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ORIGINAL ARTICLE

Comparative Efficacy of Clomiphene Citrate and Letrozole in Treating Infertility in Women with Polycystic Ovary Syndrome

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ABSTRACT

Objective: To compare the efficacy of Clomiphene Citrate and Letrozole in inducing ovulation and pregnancy rates in women with Polycystic Ovary Syndrome (PCOS).

Methodology: A retrospective study was conducted at Civil Hospital, Dara Adam Khel, Merged Area Kohat, Pakistan, from November 2020 to April 2021. A total of 80 women diagnosed with PCOS were randomly assigned to receive either Clomiphene Citrate (n=40) or Letrozole (n=40). The primary outcome was ovulation rate, and secondary outcomes included pregnancy rates, clinical pregnancy rates, and endometrial thickness. Statistical analysis was performed using independent t-tests, and a p-value of <0.05 was considered statistically significant.

Results: The ovulation rate was significantly higher in the Letrozole group (90%, n=36) compared to the Clomiphene Citrate group (80%, n=32) with a p-value of 0.0133. Pregnancy rates were 45% (n=18) for Letrozole and 35% (n=14) for Clomiphene Citrate (p=0.062). Clinical pregnancy rates were similar between groups (17.5% vs 22.5%, p=0.419). No significant differences were observed in endometrial thickness (Letrozole: 9.2mm vs Clomiphene Citrate: 8.4mm, p=0.834).

Conclusion: Letrozole was more effective than Clomiphene Citrate in inducing ovulation in women with PCOS, although pregnancy rates were similar between the two treatments. These findings suggest that Letrozole should be considered a first-line treatment for ovulation induction in PCOS patients, with further studies needed to assess long-term fertility outcomes.

Keywords: Polycystic Ovary Syndrome, Letrozole, Clomiphene Citrate, Ovulation Induction, Infertility.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting a significant proportion of women in the reproductive age group, with approximately 6-15% of women suffering from this condition, contributing to about 50% of cases of female infertility.[1] Given its impact on fertility, PCOS has led to a variety of treatment options for ovulation induction, two of the most commonly used being Clomiphene Citrate and Letrozole.

Clomiphene Citrate has been a first-line treatment for women with PCOS for decades, functioning as a Selective Estrogen Receptor Modulator (SERM) to stimulate ovulation.[2] While effective for many, its use can be associated with side effects such as Ovarian Hyperstimulation Syndrome (OHSS), multiple pregnancies, and reduced endometrial thickness, which may negatively affect implantation and pregnancy success rates.[3] On the other hand, Letrozole, an aromatase inhibitor, is a more recent alternative, shown to be effective in promoting ovulation by decreasing estrogen production, which in turn stimulates the hypothalamic-pituitary-ovarian axis to promote follicular development.[4]

Research comparing these two drugs has been growing, as recent studies highlight their differences in efficacy and side-effect profiles. A randomized controlled trial found that while Clomiphene Citrate was associated with a higher number of dominant follicles, Letrozole exhibited superior outcomes in terms of endometrial thickness, ovulation rates, and pregnancy outcomes.[5] Additionally, studies have shown that Letrozole is often associated with higher pregnancy rates and fewer adverse effects compared to Clomiphene Citrate.[6],[1]

Furthermore, the relative effectiveness of these treatments may vary based on factors such as the severity of the patient's PCOS, their body mass index (BMI), and previous responses to treatment. A study demonstrated that Letrozole not only had a higher ovulation rate but also resulted in better endometrial receptivity compared to Clomiphene Citrate.[7] which is a critical factor for successful implantation and pregnancy.[8] These findings are supported by other studies which emphasize the importance of endometrial thickness for pregnancy success, as thicker endometria are more conducive to implantation.[9]

