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A COMPARATIVE STUDY OF LETROZOLE AND CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Background: Clomiphene citrate has usually been the first choice for ovulation stimulation. But the growing evidence indicates that letrozole may be more effective and better for the endometrium. There is limited comparative data on treatment efficacy across different demographic and socioeconomic groups, particularly in South Asian populations.
Objective: To compare the outcome of letrozole versus clomiphene citrate (CC) on ovulation induction in females presenting with polycystic ovary syndrome (PCOS) having subfertility.
Methods: The was a quasi-experimental study conducted in Department of Obstetrics and Gynecology, Khawaja Muhammad Safder Medical College Hospital, Sialkot, Pakistan from July 2024 to February 2025. Total of 100 patients, were divided into two groups, CC (group 1, n= 50) and Letrozole (group 2, n=50) from treatment initiation to outcome evaluation. Women aged 20–40 years, diagnosis of PCOS and both (primary and secondary) subfertility and Male with normal semen parameters were included in this study. The main outcome was success of ovulation induction.
Results Baseline demographic and clinical characteristics were similar between the two groups. Ovulation occurred in 84% of women taking letrozole compared to 76% of those taking clomiphene citrate. This difference is statistically significant (p = 0.04). The pregnancy rate was higher in the letrozole group at 16% versus 10.5% (p = 0.00).
Conclusion: Letrozole showed significantly better ovulation induction effectiveness compared to clomiphene citrate in women with PCOs.

Keywords: Clomiphene citrate, Letrozole, Ovulation induction, Polycystic ovarian syndrome, Subfertility.

INTRODUCTION

Polycystic ovary disorder (PCOS) may be a complex condition checked by sporadic periods, high androgen levels, and cysts within the ovaries [1].
The appearances of PCOS can change, with a few cases fundamentally driven by hyperandrogenemia, leading to a biochemical dominance, whereas others are primarily characterized by polycystic ovaries, coming about in a morphological dominance. It is the foremost common hormonal disorder affecting women aged 18 to 45 years [2]. Around 6-15% of women around the world have PCOS, making it a critical concern for female fertility. In Pakistan, the predominance is 18.67% [3].
One major issue for women with PCOS is anovulation, which leads to infertility. PCOS is regularly diagnosed in women who have faced difficulty to conceive, over the top hair growth, missed periods, pimples, and overweight [4]. Other than, Women with PCOS moreover confront a higher chance of type 2 diabetes, unusual lipid levels, heart disease, and endometrial cancer [5]. The causes of PCOS are complex and likely include both genetic variables and environmental impacts. Environmental variables, such as poor diet and need of work out can lead to weight. Emotional aspects and stress related with this issue have both can harm the mental and physical wellbeing of influenced couples [2].

The Rotterdam criteria define PCOS by the presence of at least two of the following three features: (a) Infrequent or absent ovulation, indicated by menstrual cycles longer than 35 days or fewer than eight periods a year. (b) Signs of high androgen levels, which can be either clinical, such as acne or excessive hair growth, or biochemical, like elevated testosterone levels. (c) Polycystic ovarian morphology, defined as 12 or more follicles, each 2-9 mm in size, and/or at least one ovary over 10 mL in volume [6].

Effective ovulation induction is crucial for managing infertility related to PCOS. Clomiphene citrate has been the introduced since 1956 for stimulating ovulation in women with PCOs[7].

Clomiphene citrate achieves a high rate of ovulation induction (60–85%), but is associated with relatively low pregnancy rates (10–20%) and an increased risk of miscarriage (20–25%). [8]

Letrozole, an aromatase inhibitor with the ability to decrease the production of estrogen, has emerged as a prospective alternative to clomiphene citrate (CC) in recent discussions. Letrozole was initially employed in the treatment of breast cancer in postmenopausal women [9].

Recent trials have demonstrated, Letrozole exhibits more effectiveness and may be considered as a potential alternative to Clomiphene Citrate (CC) for the first treatment of anovulatory infertility, particularly in cases with PCOs [10].

For ovulation induction Letrozole administering is the standard approach which is similar to clomiphene citrate, letrozole usually starting on cycle day 3-5 either after a natural menstrual cycle or after a progesterone-induced withdrawal bleed. If ovulation does not occur, confirmed by progesterone levels or ultrasound, the patient receives progesterone to induce withdrawal bleeding, simulating a normal period. The dose gradually increases each cycle until reaching the maximum dose of letrozole [2].

Azmoodeh and colleagues showed that letrozole leads to higher ovulation and pregnancy rates. This study aims to determine whether letrozole is indeed better than clomiphene citrate and to help establish local guidelines for ovulation induction in infertile women with PCOS. [11]. The aim of this study is to compare the outcome of letrozole and clomiphene citrate (CC) on ovulation induction in women with subfertility due to PCOS.

