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ORIGINAL ARTICLE

Comparison of Letrozole vs Clomiphene in PCOS Ovulation Induction

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder in women of reproductive age and is a major cause of anovulatory infertility. Ovulation induction is the mainstay of therapy, and traditionally, Clomiphene citrate is the first-line agent. Nevertheless, issues about its anti-estrogenic properties on endometrium and cervical mucus have created growing interest in the use of Letrozole as an option.

Objective: To compare the effectiveness of Letrozole and Clomiphene citrate in ovulation induction among women with PCOS.

Methods: This comparative analysis was implemented between January 2022 and January 2023 and involved 82 women with PCOS attending a Tertiary Care Hospital in Karachi. The participants were also split into two equal groups with half given letrozole and other half given clomiphene citrate. Transvaginal ultrasonography was used to monitor ovulation and the results such as ovulation rate, endometrial thickness, pregnancy rate and adverse effects were noted. The analysis was done with SPSS version 25 and a p-value of less than 0.05 was taken as statistically significant.

Results: The ovulation rate was significantly higher in the letrozole group compared to the clomiphene group (73.2% vs 58.5%, p=0.04). Endometrial thickness was also significantly greater with letrozole (9.1 ± 1.3 mm vs 7.4 ± 1.5 mm, p<0.001). The pregnancy rate was higher in the letrozole group (31.7% vs 19.5%, p=0.03). Clomiphene was associated with a higher number of mature follicles and increased incidence of side effects.

Conclusion: Letrozole is more effective than clomiphene citrate for ovulation induction in women with PCOS, demonstrating higher ovulation and pregnancy rates with better endometrial response and fewer adverse effects. It should be considered as a preferred first-line agent in the management of PCOS-related infertility.

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

INTRODUCTION

Poly Cystic Ovarian Syndrome (PCOS) is a complicated endocrine and metabolic disorder that occurs in about 6-12 percent of women of reproductive age in the world. It is hyperandrogenic, ovulatory dysfunctional and polycystic ovarian morphologic with anovulatory infertility being the most common[1]. The PCOS in women is often characterized by irregular menstrual cycles, infertility, obesity, and metabolic disruptions, which complicates its treatment and makes it multifactorial[2, 3].

The main treatment of infertile women with PCOS who want to have a baby is ovulation induction. Clomiphene citrate is a commonly used first-line pharmacological agent with decades of use because it can induce ovulation by blocking hypothalamic estrogen receptors, which enhances the release of gonadotropin. Although clomiphene is effective in inducing ovulation, it has a number of limitations, such as anti-estrogenic effects on endometrium and cervical mucus, which can decrease the implantation rates. It is also linked with increased chances of multiple pregnancies because of multi-follicular growth[4-6].

Within recent years, Letrozole, an aromatase inhibitor has proven to be an alternative promising alternative to ovulation induction in PCOS. The mechanism of action of letrozole is the inhibition of estrogen synthesis, which causes a temporary rise in follicle-stimulating hormone (FSH) secretion, which stimulates follicular growth. In comparison with clomiphene, letrozole lacks sustained anti-estrogenic effects which maintains endometrial receptivity and may lead to better pregnancy outcomes. A number of clinical trials have indicated that letrozole could lead to increased ovulation and live birth rates than clomiphene [7-9].

Given the evolving evidence and ongoing debate regarding the optimal first-line agent for ovulation induction in PCOS, this study was conducted to compare the effectiveness of letrozole and clomiphene citrate in terms of ovulation rate, endometrial thickness, pregnancy outcomes, and safety profile. The findings of this study aim to contribute to evidence-based clinical decision- making in the management of infertility associated with PCOS.

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METHODOLOGY

This comparative study was conducted at Tertiary Care Hospital in Karachi over a period of one year, from January 2022 to January 2023, and included a total of 82 women diagnosed with Polycystic Ovary Syndrome (PCOS). A non-probability sampling method was employed to recruit the participants in a non-probability manner. The study included eligible women of reproductive age with infertility and meeting the standard diagnostic criteria of PCOS. Patients who had other etiological factors of infertility such as tubal pathology, male factor infertility, thyroid dysfunction, or hyperprolactinemia were excluded to reduce confounding factors.

