DOI: https://doi.org/10.54393/pjhs.v6i10.3317

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 10 (October 2025)

Original Article

OPEN ACCESS

Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Infertile Women with Polycystic Ovarian Syndrome

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ARTICLE INFO

Keywords:
Infertility, Polycystic Ovary Syndrome, Letrozole, Clomiphene Citrate

How to Cite:
Tabassum, S., Aziz, A., Ali, S., Suman, F., & Tarin, A. U. (2025). Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Infertile Women with Polycystic Ovarian Syndrome: Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction with PCOS. Pakistan Journal of Health Sciences, 6(10), 31-35. https://doi.org/10.54393/pjhs.v6i10.3317

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Received Date: 4th July, 2025
Revised Date: 1st October, 2025
Acceptance Date: 16th October, 2025
Published Date: 31st October, 2025

ABSTRACT

Infertility is a devastating health issue with widespread psychological effects. The most common reason for female infertility is polycystic ovary syndrome. The treatment revolves around Clomophene Citrate (CC) and Letrozole individually, but the combination has not been studied in our population. **Objectives:** To find if the combination of CC and Letrozole has better ovulation efficacy as compared to Letrozole alone. **Methods:** The foregoing quasi-experimental study was organized in the Department of Gynaecology at Nishtar Hospital of Pakistan. A total of 70 participants fulfilling the inclusion criteria were divided into two equal groups. Group A was prescribed 2.5 mg Letrozole daily, while Group B was given the composite 2.5 mg letrozole + 50 mg CC per day from the 3rd to the 7th cycle day for one treatment cycle. **Results:** The combination group yielded ovulation in 65.7% infertile women, while Letrozole alone in 37.1 % of the cases, making a net difference of 28.6% which is quite significant. The conception was achieved in 17.1% of the combination group cases and 14.2% of the Letrozole alone group, making a net difference of 2.9%. The clinical pregnancy was diagnosed in 14.2% of the combination group cases and 11.1% of the Letrozole alone cases, with a net difference of 3.1%. **Conclusions:** Our findings endorsed the hypothesis that using combined CC + Letrozole leads to a better ovulation rate than Letrozole alone in women experiencing infertility due to polycystic ovary syndrome (PCOS).

INTRODUCTION

Infertility continues to be a devastating health issue. Infertility refers to the lack of ability to conceive after a couple has practiced regular, unprotected sexual intercourse for a period of 12 months [1]. Universally, it is estimated that every one in six couples of reproductive age group experience this issue at some stage of their life, making it as prevalent as approximately 13-15% [2]. Infertility is also a matter of concern in our country, Pakistan, where its prevalence is 18.67% [3]. The stress and emotional aspects associated with this issue have both hurtful and counter-productive effects on the mental and physical health of the experiencing couples. The main etiological factors for this distressing condition comprise a long list; male factor, polycystic ovarian syndrome, and tubal factor being the common ones [4]. PCOS is currently recognized as the most prevalent endocrine disorder affecting the fertility of women [5]. It is also a leading cause of infertility, contributing to nearly 70% of anovulation-related cases. The Rotterdam criteria define PCOS based on the presence of at least two of the following three features: (a) Infrequent/absent ovulation, typically indicated by menstrual cycles longer than 35 days or less than eight periods per year. (b) Signs of elevated androgen levels, which may be clinical (such as acne, excessive hair growth, or hair thinning) or biochemical (raised testosterone levels). (c) Polycystic ovarian morphology,

