Original Article

Effects of Letrozole Compared with Danazol on Patients with Confirmed Endometriosis: A Randomized Clinical Trial

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Abstract

Background: Letrozole is an aromatase inhibitor which can decrease estrogen production in peripheral tissues and endometriosis. Danazol, as an androgen, inhibits estrogen production in ovaries and recently has been introduced as an aromatase inhibitor. This study was designed to compare the effects of Danazol with Letrozole on endometriosis symptom relief.

Materials and Methods: This study was a randomized clinical trial in which 105 patients with confirmed endometriosis were randomly assigned to one of three groups. Group 1 received Letrozole tablets (2.5 mg/day), calcium (1000 mg/day) and vitamin D (800 IU/day). Group 2 received Danazol tablets (600 mg/day), calcium (1000 mg/day) and vitamin D (800 IU/day). Group 3 (placebo group) were assigned to take two calcium tablets daily (500 mg/tablet) and vitamin D (800 IU/day). Pelvic pain, dysmenorrhea and dyspareunia were assessed in participants at baseline and monthly during the study for a total of six months. Data were analyzed via SPSS version 15 software with Freidman and Wilcoxon tests.

Results: Mean age in three groups has no significant difference. Of the 105 participants who were enrolled in this study, 38 patients were assigned to group 1 (Letrozole group), 37 patients in group 2 (Danazol group) and 31 patients were placed in group 3 (placebo group). This study showed that the mean scores for chronic pelvic pain, dysmenorrhea and dyspareunia for the Letrozole group were less than the Danazol and placebo groups.

Conclusion: This study showed that Letrozole can be more effective than Danazol for reducing chronic pelvic pain, dyspareunia and dysmenorrhea in patients suffering from recurrent endometriosis (Registeration Number: IRCT138812043414N1).

Keywords: Letrozole, Danazol, Endometriosis, Laparoscopy

Introduction

Endometriosis is a polygenic inherited disease with a multifactorial and complex etiology (1).

Endometriosis is estrogen-dependent and regresses in the absence of estrogen (2). However, based on the presence of endometriosis in menopause or its recurrence despite treatment with estrogen production inhibitors such as gonadotropin-releasing hormone (GnRH) agonists, it seems there is another source for estrogen production (3). Recent studies have shown that estrogen is produced in peripheral tissues such as the skin and adipose tissue (4).

Endometriosis tissue can locally produce estrogen via the aromatase enzyme. Ten different promoters can influence both the copy and translation of the aromatase gene in different tissues of the body (5). Any of the tissues which have the potential for aromatase expression can produce a large quantity of the aromatase enzyme under the influence of their specific activators (5, 6).

Despite the presence of a normal endometrium, endometriosis tissue has the potential for aromatase gene expression that leads to aromatase and estrogen production. Prostaglandin E2 (PGE2) causes aromatase gene expression and local production of estrogen. Produced estrogen, itself, can produce PGE2 (7).

GnRH agonists and oral contraceptive pills (OCP) inhibit estrogen production in the ovaries but have no effect on peripheral estrogen (8). On the other hand, local production of estrogen

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causes high concentrations of estrogen in endometriosis tissue (9). Thus, medications which inhibit local estrogen production via inhibition of aromatase activity have been studied by researchers. Letrozole is a competitive aromatase inhibitor which reversibly binds to the active enzyme and inhibits its action (4). Letrozol has been noted recently and researchers have done many studies to evaluate its effect (10, 11).

Danazol, a synthetic androgen, has been studied as a treatment for endometriosis since 1980. Danazol inhibits estrogen production via inhibition of the hypothalamic-pituitary-ovarian axis (12). Recent studies have shown that Danazol can inhibit aromatase enzyme activity (13) although some studies have not confirmed this finding (12). During the past decade Danazol has been the treatment of choice for endometriosis (12, 13).

With regards to the different effects of Danazol and Letrozole, their different side effects and tolerability, lower costs when compared with GnRH analogues and lack of any study on the comparison between these two medications; therefore, we designed this study to compare the effect of Danazol and Letrozole on symptom improvement in patients with endometriosis after laparoscopic treatment (cauterization).

