International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Dhanagopal S et al. Int J Reprod Contracept Obstet Gynecol. 2026 May;15(5):1601-1605
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20261158

Original Research Article

Clinical research on the relative efficacy of letrozole and clomiphene citrate in achieving ovulation among women with polycystic ovarian syndrome

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Received: 21 August 2025
Revised: 16 April 2026
Accepted: 17 April 2026

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a leading cause of anovulatory infertility. PCOS is the most common cause of infrequent periods (oligomenorrhoea) and absence of periods (amenorrhoea). It affects about 4% to 8% of women worldwide and often leads to anovulatory subfertility. Clomiphene citrate (CC) has been widely used for ovulation induction but is limited by endometrial effects and resistance. Letrozole, an aromatase inhibitor, has emerged as an alternative with potentially superior efficacy. Aim of the study was to compare the efficacy of letrozole and CC in ovulation induction among women with PCOS.
Methods: A prospective comparative study was conducted on 100 infertile women with PCOS aged 21–35 years at Government Peripheral Hospital, Tondiarpet, Chennai, from September 2024 to August 2025. Participants were allocated into two groups: letrozole (n=50) and clomiphene citrate (n=50). Follicular development and rupture were assessed by transvaginal ultrasonography. Statistical analysis was performed using statistical package for the social sciences (SPSS), with $p<0.05$ considered significant.
Results: The mean age was 26.3±2.5 years. The mean follicle number was lower in the letrozole group (1.5±0.89) compared with clomiphene (2.54±1.69). The mean number of ruptured follicles was significantly lower with letrozole (0.96±0.64) compared with clomiphene (1.48±1.07). Letrozole demonstrated a safer monofollicular response, while clomiphene induced multifollicular development.
Conclusions: Both agents are effective for ovulation induction. Letrozole offers a safer monofollicular profile with reduced risk of multiple gestations, making it preferable when minimizing multiple pregnancies is a priority.

Keywords: PCOS, Infertility, Letrozole, Clomiphene citrate, Ovulation induction

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, with a prevalence ranging from 6% to 20% worldwide.[1] The ovaries in PCOS may contain multiple sub capsular cysts that are 2 to 9 mm in diameter and numbering 12 or more, arranged peripherally (sub capsular) or scattered throughout a hyperplastic stroma. Additionally, most of these cysts contain potentially viable oocytes, within dysfunctional follicles.[2] Clomiphene citrate (CC), an estrogen receptor modulator, is a classical first-line pharmacological intervention for ovulation induction. It is a low-cost, orally administered drug with fewer side effects; 15% of women with PCOS are resistant to it. It may also induce ovarian hyperstimulation syndrome, inappropriate endometrial proliferation, and alterations in cervical mucus concentration.[3] CC is less effective than letrozole (LE) in terms of pregnancy rates and mono-follicular growth. It is also associated with a

high risk of miscarriages and prolonged depletion of receptors due to the anti-estrogenic effect of CC.[4]

Letrozole, a third-generation aromatase inhibitor initially developed for treating breast cancer, has emerged as a first-line OI agent, particularly in anovulatory PCOS.[5] The international evidence-based guideline spearheaded by the international PCOS network also endorses letrozole as the first-line ovulation induction therapy for anovulatory PCOS.[6] As per American College of Obstetrics and Gynaecologists (2016) society, letrozole should be considered as 1st line therapy for OI in patients with PCOS and BMI >30 because of increased live birth rate (LBR) compared to clomiphene citrate; as per Australian National Health and Medical Research Council (NHMRC) guidelines. LTZ being an aromatase inhibitor is not found to influence adverse anti-estrogenic effects on endometrial receptivity while the documented ovulation as well as conception rates are higher.[7] Letrozole inhibits androgens to estrogen which causes increase release of FSH from anterior pituitary due to decreased inhibitory influence of estrogen on hypothalamic-pituitary axis. Letrozole does not have any anti estrogenic peripheral action therefore it does not adversely affect endometrial development or cervical mucus production and improves endometrial receptivity compared with clomiphene citrate and increased pregnancy rate has been reported with its use. Letrozole has been shown to have good ovulation rate in CC-resistant PCOS women.[8] Indian PCOS women have high prevalence of insulin resistance and thus are likely to have high CC resistance. Letrozole could prove to be a good alternative for ovulation induction in such women.[9]

