**DOI:** https://doi.org/10.54393/pjhs.v3i06.345

PAKISTAN JOURNAL OF HEALTH SCIENCES

https://thejas.com.pk/index.php/pjhs

Volume 3, Issue 6 (November 2022)

**Original Article**

# Comparison of the Efficacy of Letrozole Versus Danazol in Pain Relief in Endometriosis

**Sundus Nawaz[1], Sadia Habib[1*], Saba Ayoub[1], Ghazala Shams[2], Nimra Naeem[1] and Ruqiya Sultana[1]**

[1]Department of Obstetrics & Gynaecology, Ayub medical Teaching Institute (AMTI), Abbottabad, Pakistan
[2]Department of Obstetrics & Gynaecology, Hayatabad Medical Complex, Peshawar, Pakistan

## ARTICLE INFO

***Key Words:***
Endometriosis, Danazol, Letrozole, Pelvic Pain.

***How to Cite:***
Nawaz, S. ., Habib, S. ., Ayoub, S. ., Shams, G. ., Naeem, N. ., & Sultana, R. . (2022). Comparison of The Efficacy of Letrozole Versus Danazol in Pain Relief in Endometriosis: Efficacy of Letrozole and Danazol in Endometriosis. Pakistan Journal of Health Sciences, 3(06). https://doi.org/10.54393/pjhs.v3i06.345

***Corresponding Author:**
Sadia Habib
Department of Obstetrics & Gynaecology, Ayub Medical College, Abbottabad.
*sadiazeb@yahoo.com*

Received Date: 11th November, 2022
Acceptance Date: 26th November, 2022
Published Date: 30th November, 2022

## ABSTRACT

Endometriosis is a chronic inflammatory disease defined as the presence of endometrium-like tissue outside the uterus which is responsive to the estrogen levels in blood circulation. **Objective:** To compare the efficacy of letrozole versus danazol in pain relief in endometriosis. **Methods:** This randomized controlled trial was conducted at the department of Obstetrics & Gynecology, Ayub Teaching Hospital, Abbottabad, Pakistan from January 2018 to December 2021. Patients diagnosed with endometriosis were enrolled and detailed medical history was taken. Patients were randomly divided into either Letrozole (n=120) or Danazol (n=120) group. Both treatment groups were evaluated after 3 months of treatment and efficacy was compared in terms of pain relief in patients of endometriosis. **Results:** In a total of 240 patients, the mean age was 28.30±4.76 years. The mean endometrial cyst size was 2.48±1.14 cm. At baseline, mean visual analog scale (VAS) score was recorded as 5.46±1.09 points in letrozole group and 5.28±1.01 points in danazol group (p=0.186). After three months of treatment, the mean VAS score was 2.94±1.96 points in letrozole group and 3.99±1.90 points in danazol group (p=0.002). Relief of symptoms was observed in 114 (47.5%) women and more patients reported relief of symptoms in letrozole group (65 patients) than the danazol group (49 patients) (p=0.039). **Conclusion:** Letrozole was more effective as compare to danazol in relief of pain in patients with endometriosis.

## INTRODUCTION

Endometriosis is considered to be a frequent gynecological issue and described as the existence of endometrial tissue present outside the uterus and cause various symptoms like infertility, chronic pelvic pain and cyclic menstrual cramps [1]. Literature reports the prevalence of endometriosis between 2-10% among females of general population but its proportions soars up to 50% among infertile females [2, 3]. Although the exact mechanisms by which the disease causes its occurrence, the pathophysiology and its progression are not yet clear. However, it has been well established now that endometriosis responds to estrogen exposure and its levels in blood. Its growth and regression have been found to be estrogen-dependent [4, 5]. Aromatase and 17b-hydroxysteroid dehydrogenase type 1 have been found to be present in endometriotic implants. These enzymes are responsible for the conversion of androstenedione to estrone and estrone to estradiol, respectively [6]. The control of symptoms of endometriosis, particularly the pain relief is very crucial in improving the quality of life including education and work, sex, intimacy and emotional wellbeing [2, 3]. More than 50% women having chronic pelvic pain secondary to or associated with endometriosis do not respond to current medications that decrease the effect of estrogen on the body. Endometriosis has been known to have recurred even after conservative surgery and these recurrences are associated with pain which is resistant to repeated surgical attempts to find a cure [7]. The presence of endometriosis in menopause or its re-emergence despite treatment with estrogen production

