COMPARISON OF OVULATION INDUCTION LETROZOLE AND CLOMIPHENE CITRATE IN SUBFERTILE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Objective: To compare the ovulation induction of letrozole and clomiphene citrate in sub-fertile women with polycystic ovarian syndrome.

Study Design: Quasi experimental study.

Place and Duration of Study: Combined Military Hospital Rawalpindi, from Jun 2018 to Aug 2019.

Methodology: A total of 116 married sub-fertile women with polycystic ovarian syndrome, 16-40 years of age were included. Patients with previous surgery related to genital tract, hypothyroidism and chronic renal failure were excluded. Letrozole 5.0 mg daily from Day 5-9 of menstruation was prescribed to group A women and clomiphene citrate 100 mg daily from Day 5-9 of menses was given to group B women.

Results: In group A and in group B, mean age was 29.78 ± 4.71 years and 29.95 ± 4.22 years respectively. Most of the patients 59 (50.86%) were between 18-30 years of age. Mean duration since marriage was 4.23 ± 1.42 years. Mean body mass index was 29.71 ± 2.65 kg/m^2. Frequency of ovulation of clomiphene citrate and letrozole in sub-fertile women with polycystic ovaries was 28 (42.28%) versus 42 (72.41%) respectively (p-value=0.008).

Conclusion: This study concluded that ovulation induction of letrozole is better than clomiphene citrate in sub-fertile women with polycystic ovarian syndrome.

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

How to Cite This Article: *Shafiq A, Akbar R, Urooj U, Zohra S, Afzal S, Tanveer M. Comparison of Ovulation Induction Letrozole and Clomiphene Citrate in Subfertile Women with Polycystic Ovarian Syndrome. Pak Armed Forces Med J 2021; 71(5): 1844-1847. doi: https://doi.org/10.51253/pafmj.v71i5.6554*

INTRODUCTION

In the women of reproductive age group out of all the endocrinopathies polycystic ovarian syndrome (PCOS) is one of the most common, affecting up to 5-10% of women.[1] These women suffer from anovulatory sub-fertility. It has been found that lifestyle modification with weight reduction in obese women with PCOS, clomiphene citrate (CC) is the first line treatment for ovulation induction (OI).[2] Approximately, 75-80% of women have ovulation after ovulation induction with clomiphene citrate. However, there is a discrepancy between the ovulation rate and pregnancy rate, which was reported to be 22% per each ovulating cycle after CC.[3] Oher treatments are, gonadotrophin injections as well as laparoscopic ovarian drilling. These treatments have disadvantages, which are, costly treatments, risks of ovarian hyperstimulation syndrome and multiple pregnancy.[4]

One of a potentially better substitutes to CC is a specific aromatase inhibitor, letrozole which acts by reducing estrogen synthesis.[5] Due to this function letrozole does not causes any anti-estrogenic effects on endometrium which is supported by recent studies reporting adequate endometrial thickness while having letrozole treatment. Furthermore, letrozole is rapidly eliminated from body due to its 45hr, short half-life as compared to CC which have 2 weeks long half-life, leading to late follicular rise in circulating estrogen thereby enhancing endometrial development with subsequent increase in the chances of pregnancy. The rising estrogen levels may also result in a shorter Follicle-stimulating hormone (FSH) window (mimicking the physiological cycle) with subsequent monoovulation and a lower risk of multiple pregnancy.[6,7] Due to ovulation rates of approximately 85% and pregnancy rates of 35-40%, CC was used as standard first-line ovulation induction (OI) agent for women with polycystic ovarian syndrome (PCOS) for several decades.[8] Few studies reported the frequency of ovulation by clomiphene citrate and letrozole in sub-fertile women with polycystic ovarian syndrome as 70.21% vs 41.25% respectively.[9] In another study, the efficacy (in terms of ovulation) of clomiphene citrate and letrozole in infertile women with polycystic ovarian syndrome was 82.90% vs 62.5% respectively.[10]

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Received: 10 Apr 2021; revision received: 23 Aug 2021; accepted: 01 Sep 2021

As the letrozole is newly introduced drug in general practice for ovulation in sub-fertile women with polycystic ovarian syndrome, so its efficacy in terms of ovulation should be strongly assessed before using it as a routine drug in our general practice. Although previously immense body of literature is present on this topic but as described above some studies have shown clomiphene citrate better while other showed letrozole better, so on the basis of these studies, we cannot make a conclusion of better drug among this. The rationale of study was to compare the efficacy (in terms of ovulation) of letrozole and clomiphene citrate in sub-fertile women with polycystic ovarian syndrome. As routinely clomiphene citrate is used in majority of our setups, so this study will provide the evidence of letrozole use in PCOS. If this drug will be proved more useful, then this study will encourage our clinicians for its routine use for treating subfertility in polycystic ovarian syndrome patients which ultimately increase the pregnancy rates in these particular patients and thus improve the psychosocial life of these particular patients.

