E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.01.683

Research Article

Comparison of Letrozole versus Danazole for Pain Management in Females Presenting with Endometriosis

Sidra Salman[1*], Hadia Zulfiqar[2], Iqra Ashraf[3], Anees Fatima[4], Ghazia Shahid[5], Zahida Zakir[6]
[1*]Senior Registrar, Department of Obstetrics and Gynaecology, Al Nafees Medical College and Hospital Islamabad, Isra University, Islamabad, Pakistan.
[2]Senior Registrar, Department of Gynecology and Obstetrics, Sharif Medical and Dental College, Lahore, Pakistan.
[3]Consultant, Department of Gynecology and Obstetrics, Rahat Health Care, Gakhar Gujranwala, Pakistan.
[4]Assistant Professor, Departm.ent of Gynecology and Obstetrics, Sharif Medical and Dental College, Lahore, Pakistan
[5]Senior Registrar, Department of Gynaecology and Obstetrics, Al Nafees Medical College and Hospital Islamabad, Isra University, Islamabad, Pakistan.
[6]Consultant, Department of Gynaecology and Obstetrics, RHC Bara Ghar, Nankana Sahib, Pakistan.
Corresponding Author: Sidra Salman
Senior Registrar, Department of Obstetrics and Gynaecology, AL Nafees Medical College and Hospital Islamabad, Isra University, Islamabad, Pakistan.
Email: dr.sidi@yahoo.com
Received: 28.03.2026, Revised: 29.05.2026, Accepted: 11.06.2026

ABSTRACT
Background: Endometriosis is a chronic gynecological condition defined by the ectopic presence of endometrial glands and stroma outside the uterine cavity, most commonly diagnosed via laparoscopy. While its exact etiology remains uncertain, a positive family history is considered a significant risk factor. Danazol has historically demonstrated efficacy in alleviating endometriosis-related pain, while letrozole, primarily used in neoadjuvant settings, has recently emerged as a promising alternative. This study aimed to compare the mean reduction in pain scores between letrozole and danazol in women with laparoscopically confirmed endometriosis.
Objective: To compare the efficacy of letrozole versus danazol in reducing pain scores among women diagnosed with endometriosis.
Material & Methods: A randomized control trial was conducted at Department of Obstetrics & Gynaecology, Sharif Medical and Dental Hospital for the duration of 2.5 years, from April 2019 to October 2021. This randomized controlled trial included 60 women with endometriosis, allocated randomly and equally into two groups (n=30 each). After obtaining informed consent and recording baseline demographics, pain scores were assessed using the Visual Analogue Scale (VAS). Group A received letrozole (2.5 mg/day) starting on the third day of the menstrual cycle for three months, while Group B received danazol (600 mg/day) for the same duration. Pain scores were re-evaluated at three months, and the mean change was compared between the groups.
Results: Baseline pain scores were comparable between the letrozole (6.20±1.60) and danazol (6.40±1.10) groups (p=0.576). After three months, the mean reduction in pain scores was significantly greater in the letrozole group (2.20±1.45) than in the danazol group (1.27±1.11) (p=0.007).
Conclusion: Letrozole was significantly more effective than danazol in reducing endometriosis-associated pain after three months of treatment.

Keywords: Letrozole, Danazol, Endometriosis, Pain.

INTRODUCTION

Endometriosis is defined by the ectopic presence of functional endometrial glands and stroma outside the uterine cavity, most commonly diagnosed via direct laparoscopic visualization (1). Clinical manifestations include dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility—each of which may significantly impair a woman's quality of life (2). It is a chronic, estrogen-dependent inflammatory condition predominantly affecting women of reproductive age, though adolescents may also be affected (3). Its true prevalence remains uncertain due to underdiagnosis and a diagnostic delay averaging nearly a decade, often attributed to

normalization of symptoms and missed recognition by primary care providers. Beyond physical symptoms, endometriosis exerts a profound psychosocial and economic burden on affected individuals, their families, and healthcare systems globally (4).