The primary objective of this study was to test the hypothesis that letrozole as a primary OI agent will generate higher pregnancy rates than CC in anovulatory women with PCOS.

Aim and objectives

The aim and objectives of the study were to evaluate and compare the effectiveness of letrozole versus clomiphene citrate in ovulation induction among women with PCOS, and to assess the number of follicles recruited and ruptured in each group.

METHODS

Study design

It was a prospective comparative study conducted from September 2024 to August 2025 at Government Peripheral Hospital, Tondiarpet, Chennai.

Sample size calculation

Sample size was calculated based on expected ovulation rates of 70% for CC and 85% for letrozole from previous studies, with 80% power and 5% significance level. Minimum required was 45 per group; hence, 50 per group were recruited.

Sampling technique

Convenience sampling of eligible patients presenting during the study period.

Inclusion criteria

Women aged 21–35 years, diagnosed with PCOS (Rotterdam criteria), infertility >1 year, and at least one patent fallopian tube were included.

Exclusion criteria

Patients with obesity (BMI >30 kg/m^2), thyroid dysfunction, liver/renal disease, and uterine abnormalities were excluded.

Procedure

Group A: Letrozole 2.5–5 mg daily, cycle days (3–7), and group B: CC 50–100 mg daily, cycle days (3–7).

Monitoring with transvaginal ultrasonography from day 9, then every 2–3 days until follicular rupture. Follicular rupture was assessed either spontaneously or post-hCG trigger when dominant follicle reached ≥18 mm. Data recorded were follicle number, rupture, ovulation achieved.

Statistical analysis

Data was analyzed using statistical package for the social sciences (SPSS) v20. Chi-square and independent t-tests applied. $p<0.05$ considered significant.

RESULTS

A total of 100 women with PCOS were enrolled and randomized into two groups: letrozole (n=50) and CC (n=50).

Baseline characteristics

The mean age of participants in the letrozole group was 26.2±2.4 years, compared to 26.5±2.6 years in the clomiphene group. The age distribution was comparable between the two groups, with the majority of participants belonging to the 25–29 years age group (62% versus 66%, respectively).

Women aged 21–24 years constituted 36% in the letrozole group and 32% in the clomiphene group, while only 2% in each group were aged 30–35 years. There was no statistically significant difference in baseline demographic characteristics between the two groups ($p>0.05$).

Table 1: Demographic profile.

Variables	Letrozole (n=50)	Clomiphene (n=50)
Mean age (years)	26.2±2.4	26.5±2.6
Age group 21–24 (%)	18 (36)	16 (32)
Age group 25–29 (%)	31 (62)	33 (66)
Age group 30–35 (%)	1 (2)	1 (2)

Ovulation outcomes

The mean number of follicles developed was significantly lower in the letrozole group compared to the clomiphene group (1.5±0.89 versus 2.54±1.69). Similarly, the mean number of ruptured follicles was lower in the letrozole group (0.96±0.64) than in the clomiphene group (1.48±1.07).

However, the ovulation rate was higher in the letrozole group, with 74% (37/50) of women achieving ovulation, compared to 68% (34/50) in the clomiphene group; this difference was not statistically significant (p>0.05).

Notably, monofollicular development was significantly more frequent in the letrozole group (84%) compared to the clomiphene group (50%), indicating a more favorable ovulatory response pattern with letrozole (p<0.05).

Table 2: Ovulation outcomes.