METHODOLOGY

It was a cross sectional comparative study carried out at department of Gynecology and Obstetrics, Combined Military Hospital, Rawalpindi from June 2018 to August 2019. The sample size was 116 i.e. 58 in both groups with 95% confidence level, 80% power of study, taking expected efficacy (in terms of ovulation) of clomiphene and letrozole in sub-fertile women with polycystic ovarian syndrome as 82.90% and 62.50% respectively.[10] By using World Health Organization (WHO) sample size calculator for two proportions,[10] sample size calculated. Convenience sampling was used to recruit the study participants.

Inclusion Criteria: About 16-40 years old married subfertile women with polycystic ovarian syndrome were included.

Exclusion Criteria: Women with prolactin levels >500 mIU/L, history of previous surgery related to genital tract, patients with chronic renal failure (assessed on history and s/creatinine >1.5 mg/dl) and hypothyroidism (TSH >5.2 mIU/L, T3 <70 ng/dl and T4 <5.2 µg/dl) were excluded.

Total 116 women fulfilling the inclusion criteria presented in OPD were selected Approval from institutional ethical review committee (IR/313/19) was taken. After taking informed consent from each patient, participants were divided into two groups by using lottery method. Women selected slips from total mixed up slips (half-slips contained letter 'A' and other half-slips contained letter 'B') and was placed in that respective group. Letrozole 5.0 mg daily from Day 5-9 of menstruation was prescribed to group A women and clomiphene 100 mg daily from day 5 of menses till 9th day, was given to group B women. In both groups' treatment was given for 12 weeks at which efficacy was noted by the researcher.

All the data were entered and analyzed by using Statistical Package for the Social Sciences (SPSS) version 23. Age, duration of marriage and BMI were presented as mean and standard deviation. Categorical variables were presented as frequency and percentages. Association between both groups was compared by Chi-square test and *p*-value ≤0.05 was considered as statistically significant.

RESULTS

A total of 116 patients included in study. Age range in this study was from 16 to 40 years with mean age of 29.82 ± 4.64 years. The mean age of women in group A was 29.78 ± 4.71 years and in group B was 29.95 ± 4.22 years. Majority of the patients 59 (50.86%) were between 18-30 years of age. Mean duration since marriage was 4.23 ± 1.42 years, mean BMI was 29.71 ± 2.65 kg/m^2.

In our study, frequency of ovulation of clomiphene citrate and letrozole in infertile women with polycystic ovarian syndrome was 28 (48.28%) versus 42 (72.41%) respectively (*p*-value=0.008) shown in the Table-I.

Ovulation according to BMI ≤27 in group A was 10 (17.2%) and in group B was 07 (12%) and ovulation BMI >27 in group A was 32 (55.1%) and in group B was 21 (36.2%) there was no significant association *p*>0.05 in both group shown in Table-II.

Table-I: Comparison of patients according to ovulation induction.

Ovulation	Group A (n=58) Letrozole	Group B (n=58) Clomiphene	*p*-value
Yes	42 (72.41%)	28 (48.28%)	0.008
No	16 (27.59%)	30 (51.72%)	

Table-II: Ovulation with respect to the body mass index.

BMI (kg/m^2)	Group A (n=58) Ovulation		Group B (n=58) Ovulation		*p*-value
	Yes	No	Yes	No	
≤27	10 (17.2%)	04 (6.8%)	07 (12%)	07 (12%)	0.246
>27	32 (55.1%)	12 (20.6%0	21 (36.2%)	23 (39.6%)	0.017

There was no statistically significance difference between ovulation with marriage duration ≤5 (*p*=0.109)

while there was statistically significance difference between ovulation with marriage duration >5 (p=0.010) shown in Table-III.

Table-III: Ovulation with respect to the duration of marriage.