Materials and Methods

This study was a randomized clinical trial conducted over a period of ten months (Sep 2008 - July 2009) on 105 patients diagnosed with endometriosis, aged 18-45 years, who were referred to the Obstetrics and Gynecology clinics at teaching hospitals in Isfahan, Iran. Women were included in the study if they were of reproductive age with regular menstrual cycles (18 to 45 days), had a confirmed diagnosis of endometriosis by laparoscopy, and had chronic pelvic pain and dysmenorrhea for at least two weeks in each month during the past three months. Exclusion criteria were: abnormal vaginal bleeding of unknown cause, ovarian cyst > 2cm, hormone therapy during the past three months, osteopenia, smoking history, hypersensitivity to Danazol and Letrozole, histories of convulsions, pulmonary, cardiac, hepatic, renal or cerebrovascular diseases and pregnancy. The Ethics Committee at Isfahan University of Medical Sciences approved this study and written consent was obtained for all study participants.

The severity and staging of endometriosis was determined by laparoscopy one month before the study. Staging was based on the degree of superficial and deep peritoneal or ovary involvement by endometriosis, and the degree of adhesion in the tubes and ovaries.

Complete blood count (CBC), serum electrolytes, as well as kidney and liver function tests were performed for all study participants on the second day of their menstrual cycles, prior to laparoscopy.

Cauterization was done during the laparoscopy (according to standard fundamentals of treatment). Following laparascopy, the participants were randomly assignev to three groups.

Group 1(Letrozole group) participants were instructed to take Letrozole tablets (2.5 mg/day), calcium (1000 mg/day) and vitamin D (800 IU/day) from the third day of the first menstrual cycle following laparoscopy. Participants assigned to group 2 (Danazol group) received Danazol tablets (600 mg/day), calcium (1000 mg/day) and vitamin D (800 IU/day), whereas those in group 3 (placebo group) received 2 calcium tablets/day (500 mg each) and vitamin D (800 IU/day). All groups received medications at the same time.

Chronic pelvic pain, dysmenorrhea and dyspareunia were assessed in participants at the beginning of the study and at monthly intervals during the study for a total of six months. The severity of pain was assessed via an 11-item scale which ranged from 0 (no pain) to 10 (most severe pain). All participants were examined at monthly intervals during the six months study period by a gynecologist. During study visits, participants were asked about any improvement in endometriosis symptoms as well as side effects of the medications. Patients were given forms to record any side effects during the treatment course. Data were analyzed via SPSS version 15 software with Freidman and Wilcoxon tests.

Results

In this study, 105 participants were enrolled and randomly assigned to three groups: 38 patients in group 1 (Letrozole group), 37 patients in group 2 (Danazol group) and 31 patients in group 3 (placebo group).

Among these participants, one patient from group 1 (Letrozole group) left the study due to noncompliance with follow up visits and form completion, and four patients from group 2 (Danazol group) left due to noncompliance with the follow up visits and the androgenic effects of Danazol. In the placebo group 22 patients did not complete the study because of pelvic pain, dysmenorrhea

and treatment dissatisfaction.
Therefore, 37 patients in group 1, 33 in group 2 and 9 in group 3 completed the study.
The mean and standard deviations for age in the three groups were: 32.3 ± 6 years (Letrozole group), 31.9 ± 6.4 years (Danazol group) and 32.3 ± 5.8 years (placebo group), which was not statistically significant.
Table 1 shows endometriosis staging in the three groups. The Kolmogrov-Smirnov test did not confirm any deviation of data from the normal distribution. Friedman's test showed that the mean pain assessment test scores (dyspareunia, dysmenorrhea and chronic pelvic pain), as measured six times, decreased in each group (Fig 1-3).

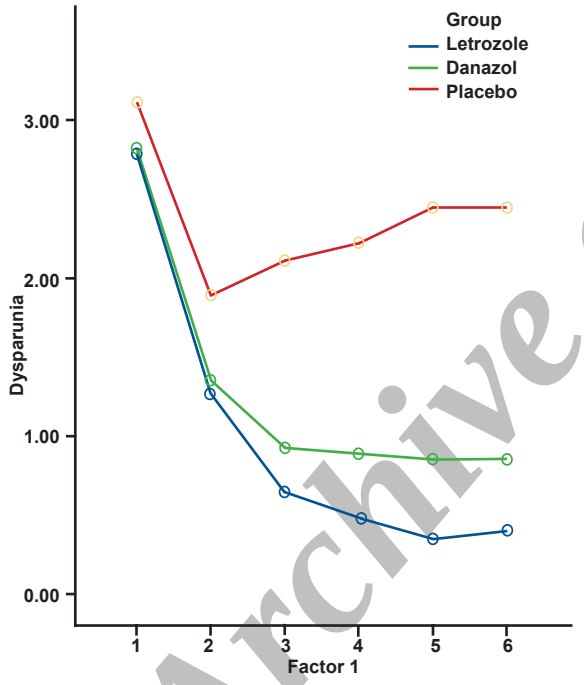

Fig 1: Dyspareunia scores at six evaluation points.

