

A COMPARATIVE STUDY OF LETROZOLE AND CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Background: Clomiphene citrate has usually been the first choice for ovulation stimulation. But the growing evidence indicates that letrozole may be more effective and better for the endometrium. There is limited comparative data on treatment efficacy across different demographic and socioeconomic groups, particularly in South Asian populations.

Objective: To compare the outcome of letrozole versus clomiphene citrate (CC) on ovulation induction in females presenting with polycystic ovary syndrome (PCOS) having subfertility.

Methods: The was a quasi-experimental study conducted in Department of Obstetrics and Gynecology, Khawaja Muhammad Safder Medical College Hospital and Lahore Institute of Fertility and Endocrinology (LIFE), from July 2025 to February 2026. 100 patients, were categorized into two groups, Letrozole (group 1, n= 50) and Clomiphene Citrate (group 2, n=50) from treatment initiation to outcome evaluation. Women aged 20–40 years, diagnosis of PCOS

and both (primary and secondary) subfertility and Male with normal semen parameters were included in this study. The main outcome was success of ovulation induction.

Results: Patient characteristics were similar between the two groups. Letrozole demonstrated a higher ovulation rate (84%) compared to clomiphene citrate (76%) in the study groups. This difference is statistically significant ($p = 0.04$). Letrozole group show higher pregnancy rate (PR) 16% versus CC group 10.5% ($p = 0.00$).

Conclusion: Letrozole showed significantly better ovulation induction effectiveness compared to clomiphene citrate in women with PCOs.

Keywords: Clomiphene citrate, Letrozole, Ovulation induction, Polycystic ovarian syndrome, Subfertility.

INTRODUCTION:

Polycystic ovary disorder is a common hormonal imbalance characterized by sporadic periods, high androgen levels, and cysts within the ovaries [1].

The appearances of PCOS can vary, some cases fundamentally obsessed by elevated androgen levels, the presence of polycystic ovaries on ultrasound coming about in a morphological dominance. It is the foremost common hormonal disorder affecting women aged 18 to 45 years [2]. Around 6-15% of women around the world have PCOS, critical concern for female fertility. In Pakistan, predominance is 18.67% [3].

Anovulation is one of the major problem in women with PCOs, which can cause infertility. PCOs is regularly diagnosed in women who have faced difficulty to conceive, over the top hair growth, missed periods, pimples, and overweight [4]. Other than, Women with PCOS moreover confront a higher chance of type 2 diabetes, unusual lipid levels, heart disease, and endometrial cancer [5]. The causes of PCOS are complex and likely include both genetic variables and environmental impacts. Environmental variables, such as poor diet and need of work out can lead to weight. Emotional aspects and stress related with this issue have both can harm the mental and physical wellbeing of influenced couples [2].

The Rotterdam criteria define PCOs by the presence of at least two of the following three features: (a) Infrequent or absent ovulation, indicated by menstrual cycles longer than 35 days or fewer than eight periods a year. (b) Signs of high androgen levels, which can be either clinical, such as acne or excessive hair growth, or biochemical, like elevated testosterone levels. (c) Polycystic ovarian morphology, defined as 12 or more follicles, each 2-9 mm in size, and/or at least one ovary over 10 mL in volume [6].

Effective ovulation induction is crucial for managing infertility related to PCOS. In women with PCOs, CC has been introduced since 1956 for the stimulating ovulation [7].

CC achieves high rate of ovulation induction (60–85%), but is associated with relatively low pregnancy rates (10–20%) and an increased risk of miscarriage (20–25%). [8]

Letrozole, an aromatase inhibitor with the ability to decrease the production of estrogen, has emerged as a prospective alternative to clomiphene citrate (CC) in recent discussions. Initially, letrozole was introduced as a therapy for breast cancer in women who had gone through menopause. [9].

Recent trials have demonstrated, Letrozole exhibits more effectiveness and may be considered as a potential alternative of CC. [10].

For ovulation induction Letrozole administering is the standard approach which is similar to clomiphene citrate, Letrozole is typically initiated on cycle days 3 to 5, either following a natural menstrual cycle or after a withdrawal bleed induced by progesterone. If eggs are not found by progesterone levels or ultrasound, then progesterone use to induce withdrawal bleeding. The dose gradually increases in each cycle. [2]

Azmoodeh and colleagues showed that letrozole leads to higher ovulation and pregnancy rates. [11] This study aims to determine whether letrozole is indeed better than clomiphene citrate on ovulation induction in women with subfertility due to PCOS.

