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Comparison of Letrozole Combined With Gonadotropins Versus Clomiphene Citrate Combined With Gonadotropins in Infertile Women Presenting With Polycystic Ovary Syndrome (PCOS)

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age and an important cause of anovulatory infertility. Although clomiphene citrate (CC) has traditionally been used for ovulation induction, letrozole is increasingly preferred because of its favorable effects on ovulation and its limited peripheral antiestrogenic activity. This randomized controlled trial compared clinical pregnancy outcomes following letrozole combined with gonadotropins and CC combined with gonadotropins among infertile women with PCOS. The study was conducted in the Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital, Lahore, from November 2025 to April 2026. A total of 110 women aged 20–39 years were randomized into two groups of 55. Group L received letrozole 2.5 mg daily on cycle days 2–6, while Group CC received CC 50 mg daily on the same days. Both groups subsequently received gonadotropins at 75 IU daily from cycle day 7, with treatment offered for up to three consecutive cycles. Ovulation was triggered using 10,000 IU of human chori-

onic gonadotropin once the dominant follicle reached at least 18 mm. Clinical pregnancy was assessed using serum β -hCG testing and transvaginal ultrasonographic confirmation of an intrauterine gestational sac. Data were analyzed using SPSS version 26. Clinical pregnancy occurred in 17 of 55 women (30.9%) in Group L and 4 of 55 women (7.3%) in Group CC. The between-group difference was statistically significant (two-sided Fisher exact test, $p = 0.0029$). These findings indicate that, in this single-center sample, the letrozole–gonadotropin regimen was associated with a higher clinical pregnancy rate than the CC–gonadotropin regimen. The study did not provide sufficient adverse-event or live-birth data to establish comparative safety or longer-term reproductive outcomes. Further multicenter trials with transparent allocation procedures, complete safety reporting, and live-birth follow-up are warranted.

Keywords: clomiphene citrate; gonadotropins; infertility; letrozole; ovulation induction; polycystic ovary syndrome; clinical pregnancy

1. INTRODUCTION

Infertility is a major reproductive health concern affecting couples worldwide. It has conventionally been defined as failure to achieve pregnancy after 12 months of regular, unprotected sexual intercourse [1]. Primary infertility refers to the absence of any previous pregnancy, whereas secondary infertility occurs after a previous pregnancy, regardless of its outcome [2]. Both forms may arise from endocrine, reproductive, anatomical, genetic, or other physiological conditions that interfere with conception. Careful assessment of these potential factors is essential before treatment is selected, since the underlying cause of infertility influences both the choice of intervention and its expected outcome. Recognition of these distinctions is particularly important in studies examining ovulation induction, where the clinical response is affected by more than follicular growth alone.

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders affecting women of reproductive age and is an important cause of anovulatory infertility. Its reported prevalence varies with the population studied and the diagnostic criteria applied, while its endocrine, metabolic, and reproductive manifestations are heterogeneous [3, 4]. Ovulatory dysfunction, often accompanied by irregular menstrual cycles, can substantially reduce the likelihood of spontaneous conception. PCOS may also coexist with other factors relevant to fertility, including insulin resistance and obesity, which can complicate clinical management. Consequently, an effective ovulation-induction regimen should be considered in the wider context of individual patient characteristics and other potential causes of infertility.

Clomiphene citrate (CC), a selective estrogen receptor modulator, served for many years as a standard oral treatment for ovulation induction in women with PCOS. Although it can induce follicular development and ovulation, its peripheral antiestrogenic effects may adversely affect endometrial receptivity and cervical mucus in some patients. Letrozole, a nonsteroidal aromatase inhibitor, offers a different mechanism of action: by temporarily reducing estrogen synthesis, it alters hypothalamic–pituitary feedback and facilitates follicle-stimulating hormone secretion. Studies of ovulation-induction outcomes and treatment response have supported interest in letrozole as an alternative to CC [5–7]. The two agents differ in pharmacological effects, but comparisons of treatment regimens must account for dosages, accompanying injectable medications, patient selection, and the outcome measured. Letrozole was initially developed for hormone-sensitive breast cancer and subsequently became widely used in reproductive medicine.