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identified as having 12 or more follicles, each 2–9 mm in diameter, and/or at least one ovary having a volume in excess of 10 mL [6]. The treatment of PCOS-related infertility aims to induce ovulation [7]. Various pharmacological agents have been employed to enhance not only ovulation, conception, and clinical pregnancy but also live birth rates, with differing levels of effectiveness. Among these, Clomiphene Citrate (CC) remains the most widely utilized. Its mode of action is as a selective estrogen receptor modulator [8], competing with estrogen for receptor sites both in the hypothalamus and pituitary gland. This disruption of the normal negative feedback from endogenous estrogen steers an increased release of two hormones, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn promote the development of ovarian follicles and induce ovulation [9]. Despite its efficacy in triggering ovulation, CC can exert anti-estrogenic effects on the endometrium as well as cervical mucus, which may lower conception rates [10]. The other drug for ovulation induction is Letrozole, which is a highly selective aromatase inhibitor and has got dual effect [11]. Letrozole inhibits the enzymatic transformation of androstenedione to estrone and testosterone to estradiol, thereby reducing the endogenous estrogen formation. The resulting low estrogen levels create a positive feedback loop within the hypothalamic-pituitary-ovarian axis, promoting the release of GnRH and, consequently, increasing FSH secretion. One proposed additional mechanism for improved ovulation rates with Letrozole is the temporary rise in intraovarian androgens, which may enhance follicular responsiveness to FSH. Unlike clomiphene citrate (CC), Letrozole does not occlude estrogen receptors sited in central or peripheral tissues, allowing the body's natural feedback systems to remain functional [12]. In women with PCOS, the hormonal profile, particularly FSH, LH, estradiol, and testosterone levels, can influence the ovulatory response to both Letrozole alone and Letrozole combined with Clomiphene Citrate. Letrozole, by inhibiting aromatase and reducing estrogen levels, can lead to a rise in FSH and LH, potentially promoting follicle development and ovulation. However, the extent of this effect can vary based on the baseline FSH levels. The study postulates that the combined Letrozole + CC is superior to Letrozole alone while considering ovulation rates. The basis of our postulation is that both drugs have different mechanism of action and their combination can have a synergistic effect, resulting in better results. This hypothesis has been explored in only a small number of studies across the world. The use of Clomiphene Citrate versus Letrozole for infertility has been researched in many studies in Pakistan. After extensive online research, it was found that the combined use of Letrozole+CC for anovulatory infertility has not been studied in our local population of Pakistan. This finding provoked us to conduct a study to test the hypothesis that the combination of Clomiphene Citrate and Letrozole results in a higher ovulation rate in comparison to Letrozole alone. The results of this study generated a useful database of our local population and will prove to be beneficial for the infertile couples.

This study aimed to find if the combination of CC and Letrozole has better ovulation efficacy as compared to Letrozole alone.

METHODS

The quasi-experimental study was conducted in the Department of Gynecology at Nishtar Hospital, Multan, Pakistan. The Ethical Review Board of Nishtar Medical University acknowledged permission for this study (Reference letter number 18984/NMU). Eligible women presenting for ovulation induction between December 2024 and May 2025 were enrolled at the start of a treatment cycle and followed through outcome assessment. Treatment (combined Letrozole + CC vs Letrozole alone) was determined by treating clinicians as part of routine care; the study recorded exposures and outcomes without intervention by the investigators. Women aged 17–40 years with infertility (failure to conceive after ≥12 months of regular unprotected intercourse) and diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria were eligible if no other identifiable cause of infertility was present. Male partners required a sperm concentration >15 million/mL and progressive motility >40%. Exclusion criteria were pregnancy, recent hormonal contraceptive use, known adrenal or thyroid dysfunction or hyperprolactinemia, prior ovarian surgery, and known allergy or contraindication to letrozole or clomiphene citrate. The WHO calculator was used to gauge the sample size. The total number of samples was 70. The sample size of 35 participants in each group was needed to achieve a statistical power of 80% for detecting a clinically significant absolute difference of 35% in ovulation rates between the treatment arms. This calculation assumed ovulation rates of 38% with letrozole alone and 73% with the combined Letrozole+CC. The anticipated 35% difference was derived from prior research that evaluated ovulation induction using the combined regimen versus letrozole alone [13]. The candidates gave voluntary consent for their participation in the study. They were briefed about the study's objectives, with assurances of confidentiality and non-maleficence. Those meeting the inclusion criteria were enrolled, and all relevant information was recorded on a proforma. Demographic data, including age, address, BMI, and duration of subfertility, were collected. Group A "Letrozole alone"