MATERIAL AND METHODS

The quasi-experimental study was conducted in Department of Obstetrics and Gynecology, Khawaja Muhammad Safder Medical College Hospital, Sialkot, Pakistan from July 2024 to February 2025. Sample size of 100 women was calculated by using 5% level of significance with 80% power of test and estimated frequency of successful pregnancy in patients taking letrozole as 46.7% and in patients taking CC as 22.8%. Enrolled patients, were allocated into two groups, CC (group 1, n= 50) and Letrozole (group 2, n=50) at the start of a treatment cycle and followed through outcome assessment. Women aged 20–40 years, diagnosis of PCOS and both (primary and secondary) subfertility and Male with normal semen parameters were included in this study. Those women were also a part of study who were referred from Lahore Institute of Fertility and Endocrinology (LIFE). Patients who have previously taken treatment of PCOS, they already taking anti-thyroid drugs determined on history and medical record and patients with any other medical disorder were excluded. The Ethical Review Board Khawaja Muhammad Safder Medical College Hospital give permission for this study (Reference letter number 79/REC/KMSMC).

Primary outcome was ovulation during the mid-cycle. We used transvaginal ultrasound on days 12 to 14 to measure the size of the dominant follicle. A follicle of 18 mm or more was deemed mature. A urinary pregnancy test was carried out seven days after ovulation. Clinical pregnancy was defined as an intrauterine fetal pole with cardiac activity visible on ultrasound. We present continuous variables as mean ± SD. Categorical variables are shown as n (%). For group comparisons, we used Student's t-test for continuous variables and the chi-square test for categorical variables. To determine the relationship between treatment (CC vs letrozole) and ovulation, all tests were two-sided, and a p-value of less than 0.05 was deemed statistically significant. We conducted the analyses using IBM SPSS Statistics 25.0.

RESULTS

The baseline characteristics of participants in the Letrozole and CC groups were generally comparable. There was no significant difference in mean age between the Letrozole group (26.52 ± 2.92 years) and the CC group (27.24 ± 2.76 years; $p = 0.20$). Similarly, BMI was slightly lower in the Letrozole group (28.02 ± 2.24) compared to the CC group (28.94 ± 2.36), but this difference did not reach statistical significance ($p = 0.06$). The duration of infertility was also similar between the two groups (3.58 ± 1.42 vs. 3.80 ± 1.47 years; $p = 0.45$).

Regarding menstrual cycle patterns, irregular menstruation and oligomenorrhea were common in both groups. Although a small proportion of women in the Letrozole group had regular cycles 3(6%), However, the overall distribution of menstrual patterns was not statistically significant ($p = 0.10$).

Hormonal profiles showed some significant differences. Mean FSH levels were slightly lower in the Group A (6.29 ± 0.42) than Group B (6.54 ± 0.51), and this difference was significant (p = 0.01). LH levels were also significantly lower in the Letrozole group (11.45 ± 2.24 vs. 13.14 ± 1.59; p < 0.001). Table 1
Endometrial thickness was significantly greater in the Group A (8.98 ± 0.73 mm) compared to the Group B (7.71 ± 0.84 mm; p < 0.001). In terms of follicular response, mono-follicular development was more common in the Group A , 30(60%). Whereas multiple follicles were developed in the Group B, 29(58%); however, this difference was not statistically significant (p = 0.47). Ovulation induction was achieved in a higher proportion of women in the Group A, 42(84%) compared to the Group B, 38(76%), and this difference was statistically significant (p = 0.04). The pregnancy rate (PR) among those who underwent ovulation induction was higher in the Group A, (16%) compared to the Group B, (10.5%), with a statistically significant difference reported (p < 0.001). Table 2

Table 1: Baseline characteristics of participants

Parameters	**Letrozole (n=50)**	**Clomiphene Citrate (n=50)**	**p-value**
	Group A	**Group B**	
Age (years) [(mean ± S.D)]	26.52 ± 2.92	27.24 ± 2.76	0.20
BMI (kg/m^2) [(mean ± S.D)]	28.02 ± 2.24	28.94 ± 2.36	0.06
Duration of infertility (years) [(mean ± S.D)]	3.58 ±1.42	3.80 ±1.47	0.45
Menstrual cycle [n (%)]			0.10
Regular	3 (6)	-	
Irregular	24 (48)	20 (40)	
Oligomenorrhea	23 (46)	30 (60)	
Hormonal profile (mean ± S.D)			
FSH	6.29 ±0.42	6.54 ±0.51	**0.01***
LH	11.45 ±2.24	13.14 ±1.59	**0.00***
Endometrial thickness on decision day **(mm)**	8.98 ±0.73	7.71 ±0.84	**0.00***