The results of this study showed that although a decrease in the mean pain scores for dyspareunia, dysmenorrhea and pelvic pain was seen initially, three months after laparoscopy the mean dysmenorrhea score began to rise in the placebo group. The Wilcoxon test showed a significant difference between the mean dysmenorrhea score at the first and fifth months after laparoscopy ($p<0.025$); however, this test also showed an increase in the mean pelvic pain score from the second month after laparoscopy, which was not significant.
By the end of the study, the mean scores for chronic pelvic pain, dysmenorrhea and dyspareunia decreased in both the Letrozole and Danazol groups.

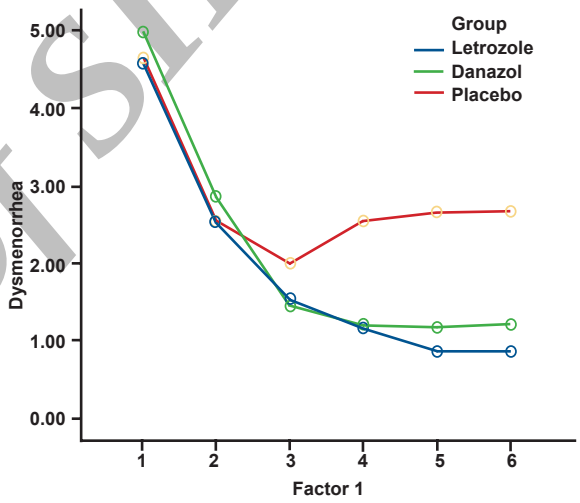

Fig 2: Dysmenorrhea scores at six evaluation points.

Among the studied groups, no significant difference was seen in the mean scores of chronic pelvic pain, dysmenorrhea and dyspareunia prior to laparoscopy and at the first month follow up.

Table 1: Mean and standard deviation of chronic pelvic pain, dysmenorrhea and dyspareunia at six measured time points

	Letrozole Group			Danazol Group			Placebo Group		
	Dysmenorrhea	Dyspareunia	Pelvic pain	Dysmenorrhea	Dyspareunia	Pelvic pain	Dysmenorrhea	Dyspareunia	Pelvic pain
Before Laparoscopy	4.58 ± 2.08	1.28 ± 2.77	1.14 ± 2.80	2.12 ± 4.66	0.60 ± 3.11	0.50 ± 3.00	2.01 ± 5.11	0.84 ± 2.88	0.48 ± 2.94
Firth month	2.52 ± 2.06	1.05 ± 1.25	1.58 ± 1.05	2.55 ± 1.42	1.88 ± 0.33	1.77 ± 0.66	3.00 ± 1.59	1.44 ± 0.61	1.55 ± 0.56
Second month	1.52 ± 1.48	0.63 ± 0.89	1.13 ± 0.96	2.00 ± 0.86	2.11 ± 0.60	1.88 ± 0.60	1.64 ± 1.09	1.05 ± 0.60	1.29 ± 0.52
Third month	1.16 ± 1.32	0.47 ± 0.77	0.88 ± 0.82	2.55 ± 0.88	2.22 ± 0.44	2.11 ± 0.60	1.27 ± 0.94	0.87 ± 0.59	1.27 ± 0.51
Fourth month	0.83 ± 1.08	0.33 ± 0.67	0.77 ± 076	2.66 ± 0.86	2.44 ± 0.52	2.11 ± 0.60	1.23 ± 0.89	0.90 ± 0.60	1.13 ± 0.50
Fifth month	0.83 ± 1.05	0.38 ± 0.80	0.80 ± 0.74	2.66 ± 0.86	2.44 ± 0.52	2.11 ± 0.60	1.24 ± 0.98	086 ± 0.58	1.10 ± 0.48
P-value	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Table 2: Incidence of drug side effects.

Side effects	Letrozole	Danazol	Placebo
Flushing	33	25	3
Headache	24	12	12
Spotting	31	5	18
Weakness	7	6	10
Greasy skin	2	18	4
Weight gain (10%)	4	14	5
Increase in appetite	6	9	3
Bone and joint pain	2	3	3
Acne	2	17	8
Hirsutism	3	24	4

Five months after therapeutic laparoscopy, patients in the Letrozole group had the lowest mean chronic pelvic pain and dyspareunia scores whereas the placebo group had the highest. The Wilcoxon test showed a significant difference among the three groups in the mean chronic pelvic pain and dyspareunia scores.