Pathophysiology and Clinical Impact of Ectopic Endometrial Tissue in Endometriosis

Ectopic endometrial tissue typically localizes in the dependent regions of the pelvis, such as the posterior and anterior cul-de-sac, uterosacral ligaments, ovaries, and fallopian tubes; however, extra-pelvic involvement is also possible (5). These implants respond to cyclic hormonal stimulation much like eutopic endometrium, undergoing phases of proliferation, secretion, and subsequent shedding. The metabolic by-products especially cytokines and prostaglandins foster a chronic inflammatory milieu characterized by neovascularization, fibrosis, and pain sensitization. Immunologic dysregulation is also implicated, including aberrant T- and B-cell responses, complement system activation, and elevated interleukin-6 (IL-6) levels in affected individuals. These immunoinflammatory mechanisms lead to adhesion formation, anatomic distortion, and chronic pelvic pain which are the hallmark features of the disease (5).

Classification of Endometriosis

Endometriosis can be classified into three main types based on lesion location. Superficial peritoneal endometriosis is the most common form, characterized by lesions affecting the peritoneum, the thin membrane lining the pelvic cavity. Endometriomas, or ovarian lesions, are dark, fluid-filled cysts ("chocolate cysts") that develop within the ovaries, often resistant to treatment and capable of damaging healthy ovarian tissue. Deeply infiltrating endometriosis extends beneath the peritoneal surface and may involve adjacent pelvic organs such as the bowel or bladder, occurring in approximately 1% to 5% of affected women (6). (Figure 1) (7).

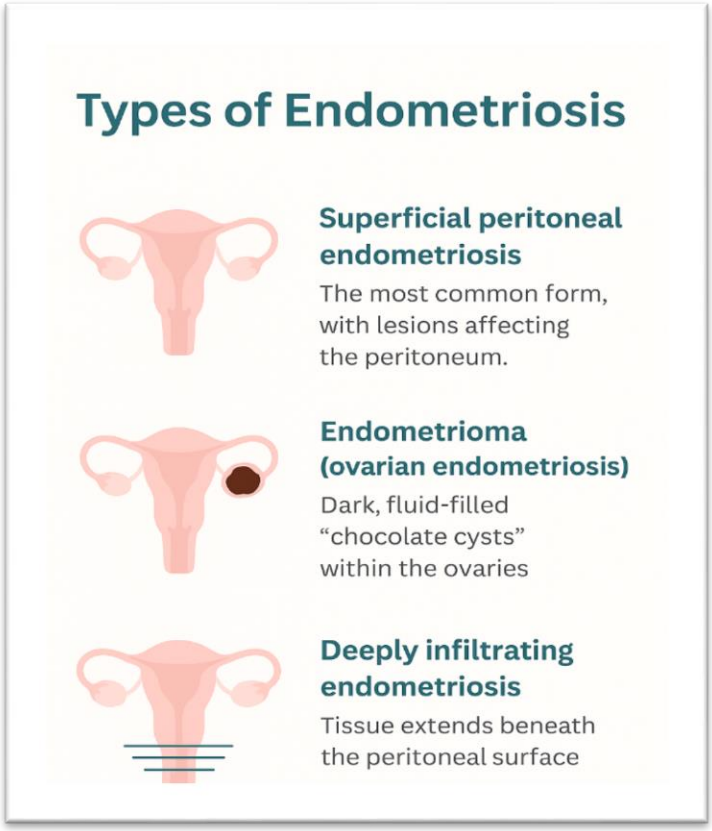

Figure 1: An Illustration that is an overview of the three primary types of endometrioses based on lesion location: superficial peritoneal lesions, ovarian endometriomas, and deeply infiltrating endometriosis (7).