Outcome	Letrozole (n=50)	Clomiphene (n=50)
Mean number of follicles	1.5±0.89	2.54±1.69
Mean number of ruptured follicles	0.96±0.64	1.48±1.07
Ovulation rate	37 (74)	34 (68)
Monofollicular cycles (%)	42 (84)	25 (50)
Multifollicular cycles (%)	8 (16)	25 (50)

*Significant difference

Figure 1 illustrates the comparison of mean follicle numbers between the two study groups. The mean number of follicles was lower in the letrozole group (approximately 1.5) compared to the clomiphene citrate group (approximately 2.5).

This finding indicates that letrozole is associated with more controlled, monofollicular development, which is desirable in ovulation induction to reduce the risk of multiple pregnancies and ovarian hyperstimulation. In contrast, clomiphene citrate showed a higher tendency for multifollicular development.

The difference between the two groups was statistically significant, thereby favoring letrozole as a safer and more physiological option for ovulation induction in women with PCOS.

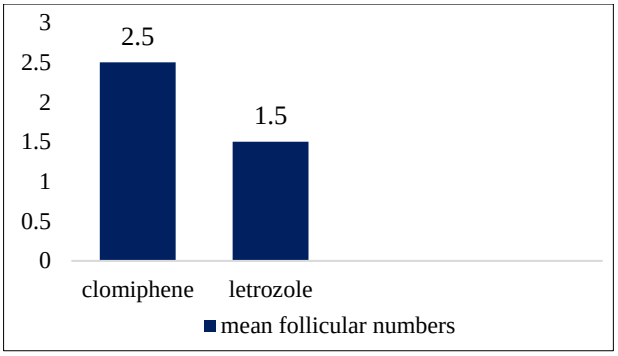

Figure 1: Comparison of mean follicle numbers.

Figure 2 demonstrates the distribution of ovulation rates between the two study groups. Ovulation was achieved in a higher proportion of women in the letrozole group compared to the clomiphene citrate group. Specifically, approximately 52.1% of ovulation cases were observed in the letrozole group, whereas around 47.9% were seen in the clomiphene group.

This indicates a comparatively better ovulation rate with letrozole. The difference between the two groups was found to be statistically significant, suggesting superior efficacy of letrozole over clomiphene citrate in inducing ovulation among women with PCOS.

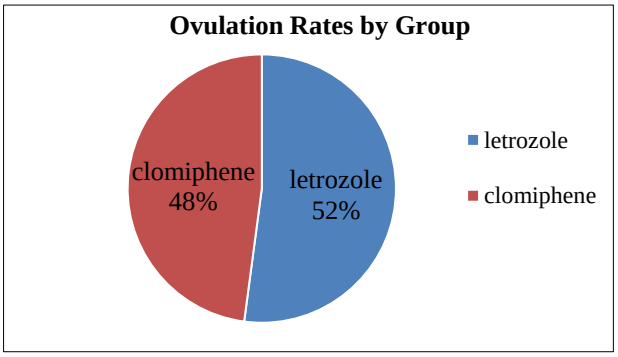

Figure 2: Ovulation rates by group.

DISCUSSION

This comparative study demonstrates that both letrozole and CC are effective agents for ovulation induction in women with PCOS, but their mechanisms and clinical outcomes differ significantly. Clomiphene was associated with a higher mean number of developing and ruptured follicles, while letrozole produced a more controlled monofollicular response.

From 1960, CC was considered to be the only first line ovulation induction agent. But clomiphene resistance (15-20%), endometrial thinning, and poor cervical mucus (15-50% of cases) makes it inefficient in many situations. Known side effects are vasomotor flushes, breast tenderness, pelvic discomfort, nausea, visual disturbances, rarely OHSS.[10] These findings highlight the clinical

importance of balancing follicular recruitment with the risk of multiple gestations.