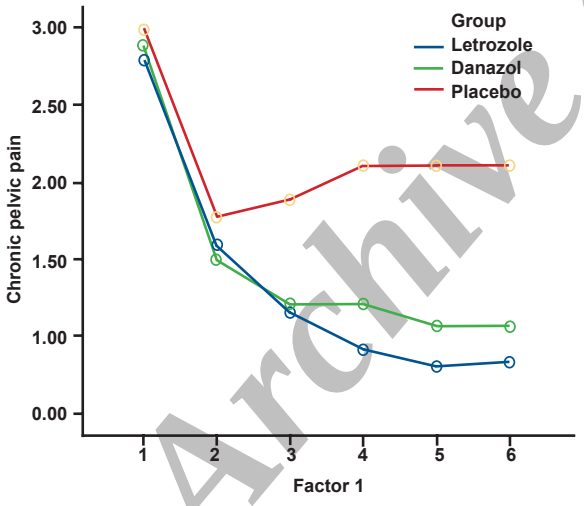

Fig 3: Chronic pelvic pain scores at six evaluation points.

At the end of the fifth month after laparoscopy, no significant difference was observed between the Danazol and Letrozole groups in mean dysmenorrhea scores ($p>0.05$) but the scores were lower in both of these groups when compared with the placebo group. No pathologic signs were seen during monthly physical examinations of the participants.

Table 2 shows a list of the side effects of Danazol, Letrozole and placebo according to forms completed by the patients.

Discussion

The results of this study demonstrated that both Danazol and Letrozole when compared with placebo can decrease pelvic pain, dysmenorrhea and dyspareunia in patients with endometriosis. In the current study therapeutic laparoscopy was done for all participants and according to the results, chronic pelvic pain, dysmenorrhea and dyspareunia were significantly decreased in all three groups. However in the placebo group an increase in pelvic pain, dysmenorrhea and dyspareunia were reported by patients two months following laparoscopy. Although, after the six months follow up period, these symptoms did not reach the baseline level in the placebo group. Jacobson et al. in a study in 2009, has confirmed this result (14).

Our study showed the symptoms of dysmenorrhea, dyspareunia and chronic pelvic pain in the Letrozole group were less than the Danazol group, although this difference was not significant for dysmenorrhea.

Several studies have been performed to evaluate the efficacy of Danazol and Letrozole. A study by Ferrero et al. has demonstrated that Letrozole can significantly reduce chronic pelvic pain and dyspareunia during a six-month treatment course (10). The main complaints by patients in this group have been the Danazol side effects such as flushing, headache, spotting and high treatment costs.

Nothnick and Zhang in a review article introduced aromatase inhibitors, particularly Danazol, as a new generation of medications for the treatment of endometriosis (15). Verma and Konje, in 2009, have reported that Letrozole is

an efficient treatment with minimal side effects for endometriosis (6).

Selak et al. in a meta-analysis have reported the effectiveness of Danazol for endometriosis symptom relief, however its use has been limited due to androgenic side effects (16) .

Danazol has been introduced as the gold treatment for endometriosis during the 1990's (12).

Until now, no study has compared Danazol with Letrozole in the treatment of endometriosis. Our study is the first comparative study on the effects of these two medications.

The results of our study showed more hypoestrogenic side effects such as flushing and spotting in the Letrozole group and more androgenic side effects such as greasy skin, acne and hirsutism in the Danazol group which have also been confirmed by numerous other studies.

Some previous studies have suggested that long term use of Letrozole alone may increase the risk of ovarian cyst (2). In the current study, Letrozole was used alone but no ovarian cysts were seen in group 1 patients. One probable reason for this finding is that although our patients were examined monthly during the study, the small size of ovarian cysts may not be detectable in physical examination.

Another side effect of treatment with Letrozole and Danazol is the decrease in bone mineral density (2). In our study, participants received daily calcium and vitamin D supplements as prophylaxis, but bone densitometry was not performed.

Razzi et al. in their case report have suggested that the concomitant use of calcium and vitamin D with Letrozole can prevent a decrease in bone mineral density (17).

The results of the current study showed that laparoscopic treatment causes significant reduction in the symptoms of endometriosis. However if it is followed by Danazol or Letrozole administration, symptom relief will be enhanced. In this study, the symptoms of endometriosis were not assessed after discontinuation of treatment.

Our study concluded that Letrozole compared with Danazol had a better effect on the symptom relief in patients with endometriosis. Although patients in the Letrozole group complained of spotting, those in the Danazol group faced many serious problems due to the androgenic side effects of Danazol.

We suggest more widespread studies and follow up evaluations of endometriosis symptoms, after treatment discontinuation.

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