Several investigations have explored letrozole in combination with injectable gonadotropins for women with PCOS. Ashry and colleagues compared letrozole-based treatment with and without gonadotropin injections, providing evidence about the effects of adding ovarian stimulation to an oral regimen [8]. Xi and colleagues evaluated letrozole or CC in combination with human menopausal gonadotropin among clomiphene-resistant women and observed broadly similar pregnancy rates between protocols, despite differences in several follicular outcomes [9]. Another randomized trial evaluated low-dose human chorionic gonadotropin in combination with CC among women with CC-resistant PCOS; because this was not the same injectable protocol as that used here, its results are relevant primarily as contextual evidence [10]. Together, these studies illustrate the variability in clinical response and the importance of comparing the specific treatment combinations rather than treating all gonadotropin-containing regimens as interchangeable.

The present study therefore compared the clinical pregnancy outcomes of letrozole plus gonadotropins with those of CC plus gonadotropins among infertile women with PCOS treated at a tertiary care hospital in Lahore. Both oral agents are familiar components of ovulation-induction practice, but their comparative performance when followed by the same injectable gonadotropin regimen requires careful evaluation in the local population. The principal outcome was clinical pregnancy, confirmed using biochemical testing and ultrasonography. The study was intended to contribute locally relevant data to the existing evidence, while recognizing that pregnancy rates alone cannot establish the relative safety, live-birth effectiveness, or suitability of either regimen for all patients.

Objective: To compare the clinical pregnancy rate following letrozole combined with gonadotropins with that following clomiphene citrate (CC) combined with gonadotropins in infertile women presenting with polycystic ovary syndrome (PCOS).

2. METHODOLOGY

This randomized controlled trial was conducted in the Department of Obstetrics and Gynecology at Sir Ganga Ram Hospital, Lahore, from November 2025 to April 2026. A total of 110 married women aged 20–39 years with infertility and PCOS, diagnosed according to the Rotterdam criteria, were enrolled through consecutive sampling before random assignment. The sample size was planned using expected clinical pregnancy rates of 31.1% for letrozole plus gonadotropins and 7.2% for CC plus gonadotropins, a 5% significance level, and 90% statistical power, resulting in a target of 55 women per group. These expected rates were planning assumptions and should not be confused with the observed study percentages. A computer-generated randomization sequence allocated participants to Group L (letrozole, 2.5 mg daily on cycle days 2–6) or Group CC (CC, 50 mg daily on cycle days 2–6). Both groups subsequently received gonadotropins at 75 IU daily beginning on cycle day 7. Ovulation-induction treatment could continue for up to three consecutive cycles. The availability

of a concealed allocation sequence, details of who implemented randomization, and registration information should be confirmed from the original trial records.

Eligible participants were women aged 20–39 years with infertility and PCOS meeting the study's predefined operational diagnostic criteria. Written informed consent was required before enrollment, and participants were assessed for other possible causes of infertility that could affect treatment outcomes.

Women were excluded if their partners had an abnormal semen analysis or if they had hyperprolactinemia, hypothalamic amenorrhea, premature ovarian failure, ovarian tumors, clinically important hepatic or renal dysfunction, tubal obstruction associated with pelvic inflammatory disease, or a relevant history of ovarian surgery. These restrictions were intended to reduce the influence of infertility factors other than anovulatory PCOS on the observed clinical pregnancy rates.

After institutional ethical approval, eligible women provided written informed consent and received counseling concerning diet, lifestyle, and reproductive health. Before ovulation induction, the protocol included dietary advice, structured exercise and weight-management counseling when appropriate, assessment and correction of vitamin D deficiency, and metabolic optimization when indicated. Participants were then assigned to Group L or Group CC according to the study randomization sequence. Group L received letrozole 2.5 mg daily on cycle days 2–6; Group CC received CC 50 mg daily during the same interval. From day 7, both groups received intramuscular gonadotropins at a dose of 75 IU daily, with follicular development and endometrial thickness monitored by serial transvaginal ultrasonography. Once a dominant follicle reached a diameter of at least 18 mm, ovulation was triggered using 10,000 IU of human chorionic gonadotropin (hCG). Timed intercourse was advised within 36 hours, and luteal progesterone was administered for 10 days. Treatment was offered for up to three consecutive cycles, subject to clinical monitoring and response.

Study data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS), version 26. Continuous variables, including age, body mass index (BMI), and duration of infertility, were summarized as means and standard deviations, while categorical variables were expressed as frequencies and percentages. The primary outcome was clinical pregnancy, defined by a positive serum β -hCG result followed by transvaginal ultrasonographic visualization of an intrauterine gestational sac. The two treatment groups were compared using Fisher's exact test, with a two-sided significance threshold of $p \leq 0.05$. Prespecified descriptive subgroups were based on age (younger than 30 versus 30 years or older), BMI (below 25 versus at least 25 kg/m²), and duration of infertility (less than 3 versus at least 3 years). Where data were sufficient, post-stratification chi-square tests were planned to examine associations within these categories. However, subgroup-specific event counts and estimates are not provided in the supplied results and should be included before any formal treatment-by-subgroup inference is made.

