Original Article

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Comparative Efficacy of Letrozole and Clomiphene in Ovulation Induction for Infertile Females with Comorbidities: A Cross-sectional Study

Komorbiditesi Olan İnfertil Kadınlarda Ovulasyon İndüksiyonu için Letrozol ve Klomifenin Karşılaştırmalı Etkinliği: Kesitsel Bir Çalışma

Ayesha LARAIB[1], Usman NAWAZ[1], Sadia RASHID[3], Jawaria KHATOON[1], Maryam KHALID[2]
Fouzia KHALID[1], Urooj FATIMA[1]

[1]CMH Kharian Medical College, Department of Pharmacology, Kharian, Pakistan
[2]CMH Hospital Kharian, Department of Gynecology, Kharian, Pakistan
[3]Nawaz Sharif Medical College, Department of Pathology, Gujrat, Pakistan

ABSTRACT

Objective: The primary objective of the study was to compare the efficacy of clomiphene and letrozole in inducing ovulation in infertile women with comorbidities. Secondary objectives included evaluating differences in pregnancy outcomes in terms of pregnancy rates, multiple gestation and adverse effects of the drugs between the two treatment groups.

Methods: A cross-sectional study was conducted at CMH Kharian Medical College and associated hospital from January to June 2025. A sum of 120 infertile women with varied comorbidities were enrolled and divided into two treatment groups: letrozole group and clomiphene group. The study estimated and statistically evaluated ovulation rates, pregnancy rates, multiple gestation and adverse effects of the drugs between the groups.

Results: The letrozole group demonstrated significantly better outcomes in terms of ovulation (86.7%) and pregnancy rates (66.7%) as compared to clomiphene group (68.3% and 40.0%, respectively). Letrozole was associated with fewer side effects and a lower prevalence of multiple gravidity (5.0%) as compared to clomiphene group (18.3%).

ÖZ

Amaç: Bu çalışmanın birincil amacı, komorbiditesi olan infertil kadınlarda ovulasyonu indüklemede klomifen ve letrozolün etkinliğini karşılaştırmaktı. İkincil amaçlar arasında, iki tedavi grubu arasında gebelik oranları, çoğul gebelik ve ilaçların yan etkileri açısından gebelik sonuçlarındaki farklılıkların değerlendirilmesi yer almaktadır.

Yöntemler: Ocak-Haziran 2025 tarihleri arasında CMH Kharian Tıp Fakültesi ve bağlı hastanede kesitsel bir çalışma yürütüldü. Komorbiditeleri farklılık gösteren toplam 120 infertil kadın çalışmaya dahil edilerek letrozol grubu ve klomifen grubu olmak üzere iki tedavi grubuna ayrıldı. Çalışmada ovulasyon oranları, gebelik oranları, çoğul gebelik ve ilaçların yan etkileri tahmin edilerek istatistiksel olarak değerlendirildi.

Bulgular: Letrozol grubu, ovulasyon (%86,7) ve gebelik oranları (%66,7) açısından klomifen grubuna (%68,3 ve %40,0) kıyasla anlamlı derecede daha iyi sonuçlar gösterdi. Letrozol, daha az yan etki ve daha düşük çoğul gebelik prevalansı (%5,0) ile ilişkilendirildi; klomifen grubunda bu oran %18,3 idi.

Sonuç: Letrozol, komorbiditesi olan infertil kadınlarda ovulasyon indüksiyonu açısından klomifen sitrata göre daha

Address for Correspondence: Ayesha Laraib MD, CMH Kharian Medical College, Department of Pharmacology, Kharian, Pakistan
E-mail: syedaash44@gmail.com
ORCID IDs of the authors: A.L.: 0009-0006-3017-7116, U.N.: 0009-0007-8844-4368, S.R.: 0009-0006-8100-4485, J.K.: 0009-0002-9634-6040, M.K.: 0009-0000-6299-0300, F.K.: 0009-0009-5587-1958, U.F.: 0009-0003-7266-5781

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ABSTRACT

Conclusion: Letrozole appears to be more effective and safer than clomiphene citrate for ovulation induction in infertile women with comorbidities. Grounded on these findings, letrozole may be considered a first line treatment option in infertile women with comorbidities.

Keywords: Infertility, ovulation induction, letrozole, clomiphene, comorbidity, polycystic ovary syndrome

ÖZ

etkili ve daha güvenli görünmektedir. Bu bulgulara dayanarak; letrozol, bu hasta grubunda birinci basamak tedavi seçeneği olarak değerlendirilebilir.