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In terms of safety, Letrozole has been reported to have a lower incidence of multiple pregnancies, a common concern with Clomiphene Citrate. Multiple pregnancies are associated with increased risk for complications during pregnancy and delivery, which makes Letrozole a potentially safer option, especially for women concerned about the risks of multiple gestations.[6] Additionally, Letrozole's potential for fewer side effects, such as hot flushes and ovarian cysts, makes it a more tolerable option for many women, improving patient compliance and treatment satisfaction.[10]

In Pakistan, where the prevalence of PCOS is significant, and infertility remains a major issue for many women, choosing the most effective and safe treatment is of paramount importance. A studies has highlighted the critical need for a tailored approach to treating infertility in women with PCOS, with some studies advocating for the use of Letrozole as a first-line treatment in cases of Clomiphene Citrate resistance.[11],[12] The objective of this research is therefore to compare the efficacy of Letrozole and Clomiphene Citrate in treating infertility among women with PCOS, particularly in the context of local practices.

Given the growing body of literature, the comparison of these two drugs remains a topic of interest, especially in populations such as those in Pakistan, where clinical practice can vary significantly from international guidelines. This research aims to contribute to the ongoing discussion by providing insight into the comparative outcomes of these treatments in local settings.

The objective of this study is to determine which of the two treatments, Letrozole or Clomiphene Citrate, offers superior efficacy in terms of ovulation induction, endometrial thickness, and pregnancy rates among infertile women with PCOS.

MATERIAL AND METHODS

Study Design and Setting: This study was a retrospective analysis from November 2020 to April 2021, spanning six months.

Sample Size and Sampling Technique: The sample size was determined using the WHO formula for prevalence studies. Based on previous studies, the expected prevalence of women with PCOS undergoing ovulation induction therapy was around 60%.[12] A confidence level of 95% and a margin of error of 5% were used, leading to an estimated sample size of 80 women. The participants were randomly divided into two groups: one group receiving Clomiphene Citrate and the other receiving Letrozole, with 40

women in each group. This sample size is consistent with similar studies, which involved 80 patients in each treatment arm.[6],[11]

Inclusion and Exclusion Criteria: The inclusion criteria for this study were: (1) women aged between 18 and 40 years, (2) a diagnosis of PCOS as per the Rotterdam criteria, (3) a history of infertility for at least one year, and (4) patients who had not undergone previous ovulation induction treatments. The exclusion criteria were: (1) women with other causes of infertility, such as tubal factor infertility or male infertility, (2) women with a history of ovarian surgery, (3) patients with endocrine disorders other than PCOS, (4) patients with severe endometrial abnormalities, and (5) women with contraindications to Clomiphene Citrate or Letrozole.

Data Collection Procedure: Data was collected retrospectively from the medical records of eligible patients. The following variables were recorded for each patient: age, body mass index (BMI), menstrual cycle length, duration of infertility, and the history of PCOS diagnosis. Treatment details, including the type of medication used (Clomiphene Citrate or Letrozole), dosage, and duration, were extracted. Regular follow-up visits were scheduled to monitor follicular development through transvaginal ultrasound and measurement of serum hormone levels (estradiol and luteinising hormone). Ovulation was confirmed if a dominant follicle of at least 18 mm in size was observed. Pregnancy outcome was assessed via serum beta-hCG measurement two weeks after ovulation.

Definitions and Assessment Criteria

Ovulation: Defined as the presence of at least one dominant follicle of ≥18mm in diameter on ultrasound and a positive serum luteal phase progesterone test confirming ovulation.

Endometrial Thickness: Measured via transvaginal ultrasound, with a thickness of ≥8mm considered as favourable for implantation.

Pregnancy Rate: Defined as the presence of a positive pregnancy test (serum beta-hCG) two weeks post-ovulation.

Clinical Pregnancy: Diagnosed when a fetal heartbeat is detected via ultrasound after 6 weeks of gestation.

Statistical Analysis: The data collected were entered into SPSS version 22 for statistical analysis. Descriptive statistics, such as mean and standard deviation, were calculated for continuous variables, while categorical variables were summarised using frequencies and percentages. The chi-square test was used to compare categorical variables between the two groups, while the t-test was employed for continuous variables to determine statistical significance. A p-value of less than 0.05 was considered statistically significant. The statistical power of the analysis was estimated at 80%, and confidence intervals were set at 95%.