Comparative Evaluation of Letrozole and Danazol for Pain Reduction in Females with Endometriosis

Despite varied symptoms, endometriosis diagnosis is often delayed due to the absence of reliable non-invasive biomarkers. Current hormone therapies and analgesics offer limited long-term efficacy, as recurrence is common. Letrozole, an aromatase inhibitor, competitively binds to the cytochrome P450 subunit, reducing estrogen biosynthesis and offering a novel approach to managing endometriosis (8). Letrozole, an aromatase inhibitor, has demonstrated effectiveness in reducing endometriosis-related pain without recurrence post-treatment (9). Danazol, a synthetic androgen, suppresses ovarian activity and modulates immune function but has shown inconsistent results in pain management across studies (10). Although hormone therapies such as letrozole and danazol are widely used for symptom management, existing literature reports conflicting evidence regarding their effectiveness in reducing endometriosis-related pain. The present study seeks to answer the research question: **"**Among females diagnosed with endometriosis, how does the reduction in pain scores with letrozole therapy compare to danazol therapy over a three-month period, and which agent offers more consistent and sustained pain relief to inform standardized treatment protocols?" Addressing this question may improve patient outcomes in management of pain. So, this study aims to compare letrozole with danazol's impact on pain reduction in females with endometriosis, to guide future treatment protocols and update local clinical guidelines.

MATERIAL AND METHODS

Study Design and Setting: This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Sharif Medical and Dental Hospital, Lahore, over 2.5 years (April 10 2019 to October 10, 2021), following approval from the institutional ethics review board (IRC No. SMDC/SMRC/79-18) and Clinical Trail number NCT07183787.

Sample Size and Sampling Technique: A total of 60 females (30 per group) were enrolled, calculated at a 95% confidence level, 90% power, and using expected mean reductions in pain score (1.03±1.09 with letrozole and 3.07±1.23 with danazol. Participants were randomly assigned to groups using the lottery method, with allocation concealment ensured through sealed, opaque envelopes (11).

Inclusion Criteria:

- Females aged 20–40 years of any parity presenting with endometriosis (as per operational definition).

Exclusion Criteria:

- Renal impairment (creatinine >1.2 mg/dl), hepatic dysfunction (ALT/AST >40 IU), anemia (Hb <10 mg/dl), cardiac disease.
- Ovarian cysts >2 cm, recent hormone therapy (past three months), osteopenia, pregnancy, or known hypersensitivity to letrozole or danazol.

Data Collection Procedure: Following informed consent, demographic data (age, marital status, parity, BMI) were recorded. Participants were randomized into two equal groups. Group A received letrozole (2.5 mg/day) starting from the third day of the menstrual cycle for three months. Group B received danazol (600 mg/day) for the same duration. Pain scores were evaluated using the Visual Analogue Scale (VAS) at baseline and after three months. All data were entered into a predesigned proforma.

Blinding: This was a single-blinded trial. Although participants and prescribing physicians were aware of treatment allocation due to the nature of the medications, outcome assessment was blinded. Pain scores were recorded by a trained nurse who was unaware of group assignment. Data analysis was performed on anonymized, coded datasets to reduce detection and analysis bias.

Data Analysis: Data were analyzed using SPSS version 21. Quantitative variables (age, BMI, symptom duration, pain scores) were expressed as means ± standard deviations. Categorical variables (marital status, parity) were presented as frequencies and percentages. The Independent Sample t-test was used to compare the mean reduction in pain scores between groups. A p-value <0.05 was considered statistically significant. Stratification was performed for age, BMI, marital status, parity, symptom duration, and educational status, followed by post-stratification analysis using the same statistical test.

RESULTS

A total of 60 patients were enrolled, with a mean age of 28.25±4.65 years (range: 20–40 years). In the letrozole group, the mean age was 28.60±3.76 years, while in the danazol group it was 27.90±5.45 years. The mean BMI of all patients was 23.02±3.18 kg/m² (range: 18–32 kg/m²) (Table 3). The mean BMI was similar between groups: 22.93±2.97 kg/m² for letrozole and 23.10±3.43 kg/m² for danazol. Among the participants, 90% (n=54) were married, 6.67% unmarried, and 3.33% separated. In group-wise distribution, 86.7% in the letrozole group and 93.3% in the danazol group were married. Regarding parity, 50% of letrozole group patients and 60% of danazol group patients were nulliparous or had primary parity, while the rest had multiple parity (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Patients

Variable	Letrozole Group (n=30)	Danazol Group (n=30)
Age (years)	28.60 ± 3.76	27.90 ± 5.45
BMI (kg/m²)	22.93 ± 2.97	23.10 ± 3.43
Marital Status – Married	86.7%	93.3%
Marital Status – Unmarried	10%	3.3%
Parity - Nulliparous/Primary	50%	60%
Parity - Multiparous	50%	40%
Duration of Symptoms (months)	11.47 ± 10.60	8.33 ± 6.49

