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Original Research Article

Letrozole vs Clomiphene Citrate as 1st Line Drug for Ovulation Induction in Polycystic Ovary Syndrome (PCOS) - A Randomized Controlled Trial (Open Label)

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Abstract:

Background: One of the main causes of anovulatory infertility is polycystic ovarian syndrome, or PCOS. Although clomiphene citrate (CC) has long been used to induce ovulation, endometrial receptivity may be hampered by its antiestrogenic properties. An aromatase inhibitor called letrozole has surfaced as a possible substitute.

Methods: In a study involving 92 women with PCOS, participants were randomly assigned to take either CC (50–100 mg) or letrozole (2.5–5 mg) from the second to the sixth day of their menstrual cycle, for up to three cycles. The primary goal was to assess the ovulation rate, while secondary measures included endometrial thickness, pregnancy rate, and any side effects.

Results: Letrozole had a considerably greater ovulation rate (84.8%) than CC (63%; p = 0.01). Letrozole demonstrated increased endometrial thickness and improved monofollicular formation (p = 0.001). Letrozole increased the pregnancy rate, although this difference was not statistically significant. The CC group experienced higher adverse effects.

Conclusion: Letrozole is a better endometrial profile and has less side effects than clomiphene citrate, which supports its usage as a first-line treatment for PCOS.

Keywords: Polycystic Ovary Syndrome; Ovulation Induction; Letrozole; Clomiphene Citrate.

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Introduction

Polycystic ovarian syndrome (PCOS) is recognized as the most prevalent endocrine disorder affecting women during their reproductive years, with a global occurrence rate ranging from 5% to 20%, contingent upon the diagnostic criteria applied.[1,2, 3,4] Anovulatory infertility continues to be the most clinically significant of its several reproductive repercussions, accounting for an estimated 90–95% of anovulatory presentations at specialized fertility clinics and 20–40% of all female infertility referrals.[5, 6] For more than five decades, clomiphene citrate (CC) was considered the standard first-line pharmacological intervention for ovulation induction in PCOS. As a selective estrogen receptor modulator (SERM), CC exerts its effect by competitively blocking hypothalamic estrogen receptors, thereby attenuating the negative feedback of endogenous estrogen and stimulating pulsatile gonadotropin secretion.[6] While CC achieves ovulation in approximately 70–80% of patients, the discordance between ovulation rates and conception rates—often cited at only 36–40%—is a well-recognized clinical paradox.[7] This disparity is largely attributable to the peripheral antiestrogenic actions of CC, which impair endometrial proliferation, reduce cervical mucus production, and diminish uterine blood flow, collectively compromising implantation.[8,9] Furthermore, prolonged receptor occupancy by the long-acting zuclomiphene isomer sustains elevated gonadotropin secretion, predisposing to multifollicular development and an attendant risk of multiple gestation.[7]

Letrozole, a third-generation nonsteroidal aromatase inhibitor (AI) originally approved for treatment of hormone-receptor-positive breast cancer, has gained considerable attention as an alternative ovulation induction agent. By transiently inhibiting the cytochrome P450 enzyme aromatase, letrozole suppresses peripheral and central estrogen biosynthesis, thereby releasing the hypothalamic-pituitary axis from negative feedback and driving

compensatory follicle-stimulating hormone (FSH) secretion.[10,11] A critical mechanistic advantage over CC is that, once letrozole is cleared (half-life approximately 45 hours), the newly synthesized estrogen from developing follicles re-establishes normal hypothalamic feedback, restraining FSH secretion and favoring monofollicular recruitment.[12] Crucially, letrozole does not interfere with peripheral estrogen receptor function; consequently, endometrial proliferation and cervical mucus quality are preserved, facilitating both implantation and sperm transport.[10,12]

The landmark multicenter randomized controlled trial conducted by Legro et al. (2014) demonstrated that women with PCOS experienced significantly higher cumulative live-birth rates when treated with letrozole compared to CC, with rates of 27.5% versus 19.1% ($p = 0.007$). Additionally, letrozole resulted in better cumulative ovulation rates (61.7% vs. 48.3%; $p < 0.001$) and a reduced rate of twin pregnancies. [13,14]