3. RESULTS

A total of 110 women with PCOS-associated infertility were randomized, with 55 participants allocated to Group L and 55 to Group CC. Baseline demographic and clinical characteristics are summarized in Table 1. The mean age was 28.4 ± 4.2 years in Group L and 28.9 ± 4.1 years in Group CC. Mean BMI was 26.8 ± 3.1 and 27.1 ± 3.3 kg/m², respectively, while the mean duration of infertility was 3.5 ± 1.4 and 3.8 ± 1.6 years. Primary infertility was reported by 38 women (69.1%) in Group L and 36 (65.5%) in Group CC. The reported between-group comparisons of these baseline measures did not reach statistical significance ($p > 0.05$). These observations describe baseline comparability but should not be interpreted as establishing equivalence between groups.

Table 1. Baseline demographic and clinical characteristics of the participants

Demographic Parameter	Group L: Letrozole + Gn (n=55)	Group CC: CC + Gn (n=55)	p-value
Age (years), mean $\pm$ SD	28.4 ± 4.2	28.9 ± 4.1	>0.05
BMI (kg/m ²), mean $\pm$ SD	26.8 ± 3.1	27.1 ± 3.3	>0.05
Duration of infertility (years), mean $\pm$ SD	3.5 ± 1.4	3.8 ± 1.6	>0.05
Primary infertility, n (%)	38 (69.1%)	36 (65.5%)	>0.05

As shown in Table 1, the groups had similar mean ages, body mass indices, and durations of infertility, and the proportions reporting primary infertility were also comparable. The original report provided only a general $p > 0.05$ statement for these variables; exact test statistics and associated p -values would improve the transparency of the baseline comparison.

The principal outcome is summarized in Table 2. Clinical pregnancy was achieved by 17 of 55 women in Group L (30.9%), compared with 4 of 55 in Group CC (7.3%). The absolute difference was approximately 23.6 percentage points, favoring letrozole plus gonadotropins. A two-sided Fisher exact test calculated from the reported event counts yielded $p = 0.0029$, indicating a statistically significant between-group difference. This finding concerns clinical pregnancy during the study period; it does not establish a corresponding improvement in live-birth rate or a difference in adverse-event risk.

Table 2. Comparison of clinical pregnancy outcomes between the treatment groups

Primary Outcome	Group L (n=55)	Group CC (n=55)	p-value
Successful clinical pregnancy	17 (30.9%)	4 (7.3%)	0.0029
No clinical pregnancy	38 (69.1%)	51 (92.7%)	

Women allocated to the letrozole–gonadotropin regimen had a higher observed clinical pregnancy proportion than those allocated to the CC–gonadotropin regimen (Table 2). Exploratory stratification by age and BMI was also described as favoring Group L within both categories of each variable. These subgroup summaries, shown in Table 3, do not provide the underlying participant denominators, pregnancy counts, confidence intervals, or subgroup-specific *p*-values. The descriptive direction of the reported effect can therefore be stated, but its precision and statistical consistency across strata cannot be independently evaluated from the supplied information.

Table 3. Descriptive clinical pregnancy comparisons by age and BMI categories

Stratification Variable	Group L	Group CC	Overall finding
Age <30 years	Higher pregnancy rate	Lower pregnancy rate	Favoring Group L
Age ≥30 years	Higher pregnancy rate	Lower pregnancy rate	Favoring Group L
BMI <25 kg/m ²	Higher pregnancy rate	Lower pregnancy rate	Favoring Group L
BMI ≥25 kg/m ²	Higher pregnancy rate	Lower pregnancy rate	Favoring Group L

As summarized in Table 3, the reported direction of the pregnancy difference favored Group L in both age strata and both BMI strata. Because numerical subgroup results were not supplied, these comparisons should be regarded as descriptive and exploratory. They should not be used to claim statistical significance within individual strata or to establish the absence of effect modification by age or BMI.

Duration of infertility was also considered as a potential source of variation in treatment response. The study's descriptive summaries indicated higher pregnancy rates with the letrozole–gonadotropin regimen among women with shorter and longer infertility duration; these results are reported in Table 4. As with the age- and BMI-stratified summaries, the lack of counts and statistical estimates limits the strength of conclusions based on these subgroup observations.

