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**Original Research Article**

# A comparative study of the efficacy of letrozole versus clomiphene citrate for ovulation induction in anovulatory cycle in subfertile women

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## ABSTRACT

**Background:** Anovulation is a leading cause of female infertility, with clomiphene citrate (CC) and letrozole (LTZ) being commonly used agents for ovulation induction. While CC has been the first-line therapy, its anti-estrogenic effects may impair endometrial receptivity. LTZ, an aromatase inhibitor, offers a potentially superior alternative by enhancing follicular sensitivity without adverse endometrial effects.
**Methods:** This randomized controlled trial was conducted at the department of obstetrics and gynecology, Government Medical College and Hospital, Akola, Maharashtra, involving subfertile women with anovulatory cycles. Participants were allocated to receive either CC or LTZ. Outcomes assessed included ovulation rate, pregnancy rate, cycles to conception, single follicle formation, and endometrial thickness. Data were analyzed using appropriate statistical methods.
**Results:** Letrozole demonstrated higher ovulation and pregnancy rates compared to clomiphene citrate. LTZ was associated with improved endometrial thickness and a greater proportion of monofollicular development. Fewer side effects and complications were observed in the LTZ group. The number of cycles required for conception was lower with LTZ.
**Conclusions:** Letrozole is more efficacious than clomiphene citrate for ovulation induction in anovulatory subfertile women. It offers better endometrial receptivity, higher pregnancy rates, and fewer adverse effects, making it a preferable first-line agent in selected cases.

**Keywords:** Anovulation, Clomiphene citrate, Letrozole, Ovulation induction

## INTRODUCTION

Infertility is a global health concern affecting approximately 10-15% of reproductive-aged couples, with female factors contributing to nearly half of these cases.[1] Among these, anovulation is a leading cause, accounting for 20-40% of female infertility.[2] The World Health Organization (WHO) defines infertility as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[3] Anovulatory infertility is particularly common in women with polycystic ovarian syndrome (PCOS), hypothalamic dysfunction, or premature ovarian insufficiency.[4]

Ovulation induction is a cornerstone in the management of anovulatory infertility. The goal is to stimulate the development and release of a mature oocyte, thereby increasing the chances of conception.[5] Clomiphene citrate (CC), a selective estrogen receptor modulator, has long been the first-line pharmacological agent for ovulation induction due to its affordability, oral administration, and established efficacy.[6]

It acts by blocking estrogen receptors at the hypothalamus, leading to increased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[7] However, despite ovulation rates of 60-85%, CC is associated with relatively low pregnancy rates (18-20%) due to its anti-estrogenic effects on the endometrium and cervical mucus.[8] Additional concerns include resistance in some patients, multifollicular development, ovarian hyperstimulation syndrome (OHSS), and formation of ovarian cysts.[9]

Letrozole (LTZ), an aromatase inhibitor originally developed for breast cancer treatment, has gained popularity as an alternative ovulation induction agent, especially in CC-resistant cases.[10] LTZ inhibits the conversion of androgens to estrogens, thereby reducing negative feedback on the hypothalamic-pituitary axis and enhancing endogenous FSH secretion.[11] This mechanism promotes monofollicular development and improves endometrial receptivity without the peripheral anti-estrogenic effects seen with CC.[12] Several studies have demonstrated that LTZ results in higher pregnancy rates, better endometrial thickness, and fewer adverse effects compared to CC.[13-15]

The WHO classifies anovulatory infertility into three groups: group I (hypogonadotropic hypogonadism), group II (normogonadotropic anovulation, commonly PCOS), and group III (hypergonadotropic hypogonadism).[16] Most women with PCOS fall under group II and respond well to ovulation induction with LTZ or CC. Recent guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the European Society of Human Reproduction and Embryology (ESHRE) recommend LTZ as the first-line agent for ovulation induction in women with PCOS due to its superior efficacy and safety profile.[17,18]

Despite growing evidence favoring LTZ, CC remains widely used in clinical practice, particularly in resource-limited settings. Therefore, comparative studies are essential to guide evidence-based treatment decisions. This study aimed to evaluate and compare the efficacy of letrozole versus clomiphene citrate for ovulation induction in subfertile women with anovulatory cycles, focusing on ovulation rates, pregnancy outcomes, endometrial parameters, and safety profiles.