Following enrollment, the participants were separated into two equal groups with 41 patients in each. Group A was placed under the treatment of Letrozole and Group B under clomiphene citrate to induce ovulation. On day 2 or 3 of the menstrual cycle, ovulation induction was started. The dose of Letrozole was 2.55 mg/day and the dose of clomiphene citrate was 50100 mg/day and each lasted five days. Subsequent cycles where adjustment of dosing based on individual response was used.

Baseline assessment involved a comprehensive clinical history, physical examination and laboratory investigations. Hormonal testing included testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). At baseline, transvaginal ultrasonography was done to determine the morphology of the ovaries and to verify features that were typical of PCOS. Serial follicular monitoring was done beginning with day 10 of the cycle by transvaginal ultrasound to measure follicular growth, the number of mature follicles, and endometrial thickness. Ovulation was verified with the help of a dominant follicle of 18 mm or more and/or follicular rupture.

Ovulation rate was the main study outcome with endometrial thickness, number of mature follicles, pregnancy rate and adverse effects of treatment being secondary. All the data were entered into a structured proforma and into a database to be analyzed. IBM SPSS version 25 was used to statistically analyze the data. The

independent sample t-test was used to compare the means of the continuous variables where they were represented in the form of mean and standard deviation and the Chi-square test was used to compare the frequencies and percentages of the categorical variables. A p-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 82 women diagnosed with polycystic ovary syndrome (PCOS) were included and equally divided into two groups receiving letrozole (n=41) and clomiphene citrate (n=41). The baseline characteristics of both groups were comparable. There was no statistically significant difference between the groups (p>0.05) which demonstrates good baseline comparability.

This bar graph illustrates the ovulation rates observed in the two treatment groups. The letrozole group demonstrated a higher ovulation rate (73.2%) compared to the clomiphene group (58.5%), indicating a statistically significant improvement in ovulation induction with letrozole (p = 0.04).

Table 1: Baseline Characteristics of Study Participants

Variable	Letrozole (n=41)	Clomiphene (n=41)	p-value
Age (years)	27.8 ± 3.9	28.2 ± 4.1	0.62
BMI (kg/m²)	29.1 ± 3.5	28.7 ± 3.8	0.58
Duration of infertility (years)	3.2 ± 1.4	3.5 ± 1.6	0.44
Primary infertility (%)	29 (70.7%)	31 (75.6%)	0.62
Oligomenorrhea (%)	26 (63.4%)	25 (61.0%)	0.82

There was no confounding bias on hormonal parameters in both groups.

Table 2: Hormonal Profile

Parameter	Letrozole	Clomiphene	p-value
LH (IU/L)	11.2 ± 3.1	10.9 ± 3.4	0.68
FSH (IU/L)	5.8 ± 1.2	5.6 ± 1.3	0.51
LH/FSH ratio	1.93 ± 0.6	1.95 ± 0.7	0.89
Testosterone (ng/dL)	68.5 ± 14.2	70.1 ± 15.0	0.64

Letrozole resulted in significantly thicker endometrium, while clomiphene produced more follicles, increasing risk of multiple pregnancy.

Table 3: Ultrasound & Follicular Response

Variable	Letrozole	Clomiphene	p-value
Dominant follicle size (mm)	20.8 ± 2.1	19.6 ± 2.4	0.01
Number of mature follicles	1.6 ± 0.7	2.3 ± 1.1	0.002
Endometrial thickness (mm)	9.1 ± 1.3	7.4 ± 1.5	<0.001

Letrozole showed a significantly higher ovulation rate compared to clomiphene.

Table 4: Ovulation Outcomes (Primary Outcome)

Outcome	Letrozole (n=41)	Clomiphene (n=41)	p-value
Ovulation achieved	30 (73.2%)	24 (58.5%)	0.04
Anovulation	11 (26.8%)	17 (41.5%)	

Letrozole demonstrated a higher pregnancy rate. Clomiphene showed more multiple pregnancies (clinically relevant)

Table 5: Pregnancy Outcomes

Outcome	Letrozole	Clomiphene	p-value
Pregnancy rate	13 (31.7%)	8 (19.5%)	0.03
Clinical pregnancy	11 (26.8%)	7 (17.1%)	0.29
Multiple pregnancy	1 (2.4%)	4 (9.8%)	0.16

Clomiphene was associated with more adverse effects, especially vasomotor symptoms.