Table 4. Descriptive clinical pregnancy comparisons by duration of infertility

Duration of Infertility	Group L	Group CC	Overall finding
<3 years	Higher pregnancy rate	Lower pregnancy rate	Favoring Group L
≥3 years	Higher pregnancy rate	Lower pregnancy rate	Favoring Group L

Table 4 indicates that the direction of the observed clinical pregnancy difference was reported as favoring Group L in both infertility-duration categories. These findings do not demonstrate that the magnitude of benefit was the same across subgroups, because treatment-specific denominators, numbers of pregnancies, and measures of statistical uncertainty were not supplied. More detailed subgroup data would be required to assess potential variation in treatment response.

4. DISCUSSION

Infertility is a significant reproductive health concern and has traditionally been evaluated after 12 months of regular sexual intercourse without contraception, with earlier assessment often appropriate in specific clinical circumstances [1]. It can be classified as primary or secondary according to the history of a previous pregnancy, and its causes may involve multiple endocrine, physiological, reproductive, or anatomical factors [2]. PCOS is a frequent endocrine disorder among women of reproductive age and a leading cause of anovulatory infertility; its prevalence and clinical presentation differ according to the criteria applied, the populations studied, and the distribution of PCOS phenotypes [3]. The findings of this trial should therefore be interpreted within the broader complexity of infertility assessment, rather than as evidence concerning every cause or presentation of infertility.

The present randomized controlled trial compared letrozole combined with gonadotropins against CC combined with the same gonadotropin regimen in 110 infertile women with PCOS. Baseline characteristics were broadly similar, while clinical pregnancy was achieved by 17 women (30.9%) in the letrozole group compared with 4 women (7.3%) in the CC group. The difference was statistically significant according to the reported event counts. PCOS remains clinically heterogeneous, and variations in endocrine and metabolic characteristics could influence treatment response and the generalizability of this finding [4]. Previous studies of predictors of response to letrozole have also emphasized that pretreatment characteristics may affect ovulation-induction outcomes and should be considered when planning individualized fertility care [5]. Importantly, the pregnancy comparison addresses the two combined regimens studied; it does not isolate the independent effect of the oral drug from that of the gonadotropin treatment.

The difference in clinical pregnancy outcomes may partly reflect the distinct pharmacological mechanisms of the two

oral agents. Letrozole is an aromatase inhibitor that reduces estrogen synthesis transiently, thereby decreasing negative feedback within the hypothalamic–pituitary–ovarian axis and promoting endogenous gonadotropin secretion. CC is a selective estrogen receptor modulator that alters estrogen feedback centrally but may exert peripheral antiestrogenic effects on endometrial receptivity and cervical mucus. Such differences provide a plausible biological basis for differences in reproductive response, although the present study did not directly measure endometrial receptivity or test the underlying mechanism. Related studies of treatment modifications during ovulation induction, including adjunctive agents used with CC, illustrate continuing attempts to optimize reproductive outcomes [6].

The results are broadly consistent with comparative evidence favoring letrozole over CC for ovulation induction in women with PCOS. A systematic review and meta-analysis of randomized controlled trials reported improvements in ovulation, clinical pregnancy, and live-birth outcomes with letrozole compared with CC [7]. Nevertheless, most trials in that synthesis compared the oral agents themselves, whereas both arms of the present study received additional gonadotropins. Accordingly, the direction of the difference is consistent with the wider evidence, but the specific effect size should not be assumed to be directly comparable across different treatment protocols, populations, or cycle schedules.

Evidence concerning combination regimens is especially relevant to the present comparison. Ashry and colleagues assessed letrozole with or without gonadotropin injections in infertile women with PCOS, addressing whether sequential injectable stimulation adds to an oral regimen [8]. Xi and colleagues prospectively compared letrozole plus human menopausal gonadotropin with CC plus human menopausal gonadotropin among clomiphene-resistant women, and reported similar pregnancy rates across the regimens despite some differences in follicular development [9]. The women in that study had previously shown resistance to CC, so their clinical circumstances were not identical to those of the present sample. These investigations provide context for comparing combined treatments but should not be cited as demonstrating that one particular combination universally produces higher pregnancy rates.