**DOI:** https://doi.org/10.54393/pjhs.v3i06.345

inhibitors such as gonadotropin-releasing hormone (GnRH) agonists, there appears to be another source of estrogen production [8]. Studies shown that estrogen is produced in nearby tissues such as skin and adipose tissue [9]. Current treatment goal (e.g. combined oral contraceptives, Depo-Provera, oral progestins, danazol and GnRH agonists) is to induce hypo-estrogenism or to counteract estrogen action. The adverse effects of danazol and the reported increase in the initial risk of ovarian cancer actually made its use obsolete [10]. As discussed above, surgical treatments are usually not appropriate for all patients, and they also fail to provide symptomatic relief in majority of patients [6]. Letrozole is a 3rd generation non-steroidal aromatase inhibitor that produces selective aromatase inhibition. It causes a significant decrease in the body's total estrogen and has become a standard cancer care estrogen receptor positive [2, 11]. The purpose of this study was to compare the efficacy of Letrozole with that of Danazol with respect to provision of pain relief in women with diagnosed endometriosis and evaluate the efficacy of letrozole and danazol in terms of reducing symptoms of chronic endometriosis.

## METHODS

After getting ethical approval from institutional review board (IRB) of Ayub Teaching Hospital Abbottabad, this randomized controlled trial was conducted at the department of Obstetrics & Gynecology from January 2018 to December 202. After informed consent, a total of 240 patients diagnosed with endometriosis were enrolled. Sample size is calculated from the WHO sample size by the following parameters; the efficacy of letrozole as 75% and the efficacy of danazol as 60%, level of significance 5% and power of test was 80% [8]. The non-probability consecutive sampling technique was used for patients' selection. All women between the age of 20-40 years who had been diagnosed as having endometriosis either radiographically or on laparoscopic examination and were having persistent endometriosis related pain including dysmenorrhea that persisted or recurred after one or more previous treatments or surgery and/or GnRH agonists and having endometrial cyst size less than 5cm were included in this study. Women who were treated successfully by other medical treatment options including GnRH agonists, oral contraceptive pills and progestins were excluded from the study. The investigator thoroughly gone through the case history, physical examination and routine investigations. Patients were randomly assigned to the letrozole (A) group and the danazol (B) group electronically. Random sequencing numbers generated electronically by biostatistician and distribution were sealed in light envelopes to ensure encryption. The data was collected on predesigned patient proforma which included 0-10cm visual analogue scale (VAS) as subjective measure. In letrozole group patients were administered per oral route letrozole 2.5 mg/day whereas, patients in danazol group were administered per oral route danazol 600 mg/day. Patients were called for follow-up after three months of treatment with either drug and they were asked to record their responses on VAS scale. Patients' response on the VAS scale were recorded at baseline (0 month) and at the end of treatment (3rd month) as shown in figure 1. Data analysis was performed with version 21 of SPSS. Data validity was assessed by the Shapiro-Wilk test for general and similarity, based on which parametric or nonparametric test was used to determine within the group and for all group differences in the two groups. To determine the effectiveness of the two groups the chi square test was applied. The confounding variables such as age, VAS score and endometrial cyst size were controlled by stratification. An independent sample t-test of post stratification was used. The value of $p \leq 0.05$ was considered significant.

