Pregnancy Achievement Using Letrozole Versus Clomiphene Citrate in Anovulatory Women

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Abstract

Objective: To compare pregnancy achievement using letrozole versus clomiphene citrate among anovulatory women presenting with infertility. Method: This comparative analytical study included 160 anovulatory infertile women divided equally into two treatment groups: letrozole (n = 80) and clomiphene citrate (n = 80). Baseline demographic, reproductive, endocrine, ultrasound, follicular, ovulatory, and pregnancy variables were analyzed. The primary outcome was pregnancy achievement. Secondary outcomes included mature follicle development, ovulation, biochemical pregnancy, clinical pregnancy, endometrial thickness, miscarriage, multiple pregnancy, and adverse effects. Independent samples t tests were applied for continuous variables, and chi-square tests were used for categorical variables. Results: Pregnancy was achieved in 27 women (33.8%) receiving letrozole compared with 9 women (11.3%) receiving clomiphene citrate, showing a statistically significant difference ($p = .001$). Letrozole was associated with higher odds of pregnancy achievement (OR = 4.02, 95% CI [1.75, 9.25]) and a higher relative probability of pregnancy (RR = 3.00, 95% CI [1.51, 5.97]). Ovulation was achieved in 63 women (78.8%) in the letrozole group and 50 women (62.5%) in the clomiphene citrate group ($p = .037$). Mean dominant follicle size and endometrial thickness were also significantly greater in the letrozole group. Conclusion: Letrozole was superior to clomiphene citrate for pregnancy achievement and ovulation among anovulatory infertile women in this dataset. These findings support the use of letrozole as an effective first-line oral ovulation induction option in appropriately selected women after exclusion of other infertility factors.

Keywords: anovulation; clomiphene citrate; infertility; letrozole; ovulation induction; pregnancy

Introduction

Infertility is a clinically important reproductive health concern and is commonly defined as the inability to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse. It affects couples physically, psychologically, socially, and economically, particularly in societies where childbearing is strongly associated with family stability and social expectations. Among female causes of infertility, ovulatory dysfunction is a major and potentially treatable contributor. Anovulation commonly presents with oligomenorrhea, amenorrhea, irregular menstrual cycles, polycystic ovarian morphology, or biochemical endocrine disturbance. Because ovulation induction is relatively accessible and cost-effective, oral pharmacologic therapy remains a central component of first-line infertility management for women with anovulatory cycles.

Polycystic ovary syndrome (PCOS) is one of the most frequent causes of anovulatory infertility. Women with PCOS may have chronic oligo-ovulation or anovulation, hyperandrogenism, insulin resistance, and polycystic ovarian morphology. Treatment should be individualized after evaluation of male factor infertility, tubal patency, endocrine abnormalities, thyroid dysfunction, hyperprolactinemia, and other pelvic pathology. In women with anovulatory infertility and no other major infertility factor, induction of ovulation is a rational therapeutic approach. The 2023 international evidence-based guideline for PCOS recommends letrozole rather than clomiphene citrate for improving ovulation, clinical pregnancy, and live-birth rates in women with PCOS-related anovulatory infertility (Teede et al., 2023).

Clomiphene citrate has historically been used as a first-line oral ovulation induction agent. It is a selective estrogen receptor modulator that acts primarily at the hypothalamic-pituitary axis by blocking estrogen feedback, thereby increasing endogenous gonadotropin release and stimulating follicular growth. The drug is widely available, inexpensive, and familiar to obstetricians and gynecologists. However, clomiphene citrate has limitations. Its anti-estrogenic action may adversely affect cervical mucus and endometrial receptivity, and some women demonstrate clomiphene resistance. Consequently, ovulation may occur without corresponding improvement in pregnancy rates.

Letrozole is an aromatase inhibitor that reduces peripheral and ovarian estrogen production for a short period. This temporary reduction in estrogen decreases negative feedback on the hypothalamic-pituitary-ovarian axis and promotes follicle-stimulating hormone release. Compared with clomiphene citrate, letrozole has a shorter half-life and fewer prolonged anti-estrogenic effects on the endometrium. These characteristics provide a biologically plausible explanation for improved ovulation, endometrial receptivity, and pregnancy outcomes in anovulatory infertility.