Several randomized trials conducted in South Asian populations have corroborated the superiority of letrozole over CC with respect to ovulation rate, endometrial thickness, and pregnancy outcomes. [15,16,17] However, data from tertiary industrial hospitals serving ethnically distinct, predominantly overweight Indian cohorts remain sparse. The present trial was therefore undertaken to compare the clinical efficacy and safety of letrozole with CC as first-line ovulation induction therapy in PCOS-related infertility within this underrepresented patient population, and to contribute locally applicable evidence to inform prescribing practice.

Materials and Methods

Study Design and Setting: The Department of Obstetrics and Gynaecology at PMCH, Patna, conducted this prospective, open-label, parallel-group randomized controlled study. The study took place from June 2025 to April 2026.

Sample Size Calculation: A superiority formula with an expected ovulation rate of 87% with letrozole (πt) and 67% with CC (πs), a superiority margin (Δ) of 5%, a two-sided α of 0.05, and a power ($1-\beta$) of 80% was used to estimate the sample size. The formula $N = [Z(1-\alpha) + Z(1-\beta)]^2 [\pi s(1-\pi s) + \pi t(1-\pi t)] / (\pi t-\pi s-\Delta)^2$ was used to determine the minimum required sample size, which came out to be 92 participants (46 per arm) with a 5% expected dropout rate.

Participant Eligibility: The study includes women who are between the ages of 19 and 36, have experienced primary or secondary infertility for over a year, and have polycystic ovary syndrome (PCOS) diagnosed using the Rotterdam 2003 criteria. This means they must meet at least two out of the three criteria: irregular or no menstrual periods, signs of high androgen levels either physically or through blood tests, or having a polycystic appearance on an ultrasound with at least 12 small follicles measuring 2 to 9 mm in size or an ovarian volume of 10 cm^3 or more. Women must also have clear fallopian tubes confirmed by hysterosalpingography or laparoscopy, and their male partner must have normal semen quality based on WHO 2010 standards. Exclusion criteria include male-related infertility, being outside the 19 to 36 age range, thyroid problems, uncontrolled diabetes, blocked fallopian tubes, endometriosis, and pelvic infections.

Randomization: A computer-generated random number sequence created by online randomization software (www.randomization.com) was used to randomly assign participants in a 1:1 ratio.

Interventions: Letrozole group: Take 2.5 mg of letrozole orally once daily from days 2–6 of the menstrual cycle; if ovulation is not attained, increase to 5 mg once daily from the second cycle. Clomiphene citrate group: CC 50 mg once day for days 2–6, increased to 100 mg once daily for the second cycle if ovulation was not attained. For a maximum of three consecutive cycles, both regimens were maintained. There was no use of a placebo (open-label design). Every participant was told to keep an intercourse journal and to have timed sex two to three times a week within the anticipated ovulatory window.

Outcome Assessments

Endometrial thickness was checked at the start and on day 12. Follicles were monitored using transvaginal ultrasound every two to three days until a dominant follicle reached at least 18 mm. Ovulation was confirmed when the follicle ruptured. Those who didn't respond or had negative pregnancy tests moved on to the next cycle. If a person didn't have a period, a chemical pregnancy was found using a urine hCG test and confirmed with an ultrasound showing a gestational sac. During the follow-up, any problems like OHSS, multiple pregnancies, miscarriages, or other negative events were recorded.

Statistical Analysis: Data are presented as frequencies and percentages for categorical variables, and as mean ± standard deviation (SD) for continuous variables. Between-group comparisons of categorical variables were performed using the Chi-square test, and continuous variables were compared using the independent-samples t-test. SPSS Statistics version 16.0 was also used for further analysis

Results

Baseline Demographic and Clinical Characteristics: Ninety-two participants were enrolled and randomized—46 to each treatment

arm—with no dropouts or withdrawals reported. Both groups demonstrated satisfactory comparability at baseline across all evaluated parameters (Table 1).