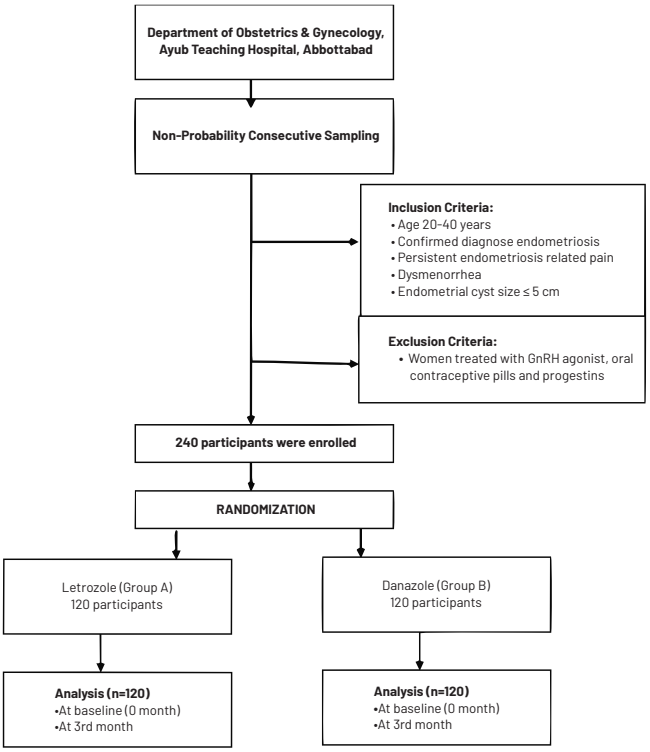


**Figure 1:** Consort diagram

## RESULTS

In a total of 240 patients, the mean age of the patients was 28.30±4.76 years with minimum 20 years and maximum 36 years of age. The mean endometrial cyst size was 2.48±1.14 cm with minimum 1cm and maximum 4cm. Relief of symptoms was observed in 114/240 (47.5%) and treatment was found efficacious in 54.2% (n=65/120) of patients in group A (Letrozole) and in 40.8% (n=49/120) of patients in

DOI: https://doi.org/10.54393/pjhs.v3i06.345

group B (Danazol).

| Efficacy of drug used | Groups | | Total | p value* |
|---|---|---|---|---|
| | Letrozole (A) | Danazol (B) | | |
| Yes | 65 (54.2%) | 49 (40.8%) | 114 (47.5%) | 0.039 |
| No | 55 (45.8%) | 71 (59.2%) | 126 (52.5%) | |
| Total | 120 | 120 | 240 | |

**Table 1:** Efficacy of treatment according to the drug used in both groups, n=240. *Chi square test

At baseline, mean VAS score was recorded as 5.46±1.09 points in letrozole group and 5.28±1.01 points in danazol group (p=0.186). After three months of treatment, the mean VAS score was 2.94±1.96 points in letrozole group and 3.99±1.90 points in danazol group (p=0.002). Mean VAS score recorded in both groups at baseline and at the end of treatment (3rd month), Table 2.

| VAS score | Letrozole group | Danazol group | p value* |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| At baseline | 5.46 ± 1.09 | 5.28 ± 1.01 | 0.186 |
| At 3rd month | 2.94 ± 1.96 | 3.99 ± 1.90 | 0.002 |

**Table 2:** VAS score for pain reported by patients before and after treatment in both groups, n=240. *Independent sample t test

Patients with an endometrial cyst size 1cm or less were 64 (26.67%), cyst size between 1-2cm were 56 (23.33%), and with cyst size between 2-3 and 3-4 cm were 60 (25%) each. The association between drug's efficacy and the endometrial cyst size was measured, Table 3.

| Efficacy of drug used | Endometrial Cyst size in cm | | | | Total | p value* |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | | |
| Yes | 32 | 27 | 27 | 28 | 114 | 0.953 |
| No | 32 | 29 | 33 | 32 | 126 | |
| Total | 64 | 56 | 60 | 60 | 240 | |