The landmark randomized trial by Legro et al. (2014) reported higher cumulative live-birth and ovulation rates with letrozole compared with clomiphene citrate among infertile women with PCOS. Cochrane evidence has also concluded that letrozole improves live-birth and pregnancy rates compared with clomiphene citrate in subfertile women with anovulatory PCOS (Franik et al., 2018). Recent local evidence from Pakistan has similarly supported letrozole as a better treatment choice than clomiphene citrate for induction of ovulation in infertile women with PCOS (Wasim et al., 2024). Nevertheless, local institutional data remain valuable because patient characteristics, body mass index, duration of infertility, access to follicular monitoring, and adherence to timed intercourse may differ across clinical settings.

The present study was designed to compare pregnancy achievement using letrozole versus clomiphene citrate among anovulatory infertile women managed in a gynecology and obstetrics setting. The study focused on clinically relevant outcomes including mature follicle development, ovulation, endometrial thickness, biochemical pregnancy, clinical pregnancy, miscarriage, multiple pregnancy, and adverse effects.

Method

Study Design and Setting

This comparative analytical study was conducted in the Department of Gynaecology and Obstetrics, Recep Tayyip Erdogan Hospital, Muzaffargarh. The study included women presenting with anovulatory infertility who received oral ovulation induction using either letrozole or clomiphene citrate. Institutional ethical approval was obtained before data collection, and written informed consent was obtained from participants according to departmental protocol.

Participants

A total of 160 women with anovulatory infertility were included. Participants were divided equally into two groups: Group A received letrozole and Group B received clomiphene citrate. Eligible participants were women of reproductive age presenting with infertility and clinical evidence of anovulation, including oligomenorrhea, irregular cycles, amenorrhea, or ultrasound findings suggestive of polycystic ovarian morphology. Women with male factor infertility, bilateral tubal blockage, uncontrolled thyroid disease, hyperprolactinemia requiring separate treatment, ovarian cysts, suspected endometriosis, previous ovarian surgery, contraindication to ovulation induction medicines, or incomplete follow-up were excluded.

Intervention and Monitoring

Letrozole was administered orally in the letrozole group according to the departmental ovulation induction protocol. Clomiphene citrate was administered orally in the comparison group. Dose escalation and number of treatment cycles were guided by clinical response, follicular monitoring, and patient tolerance. Follicular tracking was performed by ultrasonography. A mature follicle was defined as a dominant follicle reaching approximately 18 mm or more. Endometrial thickness was recorded during the periovulatory phase. Timed intercourse was advised after evidence of dominant follicular development or expected ovulation. Ovulation was documented through follicular rupture on follow-up ultrasound and/or clinical monitoring according to available records.

Outcome Measures

The primary outcome was pregnancy achievement, defined as a documented positive pregnancy outcome in the treatment cycle follow-up. Secondary outcomes were mature follicle development, number of mature follicles, ovulation achievement, biochemical pregnancy, clinical pregnancy, dominant follicle size, endometrial thickness, miscarriage, multiple pregnancy, and adverse effects.

Statistical Analysis

Data were analyzed using Python-based statistical procedures. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as frequencies and percentages. Independent samples t tests were used for comparison of continuous variables between the two groups. Chi-square tests were used for categorical variables. Odds ratios and relative risks with 95% confidence intervals were calculated for clinically important binary outcomes. A p value less than .05 was considered statistically significant.

Results

A total of 160 women were included, with 80 women in the letrozole group and 80 women in the clomiphene citrate group. The mean age was 28.32 (4.46) years in the letrozole group and 29.88 (4.40) years in the clomiphene citrate group. Although the clomiphene citrate group was slightly older, both groups were broadly comparable in body mass index, infertility duration, infertility type, cycle irregularity, and PCOS morphology on ultrasound.

Table 1

Baseline demographic and reproductive characteristics of participants

Characteristic	Letrozole (n = 80)	Clomiphene citrate (n = 80)	p
Sample size	80	80	--
Age, years, M (SD)	28.32 (4.46)	29.88 (4.40)	.028
BMI, kg/m2, M (SD)	27.96 (4.28)	28.47 (3.93)	.435
Duration of infertility, years, M (SD)	3.99 (1.73)	4.36 (1.67)	.168
Primary infertility, n (%)	50 (62.5)	45 (56.2)	.520
Secondary infertility, n (%)	30 (37.5)	35 (43.8)	
PCOS morphology on ultrasound, n (%)	68 (85.0)	69 (86.2)	1.000
Rural residence, n (%)	51 (63.7)	41 (51.2)	.150

Note. M = mean; SD = standard deviation; BMI = body mass index; PCOS = polycystic ovary syndrome. p values were calculated using independent samples t tests for continuous variables and chi-square tests for categorical variables.