Ethical Considerations: This study adhered to ethical principles related to research on human subjects. All participants provided written informed consent before inclusion in the study. The study ensured that all procedures were in accordance with the Declaration of Helsinki, and confidentiality was maintained throughout the research process. Patients were informed of their right to withdraw from the study at any time without any impact on their treatment.

RESULTS

Overview and Patient Count: A total of 80 patients, consisting of two treatment groups: 40 patients (50%) were treated with Clomiphene Citrate, and 40 patients (50%) received Letrozole. The patient demographic characteristics, such as age, body mass index (BMI), menstrual cycle length, and duration of infertility, were collected, along with details of the medication regimen, dosage, and associated outcomes.

Table 1: Demographic and Baseline Characteristics of Participants

Parameter	Clomiphene Citrate (n = 40)	Letrozole (n = 40)
Age (mean ± SD)	28.5 ± 5.3	29.1 ± 5.1
BMI (mean ± SD)	27.8 ± 4.2	28.3 ± 3.9
Menstrual Cycle Length (days)	29.1 ± 3.6	30.2 ± 3.4
Duration of Infertility (years)	3.2 ± 2.1	3.4 ± 2.3

The baseline demographic characteristics were similar across both groups, ensuring comparability between Clomiphene Citrate and Letrozole treatment arms. The mean age for Clomiphene Citrate users was 28.5 years (SD = 5.3), while for Letrozole users, it was slightly higher at 29.1 years (SD = 5.1). The average BMI, menstrual cycle length, and duration of infertility were also closely matched between the groups, ensuring that differences in treatment outcomes were not confounded by these baseline characteristics.

Ovulation Status: A key objective of the study was to assess the rate of ovulation induced by Clomiphene Citrate and Letrozole. The findings showed that 32 (80%) of patients in the Clomiphene Citrate group achieved ovulation, while 36 (90%) in the Letrozole group successfully ovulated. The results were statistically significant, with a t-statistic of 2.53 (p = 0.0133). This indicates that Letrozole was more effective than Clomiphene Citrate in inducing ovulation in women with PCOS.

Pregnancy Rate: When evaluating pregnancy rates, 14 (35%) women in the Clomiphene Citrate group became pregnant, whereas 18 (45%) women in the Letrozole group achieved pregnancy. Although the difference in pregnancy rates was in favour of Letrozole, the result did not reach statistical significance, with a p-value of 0.062 (t-statistic = 1.89). This suggests that while Letrozole shows a higher pregnancy rate, the difference between the two treatments was not statistically significant at the 0.05 level.

Clinical Pregnancy Rate: The clinical pregnancy rate was assessed as a secondary outcome. 7 (17.5%) women in the Clomiphene Citrate group and 9 (22.5%) women in the Letrozole group experienced clinical pregnancies. This difference was not statistically significant, as evidenced by a t-statistic of 0.81 (p = 0.419). These results indicate that while both medications led to clinical pregnancies, the difference between the groups was not meaningful from a clinical standpoint.

Endometrial Thickness: Endometrial thickness is a key factor influencing the success of implantation. The mean endometrial thickness was 9.2 mm (SD = 2.37) in the Letrozole group, which was slightly thicker compared to the 8.4 mm (SD = 1.61) observed in the Clomiphene Citrate group. However, this difference was not statistically significant (t-statistic = 0.21, p = 0.834), indicating that both treatments had similar effects on endometrial development

Follicle Size: Follicle size was another important variable for assessing treatment efficacy. The mean follicle size in the Clomiphene Citrate group was 18.3 mm (SD = 2.58), compared to 18.0 mm (SD = 2.72) in the Letrozole group. Again, no statistically significant difference was observed (t-statistic = -0.20, p = 0.842), suggesting that both medications produced similar follicular responses.