Assessment of Baseline Pain Scores, Symptom Duration, and Treatment Outcomes in Letrozole and Danazol Groups

The mean duration of symptoms was longer in the letrozole group (11.47±10.60 months) compared to the danazol group (8.33±6.49 months). Baseline mean pain scores were comparable: 6.20±1.60 in the letrozole group and 6.40±1.10 in the danazol group (p-value0.576). After three months, mean pain scores reduced to 4.37±2.04 with letrozole and 5.10±1.32 with danazol, with no significant difference (p-value0.104). The mean reduction in pain was significantly greater in the letrozole group (2.20±1.45) compared to the danazol group (1.27±1.11) (*p*-value =0.007) (Table 2).

Table 2: Pain Scores at Baseline and After Treatment

Time Point	Letrozole Group (Mean ± SD)	Danazol Group (Mean ± SD)	*p*-value
Baseline Pain Score	6.20 ± 1.60	6.40 ± 1.10	0.576
After 3 Months Pain Score	4.37 ± 2.04	5.10 ± 1.32	0.104
Mean Reduction in Pain Score	2.20 ± 1.45	1.27 ± 1.11	0.007

Comparative Effectiveness of Letrozole and Danazol on Pain Reduction across Clinical and Demographic Variables in Endometriosis

Among patients aged ≤30 years, letrozole demonstrated a significantly greater reduction in pain scores compared to danazol (2.52±1.41 vs. 1.22±1.16; p-value0.001), whereas in patients aged >30 years, no statistically significant difference was observed between the two treatments (p-value0.611). Similarly, in patients with a BMI ≤25 kg/m², pain reduction was significantly higher with letrozole (2.45±1.40) compared to danazol (1.13±1.18; p-value0.001), while for those with a BMI >25 kg/m², the difference was not significant (p-value0.726).

When stratified by symptom duration, no significant difference in pain reduction was observed in patients with symptoms lasting ≤12 months (p-value0.069); however, among those with symptom duration >12 months, letrozole showed a significantly greater reduction in pain compared to danazol (p-value0.032). In terms of parity, nulliparous and primary parity patients experienced significantly greater pain reduction with letrozole (2.40±1.35) compared to danazol (1.00±1.23; p-value0.004), whereas no significant difference was noted among multiparous patients (p-value0.506).

Marital status also influenced outcomes, with married patients in the letrozole group showing a significantly greater reduction in pain scores compared to those receiving danazol (p-value0.010). Educational status revealed similar trends; among patients educated up to middle school, letrozole provided significantly greater pain relief (2.64±1.69) than danazol (1.20±1.00; p-value0.022), whereas no significant difference was found among patients with matriculation or higher education (p-value0.289) (Table 3)

Table 3: Subgroup Analysis of Pain Score Reduction

Subgroup	Letrozole (Mean ± SD)	Danazol (Mean ± SD)	*p*-value
Age ≤30 years	2.52 ± 1.41	1.22 ± 1.16	0.001
Age >30 years	1.14 ± 1.06	1.43 ± 0.97	0.611
BMI ≤25 kg/m²	2.45 ± 1.40	1.13 ± 1.18	0.001
BMI >25 kg/m²	1.50 ± 1.41	1.71 ± 0.76	0.726
Symptom Duration ≤12 months	2.00 ± 1.44	1.33 ± 1.11	0.069
Symptom Duration >12 months	3.00 ± 1.26	0.67 ± 1.15	0.032
Nulliparous/Primary Parous	2.40 ± 1.35	1.00 ± 1.23	0.004
Multiparous	2.00 ± 1.55	1.67 ± 0.77	0.506

DISCUSSION

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial tissue outside the uterine cavity, most commonly on the peritoneal surfaces. Although there is no definitive cure, the condition can be effectively managed through a combination of analgesics, hormonal therapies, and surgical interventions (8).