Anahtar Kelimeler: İnfertilite, ovulasyon indüksiyonu, letrozol, klomifen, komorbidite, polikistik over sendromu

Introduction

Infertility is a major global health concern, with an estimated 17.5% of individuals worldwide suffering from it (1). Primary infertility, in which a person has never become pregnant, and secondary infertility, in which a person has failed to conceive despite having previously become pregnant, are the two main categories of infertility, which is defined as the inability to conceive after 12 months of consistent and unprotected sexual activity (2). Among several reasons of infertility, ovulatory dysfunction, notably disruptions in the hypothalamic-pituitary-ovarian axis, is a significant factor influencing female fertility. Obesity, metabolic syndrome, thyroid issues, and polycystic ovarian syndrome (PCOS) are major causes of anovulation, which can interfere with fertility treatment and diminish the chances of a healthy pregnancy (3,4).

Clomiphene citrate (CC) has long been the first-line treatment for ovulation induction medications. Clomiphene, a selective estrogen receptor modulator, stimulates the synthesis of gonadotropin, which encourages follicular growth and ovulation (5). Nevertheless, CC has a number of drawbacks despite its proven clinical application, such as poor live birth rate, increased risk of multiple pregnancies (3-8%), and notable response variability among people with metabolic problems (6). However, common adverse effects include stomach spasms, breast tenderness, hot flushes, and thrombosis-related effects, and it also shows effects like multi-follicular development and cyst formation (7). As a result, alternative forms of treatment have been studied. A third-generation aromatase inhibitor called letrozole (LE) is one such choice. It has been demonstrated to have superior ovulation and pregnancy results versus CC, particularly in individuals with comorbidities (8). LE promotes follicle-stimulating hormone secretion and follicular recruitment by reducing estrogen production, hence preventing negative feedback inhibition at the hypothalamus level (9,10). LE is less likely to cause mood and vasomotor adverse effects than CC (11).

Despite advancements in the treatment of infertility, comorbidities like as insulin resistance, obesity, thyroid problems, hypertension, and fibroids remain significant barriers to successful reproduction. Both directly and indirectly, these disorders affect ovarian function and implantation potential (12,13). Despite several studies have compared LE to CC, highlighting its usefulness in PCOS patients, there is little evidence on LE's effectiveness in infertile women with numerous comorbidities. To improve evidence-based clinical treatment, a focused assessment of ovulation induction drugs in various patients' groups is required.

The purpose of this study is to thoroughly evaluate the effectiveness of LE and CC in stimulating ovulation leading to conception in infertile women with gynecological and systemic comorbidities. In addition to offering therapeutically useful insights on refining ovulation induction procedures for patients with underlying comorbidities, this study seeks to deepen our understanding of the pharmacology of ovulation induction agents.

Methods

Study Design

Cross-sectional analytical (observational) study.

Study Setting

CMH Kharian Medical College and CMH Hospital, Kharian, Pakistan.

Ethical Approval

Approval obtained from Institutional Ethical Review Board, CMH Kharian Medical College (approval no: CKMC/IERB/AC-00202, date: 09.01.2025), written informed consent obtained from all participants, confidentiality and anonymity ensured.

Sample Size

Sample size was calculated to be 57 with the help of World Health Organization calculator taking ovulation rate with the use of LE as 61.1% and clomiphene as 35%, and keeping power of the study at 80%. After adjusting drop out ratio of 5% (n=3), sample size of 60 was finalized. The sample size determination process is shown in Figure 1.

Sampling Technique

Non-probability consecutive sampling.

Participants

One hundred-twenty infertile women with comorbidities.

Treatment Details

Treatment plans were modified depending on clinical judgment because this was an observational cross-sectional study and they were not standardized. The patients had previously received treatment for their infertility with LE or CC. The number of treatment cycles and dosages varied from participant to participant, as is customary in therapeutic practice. The majority of patients began on a starting dose of either 50 mg/day of CC or 2.5 mg/day of LE for five days per cycle; however, treatment durations and dosage modifications varied based on patient response and medical interpretation.

Inclusion Criteria

Women aged 18-40 years with infertility and comorbidities such as PCOS, obesity, thyroid dysfunction, diabetes, hypertension, or fibroids.