**Table 3:** Endometrial Cysts size in both groups, n=240. *Chi square test

## DISCUSSION

This study enrolled 240 patients who were diagnosed with endometriosis. Patients' assessment of pelvic pain was recorded at the end of third month of treatment on VAS scale. Treatment was considered effective if the responses recorded on the VAS had a maximum score of 3. In the letrozole group, 54.2% patients reported a decrease in the symptoms of endometriosis i.e., chronic pelvic pain and cyclic menstrual pain. Whereas, 45.8% patients did not report any improvement in pain associated with endometriosis. In the danazol group 40.8% patients reported a symptomatic relief while the symptoms of endometriosis were not relieved in 59.2% patients. A p value of 0.039 was obtained which was significant. There was no significant association between endometrial cyst size and the efficacy of drugs in relieving the symptoms. Ferrero et al conducted a comprehensive research to identify studies that evaluated the efficacy of aromatase inhibitors. They noted that progestogens or contraceptive reduce the severity of symptoms and improve quality of life. Letrozole was found to be more effective when administered in combination with another drug than alone. However, when administered along with the gonadotropin-releasing hormone analogue, it significantly reduced the recurrence of symptoms [12]. A randomized controlled trial by Rasul et al reported from Pakistan that letrozole was more effective than danazol in providing symptomatic relief to patients with confirmed endometriosis. They enrolled patients with confirmed endometriosis. They concluded that the most common points of chronic pelvic pain, dysmenorrhea and dyspareunia among letrozole group were less than danazol groups [13]. Earlier, similar results had been reported by Roghaei et al who studied the effects of letrozole on refractory endometriosis and chronic pelvic pain in premenopausal women [14]. They noted that aromatase inhibitors were beneficial in treating chronic pelvic pain due to refractory endometriosis and that these drugs had no negative effect on the fertility. This study also found that letrozole was superior to danazol in providing symptomatic relief to patients diagnosed with endometriosis, though no effort was made to determine its effect on the fertility of the patient. Also, no comparison was done between the side effects caused by danazol and letrozole. Almassinokiani et al treated women with either oral contraceptive pills or a combination of letrozole and OCP. With a baseline VAS score of at least 5, these women were treated for 4 months after which they were re-assessed. The researchers noted that there was a comparable effectiveness in both treatment modalities and that letrozole did not affect the outcomes [15]. These results are in contrast to other reports from the same region which showed that letrozole was both effective and superior to other drugs in treating pain associated with endometriosis [16]. A systematic review by Goenka et al concluded that aromatase inhibitors have a promising role in pain with endometriosis but because of shortage of evidence, this association is not strong enough [17]. Interestingly, a randomized controlled trial reported that letrozole was better as gonadotropin releasing hormone inhibitors in reducing the volume of endometriotic tissue and in controlling the symptoms [18]. Patients received oral letrozole (2.5 mg/day) or gonadotropin-releasing hormone agonist (goserelin, 3.6mg) for 12 weeks. Uterine volume and adenomyoma were determined at baseline and during treatment at 4, 8 and 12 weeks. At the end of the study, no significant differences were found. In this study, there was a significant difference in the symptomatic relief provided by both letrozole and danazol. The results of this study confirm earlier findings by many researchers, yet there are conflicting reports [19, 20]. However, as a first ever study of its kind in this region, the results of this study are

**DOI:** https://doi.org/10.54393/pjhs.v3i06.345

promising, thereby indicating a need for a large-scale trial to confirm these findings.

## CONCLUSIONS

Efficacy of letrozole was found better than danazol for treatment of endometriosis. Letrozole an aromatase inhibitor has shown promising results for providing symptomatic relief to patients with endometriosis.

## Conflicts of Interest

The authors declare no conflict of interest

## Source of Funding

The author(s) received no financial support for the research, authorship and/or publication of this article

## REFERENCES

[1] Kim SH, Chae HD, Kim CH, Kang BM. Update on the treatment of endometriosis. Clinical and experimental reproductive medicine. 2013 Jun; 40(2):55. doi: 10.5653/cerm.2013.40.2.55

[2] Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, et al. ESHRE guideline: endometriosis. Human reproduction open. 2022; 2022(2): hoac009. doi: 10.1093/hropen/hoac009

[3] Kuznetsov L, Dworzynski K, Davies M, Overton C. Diagnosis and management of endometriosis: summary of NICE guidance. Bmj. 2017 Sep; 358. doi: 10.1136/bmj.j3935

[4] Madny EH. Efficacy of letrozole in treatment of endometriosis-related pain. Middle East Fertility Society Journal. 2014 Mar; 19(1):64-8. doi: 10.1016/j.mefs.2013.04.007

[5] Morotti M, Vincent K, Becker CM. Mechanisms of pain in endometriosis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017 Feb; 209: 8-13. doi: 10.1016/j.ejogrb.2016.07.497