In the present study, the baseline mean pain score was 6.20±1.60 in the letrozole group and 6.40±1.10 in the danazol group (p-value0.576). After three months of treatment, the mean reduction in pain was significantly greater in the letrozole group (2.20±1.45) compared to the danazol group (1.27±1.11) (p-value0.007) as mentioned in results section.

Several previous studies support and also oppose these findings. One study reported a mean reduction in pain score of 3.42±0.76 with letrozole, whereas danazol was associated with an increase in pain score (0.43±3.78), indicating that danazol may not effectively reduce endometriosis-related pain and, in some cases, may worsen it (11).

Similarly, Asma Qayyum et al. conducted a study evaluating danazol versus letrozole for endometriosis management. Their findings demonstrated a significant decrease in mean pain scores, from 4.44±1.73 at baseline to 2.40±1.04 after three months of treatment, with a mean reduction of 20.4±1.54 (p-value0.00), favoring letrozole (12).

Conversely, Ferrero et al., in a study involving 26 patients with endometriosis, showed that danazol significantly reduced chronic pelvic pain over a three-month period, with mean baseline VAS scores decreasing from 6.0±1.3 to 3.4±1.8, and an average reduction of 2.6±0.5 (13).

In a study by Roghaei et al., danazol and letrozole were compared among 38 patients with endometriosis. The mean pelvic pain score at baseline was 1.14±2.80 in the letrozole group and 0.50±3.00 in the danazol group. After three months of treatment, the mean pelvic pain score decreased to 0.88±0.82 with letrozole and 2.11±0.60 with danazol. The mean change in pain score was 0.26±1.98 in the letrozole group versus -1.61±2.4 in the danazol group (14). It suggests that letrozole was more effective in maintaining or slightly reducing pelvic pain while danazol was associated with a worsening of pelvic pain over three months in these patients.

Seal et al. reported that treatment with letrozole (2.5 mg) combined with a daily tablet containing 0.15 mg desogestrel, 0.03 mg ethinyl estradiol, calcium (1200 mg), and vitamin D_3 (800 IU) over six months led to complete disappearance of ovarian endometriomas and a significant decrease in pelvic pain, with major pain relief observed as early as one month after initiating therapy (15). These findings align with that findings of this study and suggest that combination therapy using letrozole, desogestrel/ethinyl estradiol, calcium, and vitamin D_3 is highly effective for both early pain relief and complete resolution of ovarian endometriomas in endometriosis patients.

In a pilot prospective study, ten premenopausal women with refractory endometriosis showed 100% pain relief and a 90% reduction in lesion size after six months of treatment with letrozole combined with norethindrone acetate suggesting that pain was managed using letrozole (16).

Similarly, Elham Hussein Madny demonstrated that mean VAS scores dropped significantly from 7.65 at baseline to 6.1 after six months of letrozole therapy ($p<0.005$), and further decreased to 4 after an additional six months, indicating sustained pain relief without recurrence during follow-up. These findings suggest that letrozole not only provides

effective pain control during active treatment but also offers continued symptom relief after cessation. This sustained improvement implies a potential long-term therapeutic effect of letrozole beyond its administration period (17). Conversely, a study by Sadaf Ghulam Rasul et al. documented a greater mean reduction in pain scores with danazol (3.06±1.23) compared to letrozole (1.02±1.09), with a statistically significant difference between groups (p-value0.00), suggesting superior pain relief with danazol in their cohort (18).

Fauzia Haq Nawaz et al. concluded that the addition of letrozole to gonadotropin therapy decreased gonadotropin requirements and improved endometrial thickness, although it did not significantly affect pregnancy rates. Notably, improved pregnancy outcomes were observed in women aged over 35 years treated with letrozole. This indicates that letrozole may offer particular benefits for enhancing fertility outcomes in older reproductive-age women undergoing assisted reproductive treatments (19).

Given the contradictory findings across studies, including our own results, further research with larger sample sizes and multicenter collaboration is recommended to validate these outcomes and better inform treatment strategies for endometriosis.

Limitations: Despite the strengths of randomized design and outcome assessor blinding, the study had certain limitations. The short follow-up period (three months) precluded assessment of long-term recurrence or sustained pain relief.