Exclusion Criteria

Women with structural infertility, male factor infertility, or infertility without comorbidities.

Treatment Exposure and Clinical Decision-making

Observational design, treatment not assigned or modified by investigators, patients already receiving CC or LE at enrollment, therapy selected by treating physician as part of routine clinical practice, clomiphene commonly used as first-line agent, LE more frequently prescribed in suspected or documented CC resistance, PCOS, higher body mass index, or prior inadequate ovulatory response, no protocol-driven treatment allocation.

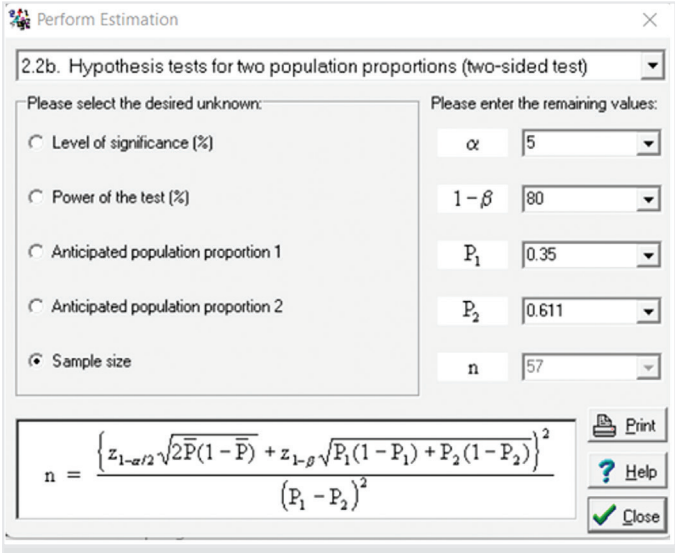

Figure 1. Screenshot of the World Health Organization sample size calculator displaying inputs used for this study: alpha: 5%, power: 80%, P1: 0.35, P2: 0.611, resulting in estimated sample size of 57 participants per group

Data Collection

Questionnaire, lab investigations and ultrasound record.

Outcomes Measured

Transvaginal ultrasound was used to confirm ovulation, and biochemical indicators such as beta human chorionic gonadotrophin hormone levels, urine pregnancy test, or ultrasound imaging were used to confirm pregnancy.

Statistical Analysis

SPSS version 20 was used to examine the data. For demographic factors, descriptive statistics were used. Results were compared between groups using independent t-tests and chi-square tests. Statistical significance was established at $p<0.05$ and a 95% confidence range was employed.

Results

The study comprised 120 infertile women with either comorbidity, 60 in each group. Both groups had comparable baseline characteristics, including mean age and duration of infertility, with no statistically significant differences found (Table 1). The study design and participant allocation are illustrated in Figure 2.

The distribution of comorbidities between the two groups is shown in Table 2. The most common comorbidity was PCOS, which affected 26 (43.3%) participants in the CC group and 25 (41.7%) in the LE group. Other comorbidities included hypothyroidism, diabetes, hypertension, fibroids, and depression, which varied in prevalence between groups.

Regarding treatment results, a substantially higher percentage of patients in the LE group (n=52; 86.7%) had

Table 1. Demographic characteristics of participants

Variable	Group 1 (clomiphene citrate)	Group 2 (letrozole)	p-value
Age (years)	29.28±3.26*	28.78±5.02*	0.519
Infertility duration (years)	4.04±1.89*	4.37±2.26*	0.392

*: Values are presented as mean ± standard deviation

Table 2. Distribution of comorbidities among groups

Comorbidity	Group 1 (clomiphene citrate) n=60	Group 2 (letrozole) n=60
PCOS	n=26 (43.3%)*	n=25 (41.7%)*
Hypothyroid	n=12 (20.0%)*	n=6 (10.0%)*
Diabetes	n=8 (13.3%)*	n=5 (8.3%)*
Hypertension	n=3 (5.0%)*	n=10 (16.7%)*
Fibroid	n=0 (0.0%)*	n=4 (6.7%)*
Depression	n=0 (0.0%)*	n=1 (1.7%)*

*: Data shown as number of patients with percentage in parentheses, PCOS: Polycystic ovarian syndrome

ovulation than in the CC group (n=41; 68.3%), with a p-value of 0.016. Likewise, with a p-value of 0.003, the LE group had a greater pregnancy rate (n=40; 66.7%) than the CC group (n=24; 40.0%) (Table 3).