Duration of Marriage	Group A (n=58) Ovulation		Group B (n=58) Ovulation		*p*-value
	Yes	No	Yes	No	
≤5	31 (53.4%)	14 (24.1%)	23 (39.6%)	21 (36.2%)	0.109
>5	11 (18.9%)	02 (3.4%)	05 (8.6%)	09 (15.5%)	0.010

DISCUSSION

One of the most common causes of anovulatory sub-fertility is Polycystic ovarian syndrome (PCOS) causing 70% of infertility cases due to anovulation.[11] One of the most common drugs used since 1960 is clomiphene citrate (CC) with an ovulation rate of 60-85% but a conception rate of only about 20%.[12] Due to long half-life (2 weeks) of clomiphene citrate may have a negative effect on the cervical mucus and endometrium, leading to discrepancy between ovulation and conception rates.[13,14] This leads to the search for a compound capable of inducing ovulation by avoiding the adverse antiestrogen effects of CC. it has been found in recent studies that Letrozole, which is an aromatase inhibitor, does not possess the adverse anti-estrogenic effects of clomiphene and is associated with higher pregnancy rates than CC treatment in patients with PCOS.[15] But evidences from larger trials are still awaited, some encouragement may be taken from the success of preliminary results showing aromatase inhibitor Letrozole may be regarded as a possible replacement for CC for the first-time treatment of anovulatory subfertility.[16]

This study is very much comparable to studies of Fouda UM et a and Sherif *et al*, which showed, mean age of 28 years and 29 years respectively.[17] On the other hand, Hussain *et al*, in his study has shown a larger mean age i.e. 32 years, compared to our study.[18] Mean duration since marriage was 4.23 ± 1.42 years. This is very much comparable to the study of Hussain NHN *et al*,[19] who had observed this as 4.5 years, but a little higher than Fouda *et al*,[20] who had found this as 3.6 years. This late presentation in our society may be due to hakeem culture, lack of awareness, some social constraints and economic hurdles.

Hendawy *et al*, showed that Letrozole had a better effect on endometrial thickness and pregnancy rate than Clomiphene citrate.[21] Roy *et al*, compared the efficacy of Letrozole and Clomiphene citrate in PCOS patients with infertility; they concluded that Letrozole had a better endometrial response and pregnancy rate compared with Clomiphene citrate.[22] In a study by Xi *et al*, use of Letrozole and Clomiphene citrate combined with gonadotropins in Clomiphene-resistant infertile women with PCOS was evaluated the rate of unifollicular development was 80.2% in the Letrozole + high mobility group (HMG), 65.3% in the Clomiphene citrate + HMG group, and 54.7% in the HMG-only group. The difference between these three groups was significant statistically. Endometrial thickness in the group receiving Letrozole was higher than other two groups.[23]

Requena *et al*,[24] in their literature review looked at randomized trials comparing letrozole versus clomiphene as first line therapy and included four studies. The ovulation rate for letrozole in comparison with clomiphene did not differ significantly (OR 1.7; 95% CI 0.66-2.09) nor did the pregnancy rate per patient (OR 1.37; 95% CI 0.70-2.71).

Letrozole has now been in use as an ovulation induction agent for more than a decade. Even though emerging evidence suggests that it is an effective ovulation induction agent, comparable if not better than clomiphene. In a local randomized controlled trial,[25] a total of 212 patients of age 20-38 years with anovulatory infertility were included. These patients were placed randomly into group A (clomiphene citrate) and group B (letrozole). The mean age of women in group A was 26.67 ± 4.23 and in group B was 26.24 ± 4.18 years. The mean duration since marriage in group A was 4.06 ± 1.95 years and in group B 4.26 ± 2.12 years. Efficacy of clomiphene citrate was 10.38% while that of letrozole was 21.70% (p=0.02).[25]

When clomiphene citrate is used as first line therapy in anovulatory women, one can expect a 25% incidence of clomiphene resistance. It has been established that although ovulation rates are in the range of 75% only 30-40% will actually conceive. Hence, about 60-65% of anovulatory women being treated with clomiphene will fall into either the resistant or failure group. Letrozole has been shown to be effective in women with either clomiphene resistance or failure. Letrozole has now been in use as an ovulation induction agent for more than a decade. Even though emerging evidence suggests that it is an effective ovulation induction agent, comparable if not better than clomiphene. Therefore, on the whole it is concluded that orally administered letrozole is more efficacious than clomi-

phene citrate in women with polycystic ovarian syndrome.

CONCLUSION

This study concluded that ovulation induction of letrozole is better than clomiphene citrate in sub-fertile women with polycystic ovarian syndrome. Therefore, we recommend that letrozole should be used as a first line therapy in sub-fertile women with polycystic ovarian syndrome which ultimately increases the ovulation induction and pregnancy rates in these particular patients.

Conflict of Interest: None.

Authors' Contribution

RK: Data collection, UU: Conceptual framework, literature review, SZ: Data collection, SA: Data collection, MT: Conceptual framework.

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