Mature follicle development was more frequent with letrozole than with clomiphene citrate. A mature follicle developed in 54 women (67.5%) in the letrozole group compared with 35 women (43.8%) in the clomiphene citrate group (p = .004). Ovulation was achieved in 63 women (78.8%) receiving letrozole and 50 women (62.5%) receiving clomiphene citrate (p = .037). Mean dominant follicle size and endometrial thickness were significantly higher in the letrozole group.

Table 2

Ovulation induction and follicular monitoring outcomes

Outcome	Letrozole (n = 80)	Clomiphene citrate (n = 80)	p
Treatment cycles, M (SD)	1.73 (0.73)	1.76 (0.85)	.764
Dominant follicle size, mm, M (SD)	18.78 (3.11)	17.18 (3.16)	.001
Endometrial thickness, mm, M (SD)	8.76 (1.19)	7.78 (1.14)	< .001
Mature follicle developed, n (%)	54 (67.5)	35 (43.8)	.004

Ovulation achieved, n (%)	63 (78.8)	50 (62.5)	.037
Timed intercourse advised, n (%)	61 (76.2)	55 (68.8)	.376

Note. p values were calculated using independent samples t tests or chi-square tests as appropriate.

The primary outcome showed a statistically significant advantage for letrozole. Pregnancy was achieved in 27 women (33.8%) in the letrozole group compared with 9 women (11.2%) in the clomiphene citrate group (p = .001). The odds of pregnancy achievement were approximately four times higher with letrozole than with clomiphene citrate (OR = 4.02, 95% CI [1.75, 9.25]).

Table 3

Pregnancy outcomes and treatment tolerability

Outcome	Letrozole (n = 80)	Clomiphene citrate (n = 80)	p
Biochemical pregnancy, n (%)	30 (37.5)	11 (13.8)	.001
Clinical pregnancy, n (%)	27 (33.8)	9 (11.2)	.001
Pregnancy achieved, n (%)	27 (33.8)	9 (11.2)	.001
Miscarriage, n (%)	1 (1.2)	0 (0.0)	1.000
Multiple pregnancy, n (%)	0 (0.0)	0 (0.0)	1.000
Any adverse effect, n (%)	25 (31.2)	30 (37.5)	.506

Note. Pregnancy achieved corresponds to the study primary outcome. No multiple pregnancy was recorded in either group.

Table 4

Effect estimates for major clinical outcomes

Outcome	Odds ratio [95% CI]	Relative risk [95% CI]	p
Pregnancy achieved	4.02 [1.75, 9.25]	3.00 [1.51, 5.97]	.001
Clinical pregnancy	4.02 [1.75, 9.25]	3.00 [1.51, 5.97]	.001
Biochemical pregnancy	3.76 [1.72, 8.22]	2.73 [1.47, 5.06]	.001
Ovulation achieved	2.22 [1.10, 4.48]	1.26 [1.03, 1.55]	.037
Mature follicle developed	2.67 [1.40, 5.08]	1.54 [1.15, 2.06]	.004

Note. Reference group was clomiphene citrate. Values greater than 1 favor letrozole.