## METHODS

The present study was a prospective randomized controlled trial conducted at the department of gynaecology and obstetrics, Government Medical College and Hospital, Akola, Maharashtra, over two years from January 2023 to March 2025. The study population comprised subfertile women aged between 20 and 35 years who were diagnosed with anovulatory infertility.

Eligibility was confirmed through clinical evaluation, ensuring normal tubal patency and semen parameters of their partners. Women with tubal blockage, male factor infertility, or endocrine disorders such as thyroid dysfunction or hyperprolactinemia were excluded from participation.

Eligible participants were randomly assigned to two intervention groups. Group A received letrozole at a dose of 2.5-5 mg/day orally from day 3 to day 7 of the menstrual cycle, while group B was administered clomiphene citrate at a dose of 50-100 mg/day orally during the same cycle window. Ovulation monitoring was performed using transvaginal sonography (TVS) and serum progesterone levels. When the dominant follicle reached a size of ≥18 mm, human chorionic gonadotropin (hCG) was administered to trigger ovulation.

The primary outcomes measured included ovulation rate, pregnancy rate, number of cycles required for conception, endometrial thickness, and follicular development. Secondary outcomes assessed were side effects and complications associated with each drug.

### *Statistical analysis*

Data were statistically analyzed using SPSS version 25. Chi-square tests were applied for categorical variables and independent t-tests for continuous variables. A p value of less than 0.05 was considered statistically significant.

## RESULTS

The Table 1 shows age distribution among both groups. The mean age in group A was 27.28±8.73 years and group B was 28.03±9.12 years. There was no significant difference in age distribution in two groups (p>0.05) (Table 1).

**Table 1: Age-wise distribution of patients.**

| Age (years) | Group A (letrozole) | Group B (clomiphene citrate) | P value |
|---|---|---|---|
| **21-25** | 10 (20.0) | 14 (28.0) | 0.78 (NS) |
| **26-30** | 34 (68.0) | 31 (62.0) | |
| **>30** | 06 (12.0) | 05 (10.0) | |
| **Total** | 50 (100) | 50 (100) | |
| **Mean age (years)** | 27.28±8.73 | 28.03±9.12 | |

NS=not significant.

**Table 2: BMI-wise distribution of patients.**

| BMI (kg/m$^2$) | Group A (letrozole) | Group B (clomiphene citrate) | P value |
|---|---|---|---|
| **Underweight (<18.5)** | 01 (02.0) | 02 (04.0) | |
| **Normal (18.5-24.9)** | 28 (56.0) | 27 (54.0) | |
| **Overweight (25-29.9)** | 15 (30.0) | 14 (28.0) | 0.62 (NS) |
| **Obese (≥30)** | 06 (12.0) | 07 (14.0) | |
| **Total** | 50 (100) | 50 (100) | |
| **Mean BMI (kg/m$^2$)** | 26.68±3.21 | 27.11±3.42 | |

NS=not significant.

**Table 3: Distribution according to type of infertility among patients.**

| Type of infertility | Group A (Letrozole) | Group B (Clomiphene citrate) | P value |
|---|---|---|---|
| **Primary** | 38 (76.0) | 32 (64.0) | |
| **Secondary** | 12 (24.0) | 18 (36.0) | 0.45 (NS) |
| **Total** | 50 (100) | 50 (100) | |

NS=not significant.

**Table 4: Distribution according to follicular and endometrial factors.**

| Variables | Group A (letrozole) | Group B (clomiphene citrate) | P value |
|---|---|---|---|
| **Antral follicle count (AFC)** | 4.18±1.19 | 3.79±1.08 | <0.001 |
| **No. of follicles >18 mm** | 3.02±1.28 | 2.20±1.1 | 0.03 (S) |
| **Endometrial thickness** | 8.06±2.19 | 7.4±2.20 | <0.0001 (S) |

S=significant.