The sample was drawn from a single tertiary care hospital using consecutive sampling, which may limit generalizability to broader populations. Additionally, adverse effects and quality-of-life metrics were not assessed, which are crucial components of treatment evaluation in chronic gynecological conditions.

Future research should focus on longer follow-up durations, multicenter enrollment, and incorporation of patient-reported outcomes, adverse effects, and fertility parameters to better inform therapeutic decisions

CONCLUSION

Letrozole was more effective than danazol in reducing pain scores over three months in women with endometriosis. It may serve as a preferable short-term hormonal therapy option in this population.

Conflict of Interest

No conflict of interest.

Funding

No applicable.

REFERENCES

1. Arafah M, Rashid S, Akhtar M. Endometriosis: a comprehensive review. Advances in anatomic pathology. 2021;28(1):30-43.
2. Khashchenko EP, Uvarova EV, Fatkhudinov TK, Chuprynin VD, Asaturova AV, Kulabukhova EA, et al. Endometriosis in adolescents: diagnostics, clinical and laparoscopic features. Journal of Clinical Medicine. 2023;12(4):1678.
3. García E, Cruz OP. Regulation of Inflammation Pathways and Inflammasome by Sex Steroid. Reproduction and the Inflammatory Response. 2022:607539061.
4. García-Gómez E, Vázquez-Martínez ER, Reyes-Mayoral C, Cruz-Orozco OP, Camacho-Arroyo I, Cerbón M. Regulation of inflammation pathways and inflammasome by sex steroid hormones in endometriosis. Frontiers in endocrinology. 2020;10:935.
5. Gomes-da-Silveira GG, Da Silveira GPG, Pessini SA. Minimally Invasive Gynecology: An Evidence Based Approach: Springer; 2018.
6. Lee S-Y, Koo Y-J, Lee D-H. Classification of endometriosis. Yeungnam University journal of medicine. 2021;38(1):10-8.
7. Imperiale L, Nisolle M, Noël JC, Fastrez M. Three Types of Endometriosis: Pathogenesis, Diagnosis and Treatment. State of the Art. J Clin Med. 2023;12(3).
8. Nawaz S, Habib S, Ayoub S, Shams G, Naeem N, Sultana R. 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. 2022:248-52.
9. Qureshi Q, Sadaf M, Rukhsana RA, Dileep A, Shahani MP. Letrozole, for the Management of Chronic Pelvic Pain Resulting from Endometriosis. Pakistan

Journal of Medical & Health Sciences. 2023;17(03):526-.

10. Utkarsh K, Srivastava N, Papayannakos C, Nayyar A, Khan A, Haque S. Breaking the silence: the role of extracellular vesicles in unraveling the diagnosis and treatment of endometriosis. Extracellular Vesicles and Circulating Nucleic Acids. 2023;4(4):599.
11. 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;4(2):67-72.
12. Qayyum A, Zahra S, Amber T. Endometriosis: Role of Danazol versus Letrozole for the Management of Endometriosis. Indo American Journal of Pharmaceutical Sciences. 2020;07(03):913-8.
13. Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini P, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Human Reproduction. 2009;24(12):3033-41.
14. Mehmud G, Akhtar T, Sadia S. Endometriosis: frequency and correlation between symptomatology and disease stage. Journal of the College of Physicians and Surgeons--pakistan: JCPSP. 2007;17(4):199-202.
15. Seal SL, Kamilya G, Mukherji J, De A, Ghosh D, Majhi AK. Aromatase inhibitors in recurrent ovarian endometriomas: report of five cases with literature review. Fertility and sterility. 2011;95(1):291. e15-. e18.
16. Arbique D, Carter S, Van Sell S. Endometriosis can evade diagnosis. Rn. 2008;71(9):28-33.
17. Madny EH. Efficacy of letrozole in treatment of endometriosis-related pain. Middle East Fertility Society Journal. 2014;19(1):64-8.
18. 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;23(4):514-8.
19. HaqNawaz F, Virk S, Qadir T, Imam S, Rizvi J. Comparison of letrozole and clomiphene citrate efficacy along with gonadotrophins in controlled ovarian hyperstimulation for intrauterine insemination cycles. Journal of reproduction & infertility. 2013;14(3):138.