An aromatase inhibitor, letrozole, was introduced into infertility practice in the year 2000 and is regarded as a second line option, particularly in women with clomiphene resistance and it has found acceptance in various clinical situations and the indications for use have expanded.[11] This study showed that endometrial thickness was higher in letrozole group than clomiphene group. It is supported by previous studies carried by Hendawy et al Mitwally and Casper found that letrozole was associated with greater endometrial thickness when they give aromatase inhibitor (letrozole) to patients with anovulatory infertility, ovulatory infertility.[12,13]

Our results are consistent with international evidence. First double blind multicentric trial of 750 patients was reported by Legro et al showing better ovulation rate and cumulative birth rates in patients who received letrozole.[14] Wang et al and Roque et al in meta-analysis comprising of 1284 and 3962 patients have demonstrated that letrozole use resulted in significantly better clinical pregnancy and live birth rate compared to CC in women with PCOS.[15] This is due to the fact that CC has a long half-life of two weeks and its anti-estrogenic effects causes unfavorable effect on the quality and the amount of cervical mucus in addition to thinning of endometrium leading to implantation failure. Despite its long-standing use, clomiphene has limitations. Resistance occurs in up to 25% of women, and its anti-estrogenic effects on the endometrium and cervical mucus may reduce conception rates despite adequate follicular development. Letrozole, by contrast, promotes endogenous FSH release through transient estrogen suppression, leading to improved endometrial receptivity and mono-ovulation, thereby explaining its clinical advantage.

PCOS patients has higher miscarriage rate than normal population.[16] The reason is abnormality in endometrial reception, corpus luteum insufficiency, poor quality of ovum, insulin resistance development and increased androgen levels in body. In our study, there was no difference in miscarriage rate in both groups

Recent studies have emphasized the potential benefits of initiating treatment with higher doses of letrozole in women with CC-resistant PCOS. For instance, one study found that ovulation induction using increased letrozole doses in CC-resistant patients improved ovulation rates without increasing adverse effects, although pregnancy rates were not significantly dose-dependent.[17] Another trial demonstrated that a protocol using incremental doses of letrozole (up to 7.5 mg/day) after metformin pretreatment achieved a cumulative pregnancy rate of 57.1%, with most patients responding to higher doses after failure with lower ones.[18] Studies have shown that ovarian stimulation with letrozole is associated with more acceptable pregnancy rates than in(s) gonadotropin therapy, and at significantly less cost, less risk, and more patient convenience.[19] Furthermore, combination protocols are less costly and equally effective, with potentially fewer multiple births than with gonadotropins alone. Letrozole may be more effective than clomiphene and tamoxifen in a combination protocol.[20]

From a clinical standpoint, letrozole should be considered as the preferred first-line agent for ovulation induction in women with PCOS, particularly for those with previous clomiphene resistance or when minimizing the risk of multiple pregnancies is a priority. Clomiphene, however, may still be valuable in low-resource settings due to its cost-effectiveness and widespread availability, and may also serve as part of combination regimens in resistant cases.

Limitations

The present study was limited by its single-center design and relatively small sample size, which may affect the generalizability of the findings. Lifestyle and metabolic factors such as BMI, insulin resistance, and dietary habits, which are known to influence ovulatory response, were not assessed. Future larger multicenter studies incorporating these parameters and long-term outcomes are warranted to provide stronger evidence.

CONCLUSION

Letrozole and clomiphene citrate are both effective ovulation induction agents in PCOS. Letrozole induces safer monofollicular ovulation, making it preferable where reduction of multiple pregnancy risk is important.

Recommendations

Larger multicenter RCTs including pregnancy/live birth outcomes are needed. Studies evaluating cost-effectiveness and patient quality of life should be encouraged.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dhanagopal S, Selvam SSM. Clinical research on the relative efficacy of letrozole and clomiphene citrate in achieving ovulation among women with polycystic ovarian syndrome. Int J Reprod Contracept Obstet Gynecol 2026;15:1601-5.