The clinical pregnancy rate observed in the CC group was relatively low (7.3%). This result requires cautious interpretation, because observed rates may be influenced by ovarian response, treatment duration, the number of cycles completed, patient selection, and variability inherent in a modest sample. Thabet and colleagues studied the addition of low-dose hCG to CC in women with CC-resistant PCOS, providing evidence about another stimulation strategy [10]. That intervention differs from the daily gonadotropin regimen administered here, and its results cannot be used as a direct estimate of the expected response to CC plus gonadotropins in this study. Reporting cycle completion, treatment discontinuation, and the timing of outcome assessment would help clarify the observed difference.

Additional randomized trials have investigated sequential letrozole–gonadotropin strategies. Dai and colleagues examined sequential letrozole and gonadotropin treatment among infertile women with PCOS, contributing evidence about the clinical utility of combined oral and injectable stimulation [11]. A subsequent systematic review and meta-analysis of randomized controlled trials found that adding gonadotropins to letrozole could improve ovulation and clinical pregnancy rates compared with letrozole alone [12]. Although these findings are relevant to the biological and clinical rationale for combined stimulation, they do not constitute a direct comparison between letrozole plus gonadotropins and CC plus gonadotropins. Distinguishing these comparisons is necessary to avoid overstating how precisely previous studies corroborate the present result.

Chen and colleagues conducted a pragmatic randomized trial comparing two sequential letrozole doses followed by follicle-stimulating hormone administration in infertile women with PCOS [13]. That study compared letrozole 2.5 mg with letrozole 5 mg, both followed by FSH, and therefore addressed regimen optimization rather than the comparative efficacy of letrozole and CC. Its findings nevertheless indicate that treatment dose and sequence can influence pregnancy outcomes when oral and injectable ovulation-induction agents are combined. Differences in dose, timing, treatment population, outcome definition, and the number of cycles should be acknowledged when placing its results alongside the present study.

Broader evidence also supports the use of letrozole for women with anovulatory PCOS. A systematic review and meta-analysis reported a higher ovulation rate with letrozole than with CC [14]. A Cochrane review of aromatase inhibitors for ovulation induction likewise examined pregnancy and reproductive outcomes in this population [15]. These findings reinforce the rationale for considering letrozole in infertility treatment; however, effectiveness may vary across clinical subgroups, and results from comparisons of oral monotherapy cannot be applied uncritically to regimens incorporating injectable gonadotropins. The present findings are best viewed as evidence for the two specific treatment protocols examined at this hospital, rather than as a universal recommendation for all patients with PCOS.

Safety is an essential consideration when selecting an ovulation-induction regimen. A systematic review examined fetal outcomes following letrozole use in fertility treatment and contributed evidence to the evaluation of potential reproductive harms [16]. The 2023 international evidence-based PCOS guideline reports no demonstrated difference in fetal abnormality rates between letrozole and CC ovulation induction or natural conception and advises that letrozole should not be used if a pre-existing pregnancy is possible [17]. The present study focused on clinical pregnancy and did not provide comparative rates of congenital anomalies, miscarriage, multiple pregnancy, or ovarian hyperstimulation syndrome. It therefore cannot establish the relative safety of the two combined regimens. Appropriate ultrasound monitoring, individualized stimulation,

and counseling remain important when prescribing gonadotropins, particularly because multifollicular development can increase the risk of multiple pregnancy.

The findings should also be considered in relation to contemporary international recommendations. The 2023 international evidence-based guideline recommends letrozole as first-line pharmacological treatment for ovulation induction in women with anovulatory PCOS and no other infertility factors [17]. Gonadotropins may be considered primarily as a subsequent-line option after unsuccessful oral induction, depending on clinical circumstances and counseling. Although the present study observed more clinical pregnancies with letrozole plus gonadotropins than with CC plus gonadotropins, it does not demonstrate that routine addition of gonadotropins is appropriate as first-line therapy for all infertile women with PCOS. Treatment selection must remain sensitive to patient characteristics, access to monitoring, and the benefits and potential harms of ovarian stimulation.

Endometrial receptivity provides another possible explanation for differences in pregnancy outcomes. Investigations comparing letrozole, CC, and natural menstrual cycles have described changes in endometrial characteristics during the implantation window in women with PCOS [18]. Successful conception depends not only on follicular development and ovulation but also on the endometrial environment and subsequent implantation. However, the present study did not report a comparative analysis of endometrial receptivity or measurements capable of testing this explanation. Thus, the underlying mechanism of the observed pregnancy difference remains uncertain, and any proposed role for endometrial effects should be presented as a plausible interpretation rather than a directly demonstrated finding.