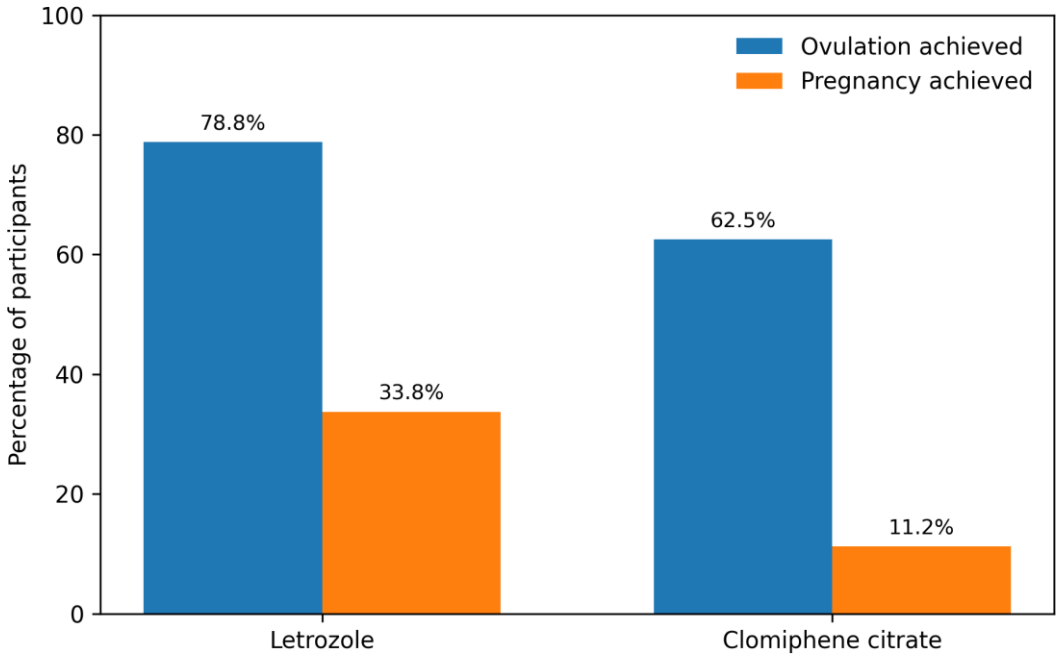

Figure 1. Ovulation and pregnancy achievement rates by treatment group.

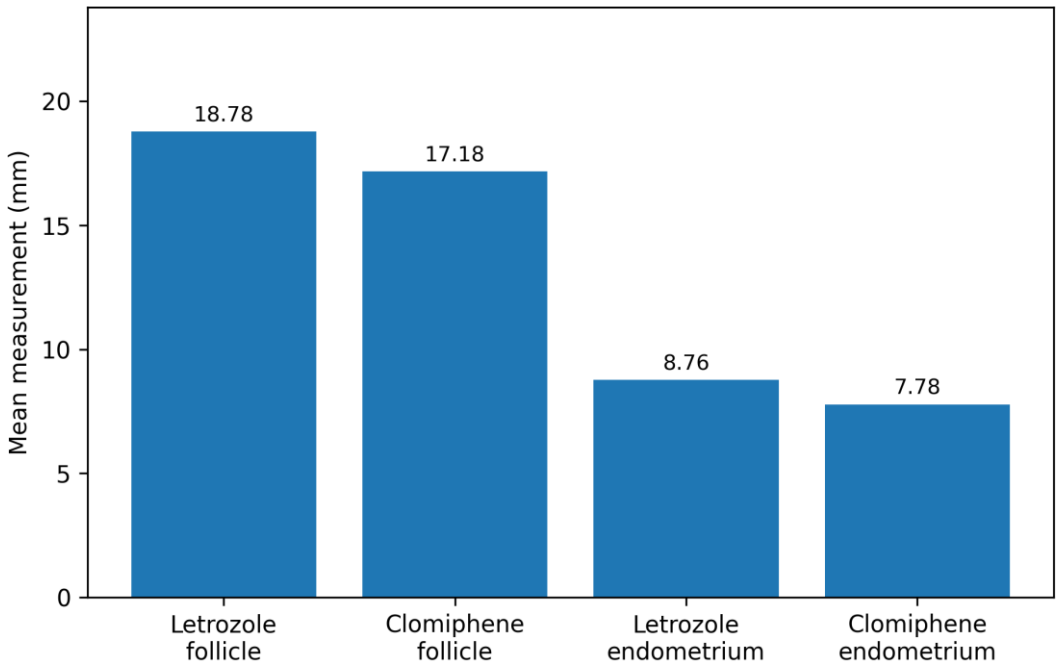

Figure 2. Mean dominant follicle size and endometrial thickness by treatment group.

Discussion

This study compared pregnancy achievement after oral ovulation induction with letrozole versus clomiphene citrate among 160 anovulatory infertile women. The main finding was that letrozole was associated with a significantly higher pregnancy achievement rate than clomiphene citrate. Pregnancy was achieved in 33.8% of women receiving letrozole compared with 11.3% of women receiving clomiphene citrate. This difference was statistically significant and clinically meaningful, with letrozole showing an odds ratio of 4.02 and a relative risk of 3.00 for pregnancy achievement compared with clomiphene citrate.

The superiority of letrozole in the present analysis is consistent with contemporary international evidence. Legro et al. (2014) demonstrated that letrozole resulted in higher live-birth and ovulation rates than clomiphene citrate among women with PCOS-related infertility. Similarly, the Cochrane review by Franik et al. (2018) concluded that letrozole improves live-birth and pregnancy rates compared with clomiphene citrate in subfertile women with anovulatory PCOS. The 2023 international PCOS guideline also recommends letrozole rather than clomiphene citrate in women with PCOS, anovulatory infertility, and no other infertility factors to improve ovulation, clinical pregnancy, and live birth (Teede et al., 2023).