There was a statistically significant difference (p=0.023) in the frequency of multiple gestations between the CC group (n=11; 18.3%) and the LE group (n=3; 5.0%).

Table 4 details the incidence of adverse effects. A considerably higher proportion of individuals in the LE group (68.3%) reported no side effects than those in the CC group (35.0%).

Discussion

LE's and CC's relative effectiveness in triggering ovulation has been a key topic of discussion when treating infertile women, particularly those with coexisting conditions like PCOS. Since LE is more effective than CC at inducing ovulation, it is advised for patients with PCOS and related conditions (3,14).

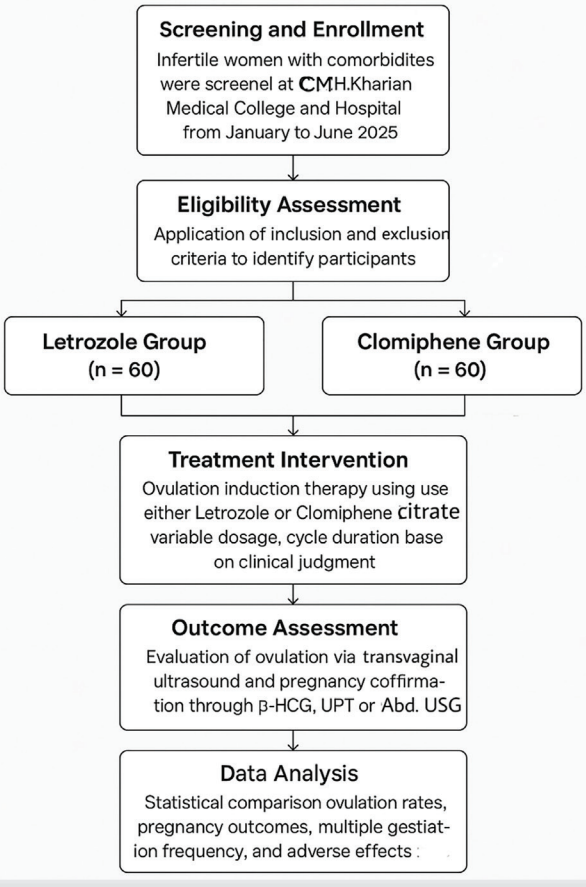

Figure 2. Flow diagram illustrating the study design, patient screening, group allocation, treatment intervention, and analysis

HCG: Human chorionic gonadotrophin, UPT: Urine pregnancy test

CC has been used for a long time most often as first-line drug for ovulation induction. However, current professional recommendations and research have progressively favored LE, particularly in women with PCOS and other metabolic disorders, due to better ovulatory and pregnancy outcomes. Despite this shift in preference, resistance to both agents remains a significant barrier to fertility management, particularly in low-resource settings where assisted reproductive technologies are less affordable.

Our results are consistent with recent research showing that LE is more effective than clomiphene at inducing ovulation and improving pregnancy outcomes. The current study found that LE significantly increased the rate of conception (66.7%) compared to CC (40%) in infertile women with a variety of comorbidities, including PCOS, obesity, thyroid, and metabolic abnormalities. Our findings are in line with a randomized control experiment that showed that LE had a 62% pregnancy rate and CC had a 38% pregnancy rate (15).

Similarly, LE was associated with significantly greater clinical pregnancy [odds ratio (OR)≈1.69] and live-birth (OR≈1.72) rates than clomiphene in a 2022 Cochrane meta-analysis of PCOS patients (16).

Comorbidities are also important since they lower fertility and interfere with folliculogenesis. Most common being obesity, insulin resistance, and metabolic syndrome. CC significantly reduces live birth rates in women with metabolic syndrome, whereas LE proves comparatively better outcomes in this group, according to analyses from major trials (12). Thyroid autoimmunity and obvious hypothyroidism also impair menstrual cycles and pregnancy (13). Although specific data in thyroid or diabetes affected patients is limited, our findings indicate that LE's pharmacological profile may better overcome such challenges.