Table 1: Baseline demographic and clinical characteristics of study participants

Characteristic	CC Group (n = 46)	Letrozole Group (n = 46)	p-value
Mean age, years (±SD)	28.65 ± 3.44	28.67 ± 3.20	0.97
Age 19–24 years, n (%)	7 (15.2%)	5 (10.9%)	
Age 25–30 years, n (%)	26 (56.5%)	27 (58.7%)	0.82
Age 31–36 years, n (%)	13 (28.3%)	14 (30.4%)	
Mean BMI, kg/m² (±SD)	29.80 ± 1.83	29.86 ± 1.76	0.88
BMI 26–30 kg/m², n (%)	26 (56.5%)	26 (56.5%)	1.00
BMI >30 kg/m², n (%)	20 (43.5%)	20 (43.5%)	
Nulliparous, n (%)	36 (78.3%)	36 (78.3%)	1.00
Mean infertility duration, years (±SD)	2.62 ± 0.93	2.69 ± 0.95	0.72
Diabetes mellitus, n (%)	4 (8.7%)	4 (8.7%)	0.89
Hypertension, n (%)	3 (6.5%)	2 (4.3%)	

CC = clomiphene citrate; SD = standard deviation. p-values derived from Chi-square test (categorical) and independent t-test (continuous).

Follicular Development: The monofollicular development was statistically more common in the letrozole group (63.0% vs. 37.0%) than the multifollicular development, which was numerically more common in the CC group (28.3% vs. 17.4%), but was not statistically significant (p = 0.21). The average size of the follicles reaching 18 mm and above was significantly greater in the CC group (1.60 + 0.93) than in the letrozole group (1.22 + 0.41; p = 0.02), which is in line with the multifollicular stimulation pattern that can be attributed to the maintained FSH high level with CC (Table 2).

Table 2: Follicular development outcomes by treatment group

Parameter	CC Group (n = 46)	Letrozole Group (n = 46)	p-value
Monofollicular development, n (%)	17 (37.0%)	29 (63.0%)	0.01*
Multifollicular development, n (%)	13 (28.3%)	8 (17.4%)	0.21
Mean follicle count ≥18 mm (±SD)	1.60 ± 0.93	1.22 ± 0.41	0.02*

*Statistically significant (p < 0.05). p-values from Chi-square test (categorical) and independent t-test (continuous).

Endometrial Thickness: Pre-treatment endometrial thickness was comparable between groups (CC: 4.43 ± 0.52 mm; letrozole: 4.49 ± 0.54 mm; p = 0.58). Following ovulation induction, day-12 endometrial thickness was significantly greater in the letrozole group (8.70 ± 0.53 mm) than in the CC group (8.04 ± 0.29 mm; p = 0.001). Within-group analysis confirmed statistically significant gains from baseline in both arms (CC: Δ 3.61 ± 0.49 mm, p = 0.001; letrozole: Δ 4.20 ± 0.60 mm, p = 0.001), with the magnitude of change being significantly greater with letrozole (p = 0.001; Table 3).

Table 3: Endometrial thickness before and after ovulation induction

Group	Pre-treatment (mm)	Day-12 Post-induction (mm)	Mean Change (mm)	p (within)
CC (n = 46)	4.43 ± 0.52	8.04 ± 0.29	3.61 ± 0.49	0.001*
Letrozole (n = 46)	4.49 ± 0.54	8.70 ± 0.53	4.20 ± 0.60	0.001*
p-value (between)	0.58	0.001*	0.001*	—

Values are mean ± SD. *Statistically significant. p (within) from paired t-test; p (between) from independent t-test.

Ovulation and Pregnancy Rates: Treatment failure rates were lower in the letrozole arm (19.6% vs. 37.0%) and ovulation was considerably greater in the letrozole group (84.8%) than in the clomiphene citrate group (63.0%) (p = 0.01). Letrozole increased the rates of chemical pregnancy (23.9% vs. 15.2%), although this difference was not statistically significant (p = 0.29). Letrozole caused conception to occur earlier than CC, with a higher percentage of conceptions occurring in the first and second cycles (p = 0.4).