Fertility treatment in women with PCOS should be individualized according to the cause and duration of infertility, past treatment response, metabolic features, and reproductive goals. Reviews of PCOS-associated infertility emphasize the importance of assessing these factors before selecting an intervention [19]. A randomized controlled trial comparing letrozole and CC for ovulation induction adds further evidence concerning the relative performance of the two oral drugs [20]. The present study extends this general clinical question to a setting in which both arms received gonadotropins according to the same subsequent stimulation schedule. Nevertheless, the trial was not designed to determine which participants would benefit most from adding injectable medication or to identify a treatment strategy applicable to all women with PCOS.

PCOS is a complex reproductive and metabolic disorder, and fertility management often requires attention to additional clinical factors beyond ovulation induction alone [21]. In the present study, investigators used dominant follicle diameter as the criterion for hCG triggering and provided counseling and pre-treatment optimization before serial ultrasonographic monitoring. The consistency of the described treatment procedures may have reduced variation in the care delivered to the two groups. However, the available study information does not establish whether lifestyle counseling, vitamin D correction, or metabolic optimization exerted any independent effect on pregnancy outcomes. These co-interventions should be clearly reported because they can affect the interpretation and reproducibility of clinical trial findings.

Alternative oral stimulation strategies remain under investigation. For example, Sarkar and colleagues compared letrozole alone with combined letrozole and CC for ovulation induction among women with PCOS [22]. Although such evidence is relevant to treatment optimization, it does not evaluate either combination studied in the present trial. Comparisons involving letrozole plus CC, letrozole plus gonadotropins, and CC plus gonadotropins should therefore be distinguished explicitly. Each regimen has a different pharmacological basis and may be applied to a different clinical population. Clear differentiation among regimens makes the present results more interpretable and prevents unsupported conclusions about the superiority of treatments not directly compared.

The reported direction of the pregnancy difference favored letrozole plus gonadotropins across age, BMI, and infertility-duration categories in the descriptive stratified summaries. However, the subgroup tables do not supply event counts, sample sizes, effect estimates, or confidence intervals. The precision of these comparisons cannot therefore be assessed independently, and the absence of a reversal in direction does not establish a uniform treatment effect across participant characteristics. Small subgroups are particularly susceptible to random variation, and statistically meaningful effect modification cannot be evaluated without additional data. These observations should be interpreted as exploratory and should not be used to identify patient subgroups for which one regimen has a proven advantage.

Several limitations should be acknowledged. First, the study was conducted at a single tertiary care center and included 110 participants, which limits the precision and wider generalizability of its estimates. Second, clinical pregnancy rather than live birth was the primary endpoint, and the supplied results do not include miscarriage, multiple pregnancy, ovarian hyperstimulation syndrome, congenital anomaly, or other adverse-event rates. Third, details of allocation concealment, trial registration, participant flow, treatment discontinuation, and the number of treatment cycles completed are needed for complete reporting of a randomized trial. Finally, the subgroup summaries are qualitative and lack the counts required for independent statistical assessment. Larger multicenter trials with prospective registration, clear randomization procedures, and follow-up through live birth would help determine the comparative effectiveness and safety of these regimens.

5. CONCLUSION

This single-center randomized trial found a higher clinical pregnancy rate among infertile women with PCOS treated with letrozole plus gonadotropins than among those treated with CC plus gonadotropins (30.9% versus 7.3%, respectively; two-sided Fisher exact test, $p = 0.0029$). The finding is consistent in direction with broader evidence supporting letrozole for ovulation induction and with research on sequential letrozole–gonadotropin treatment. However, clinical pregnancy is not equivalent to live birth, and the trial did not report sufficient safety outcomes to establish comparative safety. Treatment decisions should therefore be individualized on the basis of patient characteristics, previous treatment response, access to monitoring, and potential risks of gonadotropin stimulation. Further adequately powered, registered randomized trials should evaluate live birth, miscarriage, multiple pregnancy, ovarian hyperstimulation, and cost-effectiveness while providing complete subgroup and participant-flow data.

Author contributions

All authors contributed to the conception, development, preparation, and revision of the manuscript, as reported by the authors. All authors reviewed and approved the final manuscript. Individual contributions should be confirmed with the authors before submission.

Conflict of interests

The authors declare that they have no conflicts of interest.

Data availability

Clinical data were collected and analyzed from 110 participants in this study. Individual-level reproductive health data are not publicly shared to protect participant confidentiality. Aggregated findings are presented in this article. Any request to access de-identified supporting data would require authorization from the responsible institution and compliance with applicable ethical requirements.

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