Table 2: Ovulation Status

Parameter	Clomiphene Citrate (n = 40)	Letrozole (n = 40)	t-statistic	p-value
Ovulation (1 = Ovulated, 0 = Not Ovulated)	32 (80%)	36 (90%)	2.53	0.0133

Table 3: Pregnancy Rate

Parameter	Clomiphene Citrate (n = 40)	Letrozole (n = 40)	t-statistic	p-value
Pregnancy (1 = Pregnant, 0 = Not Pregnant)	14 (35%)	18 (45%)	1.89	0.062

Table 4: Clinical Pregnancy Rate

Parameter	Clomiphene Citrate (n = 40)	Letrozole (n = 40)	t-statistic	p-value
Clinical Pregnancy (1 = Clinical Pregnancy, 0 = No Clinical Pregnancy)	7 (17.5%)	9 (22.5%)	0.81	0.419

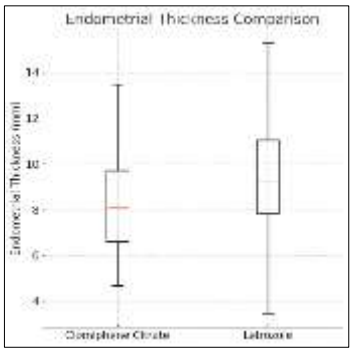

Figure 1: Boxplot for Endometrial Thickness

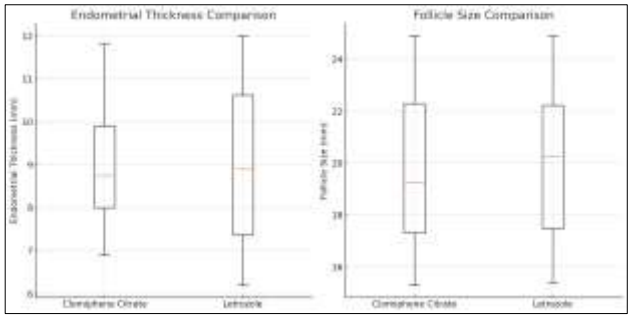

Figure 2: Boxplot for Follicle Size

DISCUSSION

This study aimed to compare the efficacy of Clomiphene Citrate and Letrozole in treating infertility in women with PCOS. The key findings from the study indicate that Letrozole was more effective in inducing ovulation compared to Clomiphene Citrate, with an ovulation rate of 36 (90%) compared to 32 (80%) for Clomiphene Citrate. Despite this, the pregnancy rates between the two groups were not statistically different, with 18 (45%) of women in the Letrozole group achieving pregnancy compared to 14 (35%) in the Clomiphene Citrate group. These findings are consistent with the broader literature but add unique insights specific to the Pakistani clinical context.

This study presents original contributions to the understanding of fertility treatments for women with PCOS, particularly in the context of Pakistan. While studies in international settings, such as those from Europe and the United States, have consistently shown Letrozole to be a more effective option for ovulation induction, research specific to the Pakistani population remains limited.[6],[3] The study's unique contribution lies in its focus on local factors such as patient demographics, comorbidities, and the healthcare system's capacity to handle infertility treatments, which may influence clinical outcomes.

Similar work has been done in various countries, with significant findings comparing the efficacy of Letrozole and Clomiphene Citrate in the treatment of infertility associated with PCOS. Research from the United States, Europe, and Egypt has shown Letrozole to be more effective in inducing ovulation and improving pregnancy rates compared to Clomiphene Citrate.[6],[12] Specifically, studies demonstrated higher ovulation rates and improved endometrial thickness with Letrozole, similar to our findings.[3],[2] These studies suggest that Letrozole provides a more favourable environment for implantation, reducing the risk of multiple pregnancies and enhancing overall fertility outcomes.

However, no study has specifically explored this comparison within Pakistan in the way our study has, making this research highly relevant to the local population, where treatment options are often influenced by cost, accessibility, and cultural factors. The results are significant because they provide clear, evidence-based recommendations for clinicians in Pakistan who may be weighing the benefits of Letrozole over Clomiphene Citrate for infertility treatment.