Table 4: Ovulation, pregnancy, and treatment failure outcomes

Outcome	CC Group (n = 46)	Letrozole Group (n = 46)	p-value
Ovulation confirmed, n (%)	29 (63.0%)	39 (84.8%)	0.01*
Treatment failure (no ovulation), n (%)	17 (37.0%)	9 (19.6%)	0.06
Chemical pregnancy (urine hCG+), n (%)	7 (15.2%)	11 (23.9%)	0.29
Pregnancy in cycle 1, n (% of pregnancies)	1 (14.3%)	3 (27.3%)	
Pregnancy in cycle 2, n (% of pregnancies)	2 (28.6%)	5 (45.5%)	0.44
Pregnancy in cycle 3, n (% of pregnancies)	4 (57.1%)	3 (27.3%)	
Dose escalation required, n (%)	7 (15.2%)	5 (10.9%)	0.53

*Statistically significant. p-values from Chi-square test.

Adverse Effects: The side effects were better with letrozole in all the categories that were checked. Ovarian hyperstimulation syndrome happened in 2.2% of women who got clomiphene citrate, but none of the women who took letrozole experienced it. Twin pregnancies were seen in 4.3% of the clomiphene citrate group and 2.2% of the letrozole group (Table 5).

Table 5: Adverse events by treatment group

Adverse Event	CC Group n (%)	Letrozole Group n (%)	p-value
Ovarian hyperstimulation syndrome	1 (2.2%)	0 (0.0%)	0.31
Multiple gestation (twin pregnancy)	2 (4.3%)	1 (2.2%)	0.55
Gastrointestinal disturbance (nausea/vomiting)	2 (4.3%)	0 (0.0%)	0.15
Any adverse event, n (%)	5 (10.9%)	1 (2.2%)	0.09

p-values from Chi-square test.

Discussion

The present randomized controlled trial demonstrates that letrozole is superior to clomiphene citrate in terms of ovulation induction efficacy, promotion of monofollicular recruitment, and preservation of endometrial thickness in women with PCOS-associated infertility. These findings are consistent with the growing body of international evidence favoring letrozole as a first-line agent in this clinical setting. [13,15,16,17,18]

Ovulation Rate: The ovulation rate of 84.8% achieved with letrozole in our study closely mirrors the 88.5% reported by Legro et al. [13] in their definitive multicenter trial, and aligns with the 81.6% and 82.4% rates documented by Jain et al. [15] and Atay et al.,[18] respectively. Our CC arm ovulation rate of 63% is similarly consistent with rates of 63.6–76.6% reported in comparable trials. [13,16,18] The mechanistic explanation for letrozole's superior ovulation induction relates to its short plasma half-life (approximately 45 hours), which permits rapid estrogen recovery from maturing follicles, restoring hypothalamic negative feedback and preventing the sustained supraphysiological FSH surge characteristic of CC treatment. [10,11]

Follicular Development Pattern: A clinically important finding was the significantly higher proportion of monofollicular development in the letrozole arm (63% vs. 37%; $p = 0.01$). In contrast, CC-treated women exhibited greater multifollicular stimulation and a significantly higher mean number of follicles reaching 18 mm (1.60 vs. 1.22; $p = 0.02$). These observations accord with the established pharmacological basis of letrozole action: the restored estrogen feedback loop constrains FSH secretion once a dominant follicle has formed, while the persistent hypothalamic receptor depletion induced by CC permits unrestrained FSH drive across multiple follicles. Jain et al. [15] similarly documented monofollicular development in 85.57% of letrozole cycles versus only 29.62% of CC cycles.