[6] Maddern J, Grundy L, Castro J, Brierley SM. Pain in endometriosis. Frontiers in Cellular Neuroscience. 2020 Oct 6; 14: 590823. doi: 10.3389/fncel.2020.590823

[7] Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. Obstetrics and gynecology. 2015 Mar; 125(3): 719. doi: 10.1097/AOG.0000000000000663

[8] Zhao Y, Gong P, Chen Y, Nwachukwu JC, Srinivasan S, Ko C, Bagchi MK, et al. Dual suppression of estrogenic and inflammatory activities for targeting of endometriosis. Science translational medicine. 2015 Jan; 7(271): 271ra9. doi: 10.1126/scitranslmed.3010626

[9] Garzon S, Laganà AS, Barra F, Casarin J, Cromi A, Raffaelli R, et al. Aromatase inhibitors for the treatment of endometriosis: a systematic review about efficacy, safety and early clinical development. Expert Opinion on Investigational Drugs. 2020 Dec; 29(12): 1377-88. doi: 10.1080/13543784.2020.1842356

[10] Bedaiwy MA, Allaire C, Yong P, Alfaraj S. Medical management of endometriosis in patients with chronic pelvic pain. InSeminars in reproductive medicine 2017 Jan; 35(1): 038-053. Thieme Medical Publishers. doi: 10.1055/s-0036-1597308

[11] Stauffer F, Furet P, Floersheimer A, Lang M. New aromatase inhibitors from the 3-pyridyl arylether and 1-aryl pyrrolo [2, 3-c] pyridine series. Bioorganic & medicinal chemistry letters. 2012 Mar; 22(5): 1860-3. doi: 10.1016/j.bmcl.2012.01.076

[12] Ferrero S, Gillott DJ, Venturini PL, Remorgida V. Use of aromatase inhibitors to treat endometriosis-related pain symptoms: a systematic review. Reproductive Biology and Endocrinology. 2011 Dec; 9(1):1-0. doi: 10.1186/1477-7827-9-89

[13] Rasul SG, Yaqub U, Manzoor M, Mubasshar H. Comparison of Letrozole versus Danazol for the Pain Management of Females Presented with Endometriosis. Annals of King Edward Medical University. 2017 Oct; 23(4): 514-8. doi: 10.21649/akemu.v23i4.2231

[14] Roghaei MA, Ghasemi Tehrany H, Taherian A, Koleini N. Effects of letrozole compared with danazol on patients with confirmed endometriosis: a randomized clinical trial. International Journal of Fertility and Sterility. 2010 Jul; 4(2): 67-72. https://dx.doi.org/10.22074/ijfs.2010.45826

[15] Almassinokiani F, Almasi A, Akbari P, Saberifard M. Effect of Letrozole on endometriosis-related pelvic pain. Medical Journal of the Islamic Republic of Iran. 2014; 28: 107.

[16] Barra F, Scala C, Mais V, Guerriero S, Ferrero S. Investigational drugs for the treatment of endometriosis, an update on recent developments. Expert opinion on investigational drugs. 2018 May; 27(5): 445-58. doi: 10.1080/13543784.2018.1471135

[17] Goenka L, George M, Sen M. A peek into the drug development scenario of endometriosis–A systematic review. Biomedicine & Pharmacotherapy. 2017 Jun; 90: 575-85. doi: 10.1016/j.biopha. 2017.03.092

[18] Badawy AM, Elnashar AM, Mosbah AA. Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial. Acta Obstetricia et Gynecologica Scandinavica. 2012 Apr; 91(4): 489-95. doi: 10.1111/j.1600-0412.2012.01350.x

[19] Seal SL, Kamilya G, Mukherji J, De A, Ghosh D, Majhi

**DOI:** https://doi.org/10.54393/pjhs.v3i06.345

AK. Aromatase inhibitors in recurrent ovarian endometriomas: report of five cases with literature review. Fertility and sterility. 2011 Jan; 95(1): 291-e15. doi: 10.1016/j.fertnstert.2010.05.021

[20] Ailawadi RK, Jobanputra S, Kataria M, Gurates B, Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertility and sterility. 2004 Feb; 81(2): 290-6. doi: 10.1016/j.fertnstert.2003.09.029