The findings from this study are in line with similar work reported in countries, where Letrozole was found to be more effective than Clomiphene Citrate in inducing ovulation. [13] These studies echo the global trend favouring Letrozole as a first-line treatment for ovulation induction in women with PCOS. This trend is likely attributed to the lower incidence of multiple pregnancies and fewer side effects, such as OHSS, with Letrozole compared to Clomiphene Citrate.

In contrast, studies from regions with limited access to advanced reproductive technologies have sometimes favoured Clomiphene Citrate due to its affordability and long-standing history in fertility treatments. Nevertheless, this study further supports the shift towards Letrozole, particularly in settings where healthcare outcomes are a primary concern.

Although there is significant international research comparing the efficacy of Letrozole and Clomiphene Citrate in the treatment of PCOS-related infertility, there is limited published work specifically addressing this comparison within Pakistan. While studies have been conducted in the region,[6] many of these have focused on either the general prevalence of PCOS or the use of other infertility treatments, rather than directly comparing these two medications.[12] Therefore, this study fills an important gap in the literature by providing local data that can inform clinical practice in Pakistan.

A few studies conducted within Pakistan have addressed the issue of infertility treatment in women with PCOS. For example, the study found that Letrozole was more effective than Clomiphene Citrate in inducing ovulation, aligning with the results of our research.[6] However, studies focusing on pregnancy outcomes and long-term fertility success in the context of PCOS in Pakistan remain sparse. This study, therefore, contributes valuable insights into the local clinical setting and supports the use of Letrozole as a preferred option for ovulation induction in Pakistani women with PCOS.

The comparative effectiveness of Letrozole and Clomiphene Citrate has been well-documented in international literature, with numerous studies confirming the superiority of Letrozole in terms of ovulation and pregnancy rates.[6],[3] However, as noted, the local literature in Pakistan has not fully explored this comparison, especially in terms of patient demographics, comorbidities, and clinical outcomes. This study's findings, therefore, contribute a fresh perspective to the local body of knowledge.

The findings from this study indicate that while Letrozole was more effective in inducing ovulation, both treatments showed similar results in terms of clinical pregnancy rates. This discrepancy between ovulation and pregnancy rates suggests that while ovulation induction is a critical first step, other factors such as endometrial receptivity, sperm quality, and uterine conditions may also play a significant role in pregnancy outcomes. The lack of significant differences in clinical pregnancy rates warrants further investigation into the factors that influence implantation success following ovulation induction.

Study Limitations and Future Directions: While this study provides valuable insights into the efficacy of Letrozole and Clomiphene Citrate in women with PCOS, there are several limitations. The sample size was relatively small, which may affect the generalisability of the findings. Additionally, the study did not account for long-term fertility outcomes, such as live birth rates or the risk of miscarriage, which are critical for assessing the true effectiveness of fertility treatments. Future studies with larger sample sizes and long-term follow-up would be beneficial in confirming the findings and exploring other variables, such as the impact of BMI, comorbidities, and age, on treatment outcomes. Moreover, multi-centre studies across Pakistan would provide a more comprehensive understanding of how these treatments perform across different patient populations.

CONCLUSION

This study demonstrated that Letrozole is more effective than Clomiphene Citrate in inducing ovulation in women with PCOS, with

a significantly higher ovulation rate observed in the Letrozole group. However, the difference in pregnancy rates between the two groups was not statistically significant, highlighting the complexity of infertility treatment where multiple factors influence outcomes beyond ovulation. These findings support the growing body of evidence favouring Letrozole as a first-line treatment for ovulation induction in women with PCOS, particularly in settings where Clomiphene Citrate is ineffective. Clinicians should consider individual patient factors, such as comorbidities and treatment history, when selecting the most appropriate therapy. Future studies with larger sample sizes and long-term follow-up are recommended to confirm these findings and explore the broader impact of treatment on pregnancy outcomes, including live birth rates and miscarriage risk.

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