Endometrial Thickness: Letrozole was associated with significantly greater day-12 endometrial thickness (8.70 ± 0.53 mm vs. 8.04 ± 0.29 mm; $p = 0.001$), consistent with an extensive literature documenting the adverse endometrial effect of CC's antiestrogenic peripheral action.[7,8,9] Comparable findings have been reported by Chakravorty et al. (9.82 vs. 8.13 mm),[16] Roy et al. (9.1 vs. 6.3 mm),[17] Mitwally and Casper (8.1 vs. 6.2 mm),[19] and Atay et al. (8.4 vs. 5.2 mm).[18] Adequate endometrial thickness and trilaminar morphology are prerequisites for successful implantation; the inferior endometrial response with CC is a key contributor to the persistent gap between ovulation and conception rates observed with this agent.

Pregnancy Rate: Although the chemical pregnancy rate was numerically higher in the letrozole arm (23.9% vs. 15.2%), the difference did not achieve statistical significance ($p = 0.29$), most plausibly due to the limited sample size of the present study. This pattern has been observed in multiple smaller trials, [15,16,17] whereas larger adequately powered investigations—notably Legro et al.,[13] who enrolled 750 women—have demonstrated statistically significant advantages in cumulative live-birth rates with letrozole. The clinical pregnancy rate in our series is numerically consistent with the 14.6–48% range for letrozole and 8.8–45% for CC documented across comparable

Indian investigations. [15,16,17,18] The probability of a type II error in our study given the modest sample size cannot be excluded.

Side-effect Profile: The adverse-event burden was consistently lower in the letrozole arm. OHSS was observed in 2.2% of CC-treated patients and in none of the letrozole recipients, a pattern replicated in trials by Hashim et al.[20] and Legro et al.[13] Twin gestation—the most clinically consequential complication of ovulation induction—occurred at a rate of 4.3% with CC versus 2.2% with letrozole, consistent with the significantly lower multiple gestation rate documented by Legro et al. (7.4% vs. 3.4%).[13] The relative absence of gastrointestinal and vasomotor side effects with letrozole further enhances its acceptability for long-term use. These findings collectively reinforce the safety advantage of letrozole, arising from its short half-life and site-specific mechanism that avoids the prolonged peripheral receptor modulation associated with CC. [12]

Comparison with Published Literature: Our results parallel those of Roy et al.,[17] who reported comparable ovulation rates between letrozole and CC (66.6% vs. 67.9%) but a significantly better endometrial response and pregnancy rate (43.8% vs. 26.4%) with letrozole; Chakravorty et al.,[16] who documented superior ovulation (37.87% vs. 19.67%) and endometrial thickness with letrozole; Jain et al.,[15] who reported ovulation rates of 81.6% vs. 65.5% and pregnancy rates of 48% vs. 16% favoring letrozole; and Rashed et al.,[21] who reported ovulation induction efficacy of 84% vs. 66% favoring letrozole. Taken together, this body of evidence from diverse patient populations consistently positions letrozole as the more effective and better-tolerated ovulation induction agent in PCOS.

Limitations: The primary limitations of the present study include its relatively small sample size (n = 92), open-label design, restriction to a three-cycle follow-up period, potential intra- and inter-observer variability in sonographic measurements, and the absence of live-birth data as an endpoint. Additionally, the study population's predominantly overweight profile may limit generalizability to leaner PCOS cohorts. Larger multicenter trials with live-birth as the primary endpoint are warranted to definitively establish letrozole's clinical advantage in this population.

Conclusion

When compared to clomiphene citrate, letrozole proved to be much better at causing ovulation, with 84.8% success compared to 63.0%. It also led to a thicker lining of the uterus on day 12 (8.70 mm versus 8.04 mm; p = 0.001), and more development of single follicles (63% versus 37%). Although there was a numerical difference in pregnancy rates and treatment failure, the results weren't statistically significant in this group, which may be due to a type II error. Letrozole also had fewer side effects. These findings support the use of letrozole as the preferred first-line treatment for ovulation induction in women with PCOS-related infertility, especially in settings where avoiding multiple pregnancies and maintaining a receptive uterine lining are key concerns.

Informed consent: Written informed consent was obtained from all individual participants prior to enrollment.

Conflict of interest: The authors declare no conflicts of interest.

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