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included women who received oral letrozole 2.5 mg daily; Group B "Combined" included women who received letrozole 2.5 mg daily + clomiphene citrate 50 mg daily from cycle day 3 to 7 in the same cycle. In the prospective scenario, treatment assignment was performed by the treating physician and documented in the clinic record; the research team did not allocate treatments. The primary outcome was ovulation during the index cycle, defined as mid-luteal serum progesterone >3.0 ng/mL. For regular cycles, 5 mL venous blood was obtained on cycle day 21(day 1 = first day of menses). For irregular cycles, samples were taken weekly from day 21 until either the ovulatory progesterone value was detected or menstruation occurred. Serum was processed (clot 30 min; centrifuge 1,500 × g for 10 min); serum was analyzed immediately or stored at −20°C (≤2 weeks) or −70°C for longer storage. Serum progesterone was measured using chemiluminescent microparticle immunoassay (CMIA) on the Abbott Architect; internal quality controls (low and high) were run with each assay and accepted when within ±2 SD. Mid-cycle transvaginal ultrasound (day 12–14) was used to record dominant follicular size; follicle ≥18 mm was considered mature. Ultrasound scans were performed by the principal investigator utilizing a Mindray DP-50 to maintain consistency. A urinary pregnancy test was performed 7 days after ovulation, and clinical pregnancy was defined as an intrauterine fetal pole with cardiac activity on ultrasound. Continuous variables are presented as mean ± SD or median (IQR) as appropriate; categorical variables as n(%). Group comparisons used Student's t-test or Mann–Whitney U test for continuous variables and χ^2 or Fisher's exact test for categorical variables. To estimate the association between treatment (combined vs letrozole alone) and ovulation, we fitted multivariable logistic regression models adjusting a priori for age, BMI, and infertility duration; All tests were two-sided, and $p<0.05$ was considered statistically significant. Analyses were performed in IBM SPSS Statistics 26.0.

RESULTS

Out of the total 70 participants, most were of age around 30 years, with a mean age of 29.32 years in Group A and 30.01 years in Group B. BMI was also around 30 kg/m2, with a mean of 29.72 in Group A and 29.21 in Group B(Table 1).

Table 1: Demographics of Participants

Characteristics	Group A Letrozole (n= 35), Mean ± SD	Group B Letrozole + CC (n= 35), Mean ± SD
Age (Years)	29.32 ± 3.532	30.01 ± 4.23
BMI (kg/m^2)	29.72 ± 3.38	29.21 ± 3.46
Duration of Marriage (Years)	6.44 ± 3.21	5.92 ± 2.815

Ovulation was observed among 37.1% in Group A and 65.7% in Group B. The same data findings were observed for mid-cycle follicular size >18mm(Table 2).

Table 2: Reproductive Outcomes

Outcomes	Group A Letrozole, n= 35 (%)	Group B Letrozole + CC, n= 35 (%)	p-Value
Mid Cycle Follicle>18 mm	13 (37.1%)	23 (65.7%)	0.030*
Ovulation	13 (37.1%)	23 (65.7%)	0.030*
Conception	05 (14.2%)	06 (17.1%)	0.50
Clinical Pregnancy	04 (11.4%)	05 (14.2%)	0.50