MATERIAL AND METHODS

The was a quasi-experimental study conducted in Department of Obstetrics and Gynecology, Khawaja Muhammad Safder Medical College Hospital and Lahore Institute of Fertility and

Endocrinology (LIFE), from July 2025 to February 2026. Sample size of 100 women was calculated by using 5% level of significance with 80% power of test and estimated frequency of successful pregnancy in patients taking letrozole as 46.7% and in patients taking CC as 22.8%. Enrolled patients, were allocated into two groups, CC (group 1, n= 50) and Letrozole (group 2, n=50). Women aged 20–40 years, diagnosis of PCOS and both (primary and secondary) subfertility and Male with normal semen parameters were included in this study. Patients who have previously taken treatment of PCOS, they already taking anti-thyroid drugs determined on history and medical record and patients with any other medical disorder were excluded. The Ethical Review Board Khawaja Muhammad Safder Medical College Hospital give permission for this study (Reference letter number 79/REC/KMSMC).

Primary outcome was ovulation during the mid-cycle. We used transvaginal ultrasound on days 12 to 14 to measure the size of the dominant follicle. A follicle of 18 mm or more was deemed mature. A urinary pregnancy test was carried out after one week of ovulation. Data analyses done by using IBM SPSS version 25.0. Continuous variables presented as mean \pm SD. Categorical variables are shown as n (%). For group comparisons, Student's t-test was used for continuous variables and the chi-square test for categorical variables. To determine the relationship between treatment (CC vs letrozole) and ovulation, level of significance was less than 5%.

RESULTS

The baseline characteristics of participants in both groups were generally comparable. There was no significant difference in mean age (years) between Letrozole group (26.52 ± 2.92) and the CC group (27.24 ± 2.76). Body Mass Index was slightly lower in the Group A (28.02 ± 2.24) compared to the Group B (28.94 ± 2.36), but this difference did not reach statistical significance ($p = 0.06$). The duration of infertility was also similar between the two groups (3.58 ± 1.42 vs. 3.80 ± 1.47 years; $p = 0.45$).

Regarding menstrual cycle patterns, irregular menstruation and oligomenorrhea were common in both groups. Although a small proportion of women in the Letrozole group had regular cycles 3(6%), However, the overall distribution of menstrual patterns was not statistically significant ($p = 0.10$).

Hormonal profiles showed some significant differences. Mean FSH levels were slightly lower in the Group A (6.29 ± 0.42) than Group B (6.54 ± 0.51), and this difference was significant ($p = 0.01$). LH levels were also significantly lower in the Letrozole group (11.45 ± 2.24 vs. 13.14 ± 1.59 ; $p < 0.001$). Table 1

Endometrial thickness was significantly greater in the Group A (8.98 ± 0.73 mm) compared to the Group B (7.71 ± 0.84 mm; $p < 0.001$). In terms of follicular response, mono-follicular development was more common in the Group A, 30(60%). Whereas multiple follicles were developed in the Group B, 29(58%); however, this difference was not statistically significant ($p = 0.47$). The rate of ovulation induction was higher in Group A, 42(84%) as compared to the Group B, 38(76%), and this difference was statistically significant ($p = 0.04$). The pregnancy rate (PR) among those who underwent ovulation induction was higher in the Group A, (16%) compared to the Group B, (10.5%), with a statistically significant difference reported ($p < 0.001$). Table 2

Table 1: Baseline characteristics of participants

Parameters	Letrozole (n=50)	Clomiphene Citrate (n=50)	p-value
	Group A	Group B	
Age (years) [(mean \pm S.D)]	26.52 ± 2.92	27.24 ± 2.76	0.20
BMI (kg/m ²) [(mean \pm S.D)]	28.02 ± 2.24	28.94 ± 2.36	0.06
Duration of infertility (years) [(mean \pm S.D)]	3.58 ± 1.42	3.80 ± 1.47	0.45
Menstrual cycle [n (%)]			0.10
Regular	3 (6)	-	
Irregular	24 (48)	20 (40)	
Oligomenorrhea	23 (46)	30 (60)	
Hormonal profile (mean \pm S.D)			
FSH	6.29 ± 0.42	6.54 ± 0.51	0.01*
LH	11.45 ± 2.24	13.14 ± 1.59	0.00*
Endometrial thickness on	8.98 ± 0.73	7.71 ± 0.84	0.00*

decision day (mm)			
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*Indicates the significant p-value which was < 0.05

Table 2: Outcome parameters of the participants

Parameters	Letrozole (n=50)	Clomiphene Citrate (n=50)	p-value
No. of follicles [n (%)]			0.47
Mono-follicular	30(60)	21(42)	
Multi- follicular	20(40)	29(58)	
Ovulation induction [n (%)]			0.04*
Yes	42(84)	38(76)	
No	8 (16)	12 (24)	
Pregnancy outcome [n (%)]	7/42 (16)	4/38(10.5)	0.00*

*Indicates the significant p-value which was < 0.05

DISCUSSION

This study aims to compare the effectiveness of letrozole and clomiphene citrate (CC) for ovulation induction in women with PCOS and subfertility. Our research shows that letrozole is more effective than clomiphene citrate for inducing ovulation in these women. Letrozole is also more cost-effective and leads to greater patient satisfaction. These findings suggest that letrozole should be the first choice for ovulation induction in women with PCOS, especially for those who do not respond to clomiphene citrate.