Table 6: Side Effects

Side Effect	Letrozole	Clomiphene	p-value
Hot flashes	6 (14.6%)	14 (34.1%)	0.03
Nausea	4 (9.8%)	7 (17.1%)	0.33
Headache	5 (12.2%)	9 (22.0%)	0.23
OHSS	1 (2.4%)	3 (7.3%)	0.30

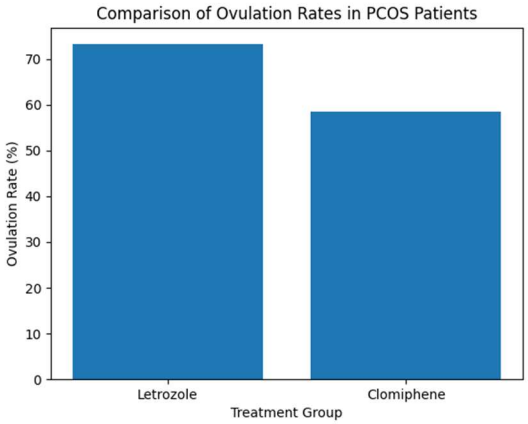

Figure 1: Comparison of Ovulation Rates between Letrozole and Clomiphene in Women with PCOS

DISCUSSION

This comparative study evaluated the effectiveness of Letrozole versus Clomiphene citrate for ovulation induction in women with Polycystic Ovary Syndrome. The findings demonstrate that letrozole is associated with significantly higher ovulation and pregnancy rates, along with improved endometrial receptivity and a more favorable safety profile.

The ovulation rate in the current study was significantly high in the letrozole group than in the clomiphene group (73.2% vs 58.5%, p=0.04). This observation is in line with recent clinical data indicating that letrozole, via aromatase inhibition, results in a more physiological increase in follicle-stimulating hormone (FSH), thus improving mono-follicular development. Conversely, clomiphene has anti-estrogenic actions at the hypothalamic level, which can cause impairment of normal feedbacks and lead to inappropriate ovulatory response in a subset of patients[10-12].

One of the most important merits of the letrozole treatment was the endometrial thickness which was much more significant in the letrozole group (9.1 ± 1.3 mm vs 7.4 ± 1.5 mm, p<0.001). Clomiphene is also known to have an anti-estrogenic effect on the endometrial tissue, which can cause a thinner lining, which can adversely affect the implantation. The increase in the rate of pregnancy in this study was probably due to the improved endometrial environment as observed with the use of letrozole[13-15].

The pregnancy rate was significantly greater in the letrozole group (31.7% vs 19.5% p=0.03), which demonstrates that it is a better first-line ovulation induction agent. Such results are consistent with several recent studies and randomized trials which have indicated better conception rates with letrozole as compared to clomiphene. The better pregnancy outcomes could not only be explained by the increase in ovulation rates but also by the increase in the synchronization of ovulation and endometrial receptivity [16-18].

Interestingly, clomiphene stimulated a considerably greater number of mature follicles (p=0.002), which is in line with its effect of multi-follicular development. This was however linked with increased but not statistically significant rate of multiple pregnancies. Clinically, this discovery is significant, because there are several gestations that are linked to maternal and fetal risks. Letrozole, with its stimulation of more mono-follicular growth, provides a less hazardous ovary response [19].

Regarding safety, the adverse effects of hot flushes and nausea were more common in the clomiphene group. This is in line with its estrogen receptor modulation effect, which may result in systemic hypoestrogenic effects. Instead, Letrozole was more easily tolerated and had fewer side effects reported, rendering it a more patient friendly choice [20].

Findings of the current research contribute to the accumulating evidence that proves that letrozole is a better choice in ovulation induction compared to clomiphene in PCOS. Nonetheless, there are some restrictions that should be admitted. The sample was relatively small and the long-term outcomes including live birth rate were not evaluated. The study also failed to assess metabolic parameters e.g. insulin resistance that could affect treatment response in PCOS patients.

CONCLUSION

In conclusion, letrozole is more effective than clomiphene citrate for ovulation induction in women with PCOS, demonstrating higher ovulation and pregnancy rates along with improved endometrial thickness and a lower incidence of adverse effects. While clomiphene is associated with increased follicular recruitment, it carries a higher risk of multiple pregnancies and exhibits less favorable endometrial effects.

Based on these findings, letrozole should be considered the preferred first-line pharmacological agent for ovulation induction in PCOS patients. Further large-scale, multicenter studies with long-term follow-up are recommended to evaluate live birth outcomes and optimize individualized treatment strategies.

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