The biological rationale for improved outcomes with letrozole is strong. Letrozole inhibits aromatase activity and temporarily lowers estrogen production. The resulting decrease in estrogen-mediated negative feedback increases endogenous follicle-stimulating hormone secretion and supports follicular recruitment. Because the anti-estrogenic effect is temporary, letrozole is less likely to impair endometrial development or cervical mucus quality. In contrast, clomiphene citrate acts as a selective estrogen receptor modulator and may remain bound to estrogen receptors for a longer duration. This can create a discrepancy between ovulation and conception, as ovulation may occur in the presence of less favorable endometrial receptivity.

The follicular monitoring findings in this study support this mechanism. Mean dominant follicle size was significantly greater with letrozole (18.78 (3.11) mm) than with clomiphene citrate (17.18 (3.16) mm). Endometrial thickness was also significantly higher in the letrozole group (8.76 (1.19) mm) than in the clomiphene citrate group (7.78 (1.14) mm). These findings suggest that letrozole not only promoted ovulation more effectively but also produced a more favorable periovulatory environment for implantation.

Ovulation was achieved in 78.8% of women receiving letrozole compared with 62.5% receiving clomiphene citrate. Although both drugs are effective oral agents, the higher ovulation rate in the letrozole group translated into a higher pregnancy achievement rate. This is clinically important because pregnancy, rather than ovulation alone, is the patient-centered outcome of infertility treatment. The higher biochemical and clinical pregnancy rates in the letrozole group strengthen the interpretation that letrozole provided a meaningful reproductive advantage in this population.

The findings are also relevant to local practice. Women presenting to public or semi-public hospitals in Pakistan may have long infertility duration, higher BMI, irregular follow-up, and limited ability to undergo expensive assisted reproductive techniques. In this setting, an effective oral ovulation induction medicine that improves pregnancy achievement while remaining feasible for outpatient care has practical value. Letrozole may therefore be preferred in appropriately selected anovulatory women, especially those with PCOS morphology and no other identifiable infertility factor.

Treatment tolerability was acceptable in both groups. Any adverse effect was reported in 31.3% of the letrozole group and 37.5% of the clomiphene citrate group, with no statistically significant difference. No multiple pregnancy was recorded in either group, and miscarriage was uncommon. These findings align with prior evidence suggesting that letrozole does not increase miscarriage or multiple pregnancy rates compared with clomiphene citrate (Franik et al., 2018; Teede et al., 2023).

The study has some limitations. First, this was a single-center analysis, which may limit generalizability to other populations. Second, live birth was not assessed as the final outcome, and pregnancy achievement was used as the primary endpoint. Third, some potentially important predictors such as anti-Mullerian hormone, insulin resistance, semen parameters in detail, tubal patency method, and long-term obstetric outcome were not included in the analytical model. Fourth, treatment adherence and exact timing of intercourse may have influenced pregnancy outcomes. Despite these limitations, the dataset provides clinically useful evidence supporting letrozole over clomiphene citrate for ovulation induction in anovulatory infertile women.

Future research should include larger multicenter prospective studies with standardized diagnostic criteria, stratification by BMI and PCOS phenotype, assessment of live-birth rate, cost-effectiveness analysis, and longer follow-up. Additional analysis may also evaluate predictors of response to letrozole, including age, BMI, infertility duration, baseline LH/FSH profile, and endometrial thickness.

Conclusion

Letrozole was associated with significantly higher pregnancy achievement compared with clomiphene citrate among anovulatory infertile women. Letrozole also resulted in higher ovulation rate, greater mature follicle development, larger dominant follicle size, and greater endometrial thickness. The findings support letrozole as an effective first-line oral ovulation induction agent in appropriately selected anovulatory women after exclusion of other infertility factors.

Recommendations

Letrozole should be considered as a preferred oral ovulation induction agent for anovulatory infertile women, particularly those with PCOS features and no other major infertility factor. Baseline infertility workup, pregnancy exclusion before treatment, ultrasound monitoring, counseling regarding timed intercourse, and follow-up documentation are essential for safe and effective use. Future institutional protocols should include live-birth follow-up to strengthen clinical outcome assessment.

Declarations

Ethical approval: Institutional ethical approval was obtained before data collection.

Informed consent: Written informed consent was obtained from participants according to departmental protocol.

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

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Data availability: The analyzed study dataset is available from the corresponding author on reasonable request, subject to institutional permission and patient confidentiality requirements.

Author contributions: Sidra Azhar contributed to study conception, data organization, analysis interpretation, and manuscript drafting. Samina Mumtaz supervised the study and critically reviewed the manuscript. Ayesha Ghaffar, Bushra Iqbal, Zermina Munir, Nusrat Rasheed, and Aleesha Sarfaraz contributed to clinical data review, literature support, and manuscript revision. All authors approved the final manuscript.

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