed Letrozole in combination with OCP and the pain reduced significantly, but it is not known that the reduction in pain severity is due to OCP as a standard regimen for endometriosis or due to Letrozole itself or synergistic effect of the two. Therefore, we suggest another study to be conducted using larger sample sizes on single sexually inactive women to know the isolated effect of Lerozole on pelvic pain and dysmenorrhea secondary to endometriosis.

2. We did not perform a second-look lap-

aroscopy to determine the effect of treatment on the size of endometriotic lesions. Of course it is possible that Letrozole has a reductive effect on the size of the endometriotic lesion without significant reduction in severity of subjective pain experience in patients, because the severity of symptoms is not directly related to the severity of endometriosis (1).

## Conclusion

The outcomes of 2 groups were similar so we may can conclude that Letrozole had not any positive effect on decreasing endometriotic pain.

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