Table 3. Treatment outcomes

Outcome	Group 1 (clomiphene citrate) n=60	Group 2 (letrozole) n=60	p-value
Ovulation rate	n=41 (68.3%)*	n=52 (86.7%)*	0.016
Pregnancy rate	n=24 (40.0%)*	n=40 (66.7%)*	0.003
Multiple gestation rate	n=11 (18.3%)*	n=3 (5.0%)*	0.023

*: Data presented as number of patients with percentage in parentheses, statistical significance at p<0.05

Table 4. Adverse effects

Adverse effect status	Clomiphene citrate group (n=60)	Letrozole group (n=60)
No adverse effects	n=21 (35.0%)*	n=41 (68.3%)*
One or more side effects	n=39 (65.0%)*	n=19 (31.7%)*

*: Data shown as number of patients with percentage in parentheses

By specifically assessing ovulation induction in a sample of infertile women with a variety of gynecologic and systemic comorbidities such as hypothyroidism, hypertension, and fibroids in addition to PCOS, our study contributes to the field of current literature. This study offers a more comprehensive understanding of how LE and CC function in more complicated, real-life circumstances, in contrast to the majority of earlier research that concentrated largely on PCOS alone. Furthermore, our geographic context focuses on treatment patterns and outcomes in the South Asian community, where data on infertility therapy in the presence of comorbidities is limited.

To summarize, while CC achieved pregnancies in a large percentage of instances and remains a cost-effective alternative, the collective evidence, including our data, suggests an apparent efficacy advantage of LE for ovulation induction in infertile women with comorbidities (15,17). Infertile women with metabolic comorbidities should select LE as their first-line treatment; although more research is needed to confirm these results.

Considering the higher pregnancy rates with LE, clinicians ought to recommend it as a first-line ovulation induction medicine in infertile women with comorbidities, in compliance with changing clinical guidelines. CC is still a viable choice, especially in resource-constrained situations or for patients allergic to LE. However, patient selection should take into account comorbidities, prior treatment outcomes, and hormonal indicators. Comorbidity management (such as metabolic and thyroid optimization) paired with pharmacological ovulation stimulation may improve reproductive outcomes even more.

Study Limitations

To determine the effectiveness of treatment within each subgroup, future studies should stratify people according to particular comorbidities such PCOS, hypothyroidism, obesity, and insulin resistance. LE's advantage needs to be confirmed by randomized controlled studies with larger sample sizes and live birth outcomes. The clinical significance of these results would also be enhanced by long-term follow-up research on maternal and neonatal outcomes.

Conclusion

Comorbid conditions such as PCOS, hypothyroidism, diabetes, hypertension, and fibroids have been proven to reduce female fertility by interfering with hormonal balance, ovulatory function, and endometrial sensitivity. These illnesses typically hinder ovulation induction, lowering the likelihood of pregnancy in affected women.

In this case, pharmaceutical medicines like CC and LE are essential for inducing ovulation. Both medications are commonly used to treat anovulatory infertility; however, their efficacy varies depending on the underlying metabolic or endocrine problems. Our data revealed that LE resulted in considerably higher ovulation (86.7%) and conception rates (66.7%) than CC (68.3% and 40.0%, respectively), particularly in women with comorbidities. This indicates that LE may be more effective in overcoming the ovulatory problems posed in such conditions.

These findings are consistent with prior research showing that LE improves ovulatory and pregnancy outcomes, particularly in patients with PCOS and metabolic syndrome. For example, significant clinical trials have demonstrated that LE continues to provide positive results in women with metabolic dysfunction, whereas CC may be associated with lower live-birth rates in this group.

Moreover, LE was associated with fewer adverse effects, with a higher proportion of subjects claiming no side effects during therapy, indicating superior tolerance than CC.

In conclusion, despite the fact that this was not a cohort trial, the findings strongly supported LE over CC for ovulation induction in infertile women with accompanying diseases. LE appears to have both increased efficacy and improved tolerability, making it a better option in this patient population.

Ethics

Ethics Committee Approval: Approval obtained from Institutional Ethical Review Board, CMH Kharian Medical College (approval no: CKMC/IERB/AC-00202, date: 09.01.2025).

Informed Consent: Written informed consent obtained from all participants, confidentiality and anonymity ensured.

Footnotes

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions

Surgical and Medical Practices: S.R., M.K., Concept: A.L., Design: A.L., U.N., U.F., Data Collection or Processing: S.R., J.K., M.K., Analysis or Interpretation: A.L., U.N., S.R., J.K., F.K., Literature Search: A.L., U.N., S.R., J.K., F.K., U.F., Writing: A.L., F.K., U.F.

Conflict of Interest: No conflict of interest was declared by the authors.

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