*: statistically significant

DISCUSSIONS

Infertility is a crucial issue due to its considerable impact on couples as well as society. Many treatment modalities have been tried for this problem with variable success rates. However, the idea of combined Letrozole and Clomiphene Citrate may add up as a novel regime to the existing treatment therapies. Our findings confirmed that using a combination of Clomiphene Citrate+ Letrozole leads to a better ovulation rate than Letrozole alone in women experiencing infertility due to polycystic ovary syndrome. The combination group yielded ovulation in 65.7% infertile women, while Letrozole alone was successful in inducing ovulation in 37.1 % of the cases, making a net difference of 28.6% which is quite significant. The conception was achieved in 17.1% of the combination group cases and 14.2% of the Letrozole alone group, making a net difference of 2.9%. The clinical pregnancy was diagnosed in 14.2% of the combination group cases and 11.4% of the Letrozole alone cases, with a net difference of 2.8%. An analogous study was organized by Mejia et al. where ovulation was found to occur in 77% of the combined Letrozole and Clomiphene citrate group and 43% of the letrozole group, with a net difference of 34% [14]. The results of this study regarding ovulation are quite close to our study. However, Mejia found no difference between the groups as regards the conception and the clinical pregnancy rates. The difference in conception and clinical pregnancy rate between the two groups in our study is also not marked enough, thus almost matching the results of Mejia. Similarly, the side effect profile of the two groups was found to be the same in Mejia's study, thus supporting our findings regarding the side effect profile. The closely similar results between our study and that of Mejia might be due to the same sampling technique adoption based on age and BMI. Another study was organized by Panda et al. in India to evaluate the same as our study. They obtained ovulation in 72.5% of the combined group participants and 37.5% of the Letrozole group [13]. Their findings also lie alongside our results. Their study resulted in conception in 10% of the combined group and 7.5% of the Letrozole group. Clinical pregnancy was confirmed in 7.5% of the combined group and 5% of the Letrozole group. Both the conception and the clinical pregnancy rates revealed a net

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difference of 2.5% between the two groups. This result figure approximates our findings, thus endorsing our results. Also, though they found differences in side effects between the two groups but it was not statistically significant. Khodary *et al.* organized a similar research in Egypt [15]. They concluded that the Letrozole only group had ovulation in 79% cases and the combined Letrozole +CC had ovulation in 81% cases. Their resulting ovulation rate is quite high compared to our study. It might be because they used double the dose of lertozole (5 mg) and CC (100 mg) than that given in our study. Also, they included only those women who were up to 35 years of age and had a BMI less than 30 kg/m^2. These women have more chances of ovulation due to relatively younger age and appropriate BMI. A study was carried out by Ibrahem in Egypt using the same medication as our study [16]. However, they had a similar ovulation rate (63.3%) in both the Letrozole only and the Letrozole +CC group. So they concluded that the addition of CC to Letrozole poses no benefit. Their results were contrary to ours. However, it was quite expected as Ibrahem included those cases who were CC resistant. In his study, a combination of Letrozole + CC meant the same as Letrozole alone due to proven CC resistance of the participants. Ashkar *et al.* conducted a systematic review and meta-analysis by examining five different databases to validate the efficacy of combining Letrozole and Clomiphene Citrate (CC) compared to using either drug individually [17]. Their findings indicated that the combination therapy was more effective for inducing ovulation in sub-fertile women diagnosed with PCOS. Thus, their study supports our results regarding ovulation. However, they found no difference between the groups as regards conception and clinical pregnancy. Similarly, Sarkar *et al.* [18] and Eskandar *et al.* [19] also found the combination to be superior to Letrozole alone as regards ovulation. While the above studies concluded a better ovulation rate in the combination group, this does not always lead to higher conception and clinical pregnancy rates due to several reasons. The CC exerts anti-estrogenic effects on the endometrial lining, resulting in its thinning and reduced implantation. Also, the possibility of multiple pregnancies is increased with CC, with all the anticipated complications [20]. As far as the optimal dose of Letrozole+CC for maximizing ovulation without adverse effects is concerned, the various studies have suggested different dosage schedules. However, more large-scale studies are required to reach any evidence-based conclusion.

CONCLUSIONS

Our findings endorsed the hypothesis that using combined CC + Letrozole leads to a better ovulation rate than Letrozole alone in women experiencing infertility due to PCOS. The findings suggest that this low-cost treatment can be an effective option for the despair infertile couples, with promising results. Additional research studies are needed to observe the effects on conception and live pregnancy rate.

Authors Contribution

Conceptualization: ST
Methodology: FS, AUT
Formal analysis: AA
Writing review and editing: ST, SA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

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

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