*Indicates the significant p-value which was < 0.05

Table 2: Outcome parameters of the participants

Parameters	**Letrozole (n=50)**	**Clomiphene Citrate (n=50)**	**p-value**
No. of follicles [n (%)]			0.47
Mono-follicular	30(60)	21(42)	
Multi- follicular	20(40)	29(58)	
Ovulation induction [n (%)]			**0.04***
Yes	42(84)	38(76)	
No	8 (16)	12 (24)	
Pregnancy outcome [n (%)]	7/42 (16)	4/38(10.5)	**0.00***

*Indicates the significant p-value which was < 0.05

DISCUSSION

This study aims to compare the effectiveness of letrozole and clomiphene citrate (CC) for ovulation induction in women with PCOS and subfertility. Our research shows that letrozole is more effective than clomiphene citrate for inducing ovulation in these women. Letrozole is also more cost-effective and leads to greater patient satisfaction. These findings suggest that letrozole should be the first choice for ovulation induction in women with PCOS, especially for those who do not respond to clomiphene citrate.
The comparable baseline demographic characteristics between treatment groups demonstrate that the observed difference in ovulation rates is improbable to be inferable to confounding by age, BMI, residential status, or financial background. The mean age and BMI of the patients in this study were comparative to those reported in other South Asian studies assessing ovulation induction therapies [12].
Women diagnosed with PCOS who received letrozole for ovulation induction had higher rates of ovulation, pregnancy, and endometrial thickness. A lower resistance index of subendometrial arteries can improve circulation

within the uterus, creating better conditions for embryo implantation and development. In our study, endometrial thickness was significantly greater in the letrozole group (8.98 ± 0.73 mm) compared to the clomiphene citrate group (7.71 ± 0.84 mm; $p < 0.001$). Optimal endometrial thickness is crucial for successful implantation, and letrozole's ability to maintain a thicker endometrium likely contributes to its higher pregnancy rates. In contrast, clomiphene citrate has anti-estrogen effects on the endometrium, which can negatively affect implantation [13].

The observed efficacy of letrozole in this study closely aligns with previously published regional and international trials. Shafiq et al. and Khakwani et al. So also recorded significantly higher ovulation rates favoring letrozole [14]. In spite of the fact that absolute ovulation rates change over studies, likely reflecting contrasts in patient characteristics, diagnostic criteria, and monitoring protocols, the consistent pattern of letrozole prevalence over different populations strengthens the validity of the present findings [15].

Several case reports have highlighted the positive of metformin in PCOS patients by improving conception rates and metabolic profiles. Clomiphene citrate does not elicit a consistent response in all patients for ovulation induction. It works by blocking estrogen effects, which elevates gonadotropin levels from the pituitary gland and stimulates ovarian follicle development and ovulation [16]. Letrozole inhibits the enzyme aromatase, blocking the change of androgens to estrogens in ovarian follicles. This leads to lower estrogen levels within the circulatory system and increased intraovarian androgens. The diminished estrogen levels can cause a rise in FSH levels, enhancing ovarian follicle advancement [17]. The efficacy of letrozole in clomiphene-resistant PCOS patients has been documented using 2.5 mg daily doses on the third to seventh days of the menstrual cycle in various studies [18].

A study evaluating clomiphene citrate over six months noted a 25% failure rate for ovulation induction and a live birth rate of 22.5%. CC results in ovulation induction rates between 50-85%, but conception rates are not very high (15-27%). Since letrozole is an aromatase inhibitor, it does not have negative anti-estrogen effects on endometrial receptivity. The documented rates for ovulation and conception are higher with letrozole (14). In another study found that ovulation rates was 67.6% in Letrozole group while 32.4% in CC group [19]. In our study significantly more patients to report ovulation induction in letrozole group as compare to the CC group (84% vs 76%, p=0.04).

Begum MR et al. noted that letrozole resulted in significantly better ovulation induction rates compared to clomiphene citrate. Debashi S et al. found that letrozole achieved a 60% ovulation induction rate, while clomiphene citrate had a 32% rate. However, Bayer U et al. conducted a randomized clinical trial and found no significant difference in ovulation induction between the letrozole and clomiphene citrate groups (65.7% versus 74.7%; $p = 0.17$).[14].

CONCLUSION

Letrozole is more effective than clomiphene citrate at triggering ovulation and achieving better reproductive outcomes in women with Polycystic Ovary Syndrome. It also has a better safety profile. This study supports the use of letrozole as the first-line medication for ovulation induction in these women.

ETHICAL APPROVAL

Ethical Board of Allama Iqbal Memorial Teaching Hospital, Sialkot, was approved this study under the IRB reference number: 79/REC/KMSMC.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTION

Hajra Sajid: Principal Investigator, Design, writing, and editing of manuscript
Asma Nayab: Collection of data, literature search and writing of manuscript
Rohina Gul: Data analysis, literature review, writing of results
Nosheen Bano: Conceiving of study idea, writing, and editing of manuscript
Mahwish Pervaiz: Collection of data and literature review
Muneeba Sheraz: Writing, and editing of manuscript add this before references