The comparable baseline demographic characteristics between treatment groups demonstrate that the observed difference in ovulation rates is improbable to be inferable to confounding by age, BMI, residential status, or financial background. The mean age and BMI of patients were comparative to others in South Asian studies assessing ovulation induction therapies [12].

Women diagnosed with PCOS who received letrozole had higher rates of ovulation, pregnancy and endometrial thickness. A lower resistance index of subendometrial arteries can

improve circulation within the uterus, creating better conditions for embryo implantation and development. In our study, endometrial thickness was significantly greater in the letrozole group (8.98 ± 0.73 mm) compared to the clomiphene citrate group (7.71 ± 0.84 mm; $p < 0.001$). An optimal endometrial thickness plays a key role in successful implantation. Letrozole tends to help maintain a thicker uterine lining, which may be one reason it's associated with higher pregnancy rates. In contrast, clomiphene citrate has anti-estrogen effects on the endometrium, which can negatively affect implantation [13].

The observed efficacy of letrozole in this study closely aligns with previously published regional and international trials. Shafiq et al. and Khakwani et al. So also recorded significantly higher ovulation rates favoring letrozole [14]. In spite of the fact that absolute ovulation rates change over studies, likely reflecting contrasts in patient characteristics, diagnostic criteria, and monitoring protocols, the consistent pattern of letrozole prevalence over different populations strengthens the validity of the present findings [15].

Several case reports have highlighted the positive of metformin in PCOS patients by improving conception rates and metabolic profiles. Clomiphene citrate does not elicit a consistent response in all patients for ovulation induction. It works by blocking estrogen effects, which elevates gonadotropin levels from the pituitary gland and stimulates ovarian follicle development and ovulation [16]. Letrozole inhibits the enzyme aromatase, blocking the change of androgens to estrogens in ovarian follicles. This leads to lower estrogen levels within the circulatory system and increased intraovarian androgens. The diminished estrogen levels can cause a rise in FSH levels, enhancing ovarian follicle advancement [17]. The efficacy of letrozole in clomiphene-resistant PCOS patients has been documented using 2.5 mg daily doses on the third to seventh days of the menstrual cycle in various studies [18].

A study evaluating clomiphene citrate over six months noted a 25% failure rate for ovulation induction and a live birth rate of 22.5%. CC results in ovulation induction rates between 50-85%, but conception rates are not very high (15-27%). Since letrozole is an aromatase inhibitor, it does not have negative anti-estrogen effects on endometrial receptivity. The documented rates for ovulation and conception are higher with letrozole(14).In another study found that ovulation rates was 67.6% in Letrozole group while 32.4% in CC group [19]. In our study significantly

more patients to report ovulation induction in letrozole group as compare to the CC group (84% vs 76%, $p=0.04$).

Begum MR et al. noted that letrozole resulted in significantly better ovulation induction rates compared to clomiphene citrate. Debashi S et al. found that letrozole achieved a 60% ovulation induction rate, while clomiphene citrate had a 32% rate. However, Bayer U et al. conducted a study and found no significant difference in ovulation induction between the letrozole and clomiphene citrate groups (65.7% versus 74.7%; $p = 0.17$).[14].

CONCLUSION

Letrozole is more effective than clomiphene citrate at triggering ovulation and achieving better reproductive outcomes in women with Polycystic Ovary Syndrome. It also has a better safety profile. This study supports the use of letrozole as the first-line medication for ovulation induction in these women.

ETHICAL APPROVAL

Ethical Board of Allama Iqbal Memorial Teaching Hospital, Sialkot, was approved this study under the IRB reference number: 79/REC/KMSMC.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTION

Hajra Sajid: Principal Investigator, Design, writing, and editing of manuscript

Nosheen Bano: Conceiving of study idea, writing, and editing of manuscript

Asma Nayab: Collection of data, literature search and writing of manuscript

Rohina Gul: Data analysis, literature review, writing of results

Mahwish Pervaiz: Collection of data and literature review

Muneeba Sheraz: Writing, and editing of manuscript add this before references