**Table 5: Distribution according to follicular size factor.**

| No. of days to reach follicles >18 mm | Group A (letrozole) | Group B (clomiphene citrate) | P value |
|---|---|---|---|
| **Mean (days)** | 15.28±1.63 | 14.01±1.28 | 0.01 (S) |

S=significant.

Table 2 shows BMI distribution among both groups. The mean BMI in group A was 26.68±3.21 and group B was 27.11±3.42 kg/m$^2$. There was no difference when two groups were compared statistically with respect to BMI (p>0.05).

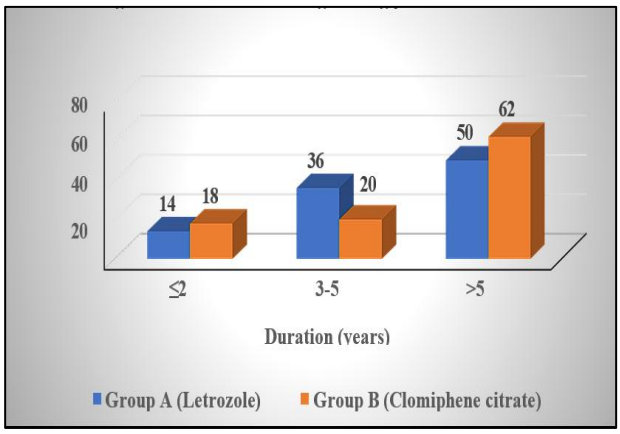


**Figure 1: Duration of marriage among participants.**

Table 3 shows type of infertility among both groups. Out of total 100 patients, there were 38 (76%) and 32 (62%) patients of primary infertility among group A and group B respectively. The secondary infertility was seen in 12 (24%) and 18 (36%) patients in group A and group B respectively. There was no difference when two groups were compared statistically with respect to type of infertility (p>0.05).

Table 4 shows follicular and endometrial factors among both groups.

The mean antral follicle count (AFC) was significantly higher in the letrozole group (4.18±1.19) compared to the clomiphene group (3.79±1.08), with a highly significant p-value of <0.001. The number of follicles measuring more than 18 mm was also significantly greater in group A (3.02±1.28) than in group B (2.20±1.1), with a p value of 0.03. Additionally, endometrial thickness was notably thicker in the letrozole group (8.06±2.19 mm) than in the clomiphene group (7.4±2.20 mm), with a highly significant difference (p<0.0001). These findings suggest a superior ovarian and endometrial response in the letrozole group.

Figure 3 outlines the side effect profile associated with letrozole (group A) and clomiphene citrate (group B). Headaches were reported by 5 (10%) individuals in the letrozole group and 7 (14%) in the clomiphene group, with

a non-significant p value of 0.72. Hot flushes occurred in 2 (4%) and 4 (8%) participants respectively (p=0.76), while abdominal pain was noted in 1 (2%) case from group A and 2 (4%) from group B (p=0.56).

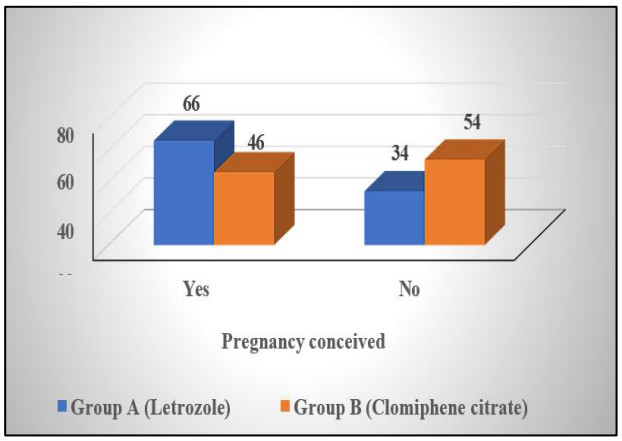


**Figure 2: Distribution according to pregnancy outcome.**

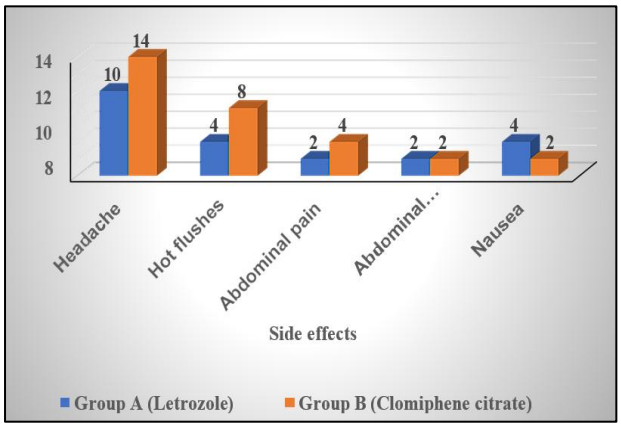


**Figure 3: Distribution according to side effects.**

Both groups reported 1 (2%) case of abdominal bloating (p=0.98), and nausea affected 2 (4%) participants in group A and 1 (2%) in group B (p=0.56). Overall, no significant differences in side effects were observed between the two treatment groups

## DISCUSSION

In this randomized controlled trial comparing letrozole and clomiphene citrate for ovulation induction in anovulatory subfertile women, both groups were demographically comparable in terms of age, BMI, and infertility type, consistent with previous studies by Badawy et al and Bayar et al.[13,14]

Letrozole demonstrated superior ovarian responsiveness, with significantly higher antral follicle count and dominant follicles (>18 mm) compared to clomiphene citrate (p<0.05), aligning with findings from Bayar et al and Badawy et al.[13,14] Endometrial thickness was also greater in the letrozole group (8.06±2.19 mm versus 7.4±2.20 mm; p<0.0001), likely due to its shorter half-life and lack of peripheral anti-estrogenic effects, as supported by Holzer et al and Casper and Mitwally.[11,12]

Ovulation and pregnancy rates were significantly higher with letrozole (66% and 32%) than with clomiphene citrate (46% and 18%) (p<0.05), consistent with Badawy et al, Bayar et al and the Cochrane review by Franik et al.[13-15] Letrozole's physiological induction of monofollicular development and improved endometrial receptivity contribute to its superior conception outcomes, as noted by Homburg.[6]

Follicular maturation time was slightly longer with letrozole (15.28±1.63 days versus 14.01±1.28 days; p=0.01), reflecting its gradual estrogen suppression and more natural follicular recruitment, as described by Holzer et al.[11]

Both agents were well tolerated, with no significant difference in adverse effects (p>0.05), echoing safety profiles reported by Badawy et al and Bayar et al.[13,14] Letrozole's favorable tolerability is attributed to its minimal systemic estrogen receptor blockade.

Overall, our findings reinforce existing literature supporting Letrozole's efficacy and safety. Studies by Mitwally and Casper, Casper and Mitwally, and Franik et al highlight its advantages in endometrial development and pregnancy outcomes.[10,12,15] Given this evidence, letrozole should be considered the first-line agent for ovulation induction in anovulatory infertility, particularly in PCOS cases, as endorsed by ACOG and ESHRE guidelines.[17,18]

The study was limited by its small sample size and single-center design, which may restrict generalizability. Follow-up was short, so long-term outcomes such as live birth and miscarriage rates could not be evaluated. Additionally, hormonal monitoring and control of confounding factors like lifestyle and diet were limited. Larger multicentric studies with longer follow-up are needed to confirm these results.

## CONCLUSION

Letrozole proved more effective than clomiphene citrate for ovulation induction, with higher ovulation and pregnancy rates and better endometrial response. The study supports letrozole as a safer and more physiological first-line option in anovulatory infertility, contributing evidence that can refine fertility management and clinical decision-making.

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