

Original Article

Comparison of Clomiphene Citrate and Letrozole in Induction of Ovulation Among Patients Polycystic Ovarian Syndrome (PCOS) Primary Sub-fertility

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Abstract

Objective: To compare the efficacy of clomiphene and Letrozole in the induction of ovulation in patients with primary ovarian sub-fertility.

Methodology: This was a Randomized control trial study carried out at Dow University Hospital Karachi, Ojha Campus, Karachi after approval of synopsis from February 2016 to January 2017. The required sample size was 164 (82 in the Letrozole group and 82 in the CC group). The patients were divided into two groups using lottery method. Females of 18-40 years irrespective of weight, years of marriage, and duration of sub-fertility with primary ovarian sub-fertility were included in the study. SPSS version 20 was used for data analysis.

Results: Total of 164 women were enrolled in the study. 82 women were given Clomiphene Citrate and 82 were treated with Letrozole. The mean age was found to be 28.48±4.12 in the clomiphene citrate group whereas 28.45±3.01 in the Letrozole group. The results showed improved results among the group with Letrozole drug compared to Clomiphene Citrate. Efficacy was positively found with 1st cycle, 2nd cycle & 3rd cycle in 2 (2.4%), 23 (28.05%) & 32 (39.02%) respondents respectively with Clomiphene Citrate. Whereas efficacy was positive with 1st cycle, 2nd cycle & 3rd cycle in 18 (21.9%), 34 (41.4%) & 24 (29.2%) respondents respectively with Letrozole.

Conclusion: Letrozole appeared to be the effective drug of choice in ovulation induction among patients who failed to conceive, however, the clomiphene citrate was found to be most effective in women. The dosage of Letrozole is much lower mg with effective pregnancy results compared to Clomiphene Citrate clomiphene citrate.

Key Words: Clomiphene citrate, Letrozole, Primary ovarian sub-fertility.

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Introduction

World Health Organization (WHO) has estimated that almost 60-80 million couples suffer from subfertility.¹ The sub-fertility varies from case to case around the world and almost affects 8-12 % of couples around the globe². The 5% of couples suffer from unknown reasons and unpreventable conditions, the rate of prevalence of sub-fertility more than this level suggests the multiple treatable and unpreventable options.³

However, sub-fertility tends to show higher fertility rates, and many studies have reported major two categories of sub-fertility, primary and secondary sub-infertility.⁴ The WHO defines the primary sub-fertility as the "Inability to conceive within two years of exposure to pregnancy (*i.e.*- sexually active, non-contraception,

and non-lactating) among women 15 to 49 years old. The secondary sub-fertility refers to the patients who failed to conceive after one pregnancy. Studies have shown that the majority suffer from primary infertility more as compared to secondary infertility.⁵

The fundamental difficulties in producing worldwide evaluations of sub-infertility are the shortage of populace-based examinations and the conflicting definitions utilized in a couple of excellent investigations accessible.⁶ In general population-based investigations of sub-infertility, there has been little consistency in how prevalence is determined. In a survey, the data showed that it is unbelievable to expect to blend sub-infertility prevalence information in

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the study in light of the exceptional definitions used.⁷

The effective sound birth (sub-infertility) can be characterized as either a sickness of the conceptive strategy (no regenerative accomplishment following 1 year of effectively endeavoring for a pregnancy) or a handicap that outcomes in an impedance of capability.⁸

The PCO is one of the main common causes of sub-infertility, which is often manageable with the optimal treatment, the clomiphene citrate has been introduced to be the first choice for sub-infertility among patients with PCOs. The insulin resistance among PCO patients is well treatable with metformin insulin-sensitizing agents and other anti-diabetic drugs.⁹

The PCOs are considered to affect almost 70% of women in their early ages, and this may affect their cervical mucus and endometrium which causes discrepancies and delays in the ovulation and conception rates.¹⁰ Clomiphene is considered to be effective for 60-80% of cases with delayed ovulation rates however 20% success rates have been shown among the patients for conception among women. The ovulation induction therapies are various, but the effects of clomiphene citrate are considered to be effective and comparative less anti-estrogen adverse effects. The studies have demonstrated that Letrozole does not have such anti-estrogen effects when administered among patients with PCOs.¹¹

The rate of prevalence of Sub-fertility appears to be unstable over the past decades, epidemiological studies¹²⁻¹⁴ have shown that prevalence varies within the countries. The American Society of Reproductive Medicines has estimated that around 5 million couples faced difficulty in achieving successful pregnancies and 1.3 million acquired the treatment and management throughout their life.¹⁵

Clomiphene citrate is one of the oldest, non-expensive, and highly effective drugs and remains the choice of drug for induction of ovulation. The studies have shown that 20% of patients do not ovulate in CC-resistant patients.¹⁶ Letrozole seems to be effective in higher pregnancy rates and equivalent to gonadotropin injections with considerably fewer adverse effects.¹⁷

The rates of sub-infertility in countries like Pakistan are high due to high rates of population where the growing rate of population is 2% in Pakistan, the high rate of sub-infertility is 21.9% and 3.5% of cases found were primary, and 21.9% of cases of secondary infertility.¹⁴

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Methodology

A Randomized control trial was conducted at tertiary care DOW Hospital Ojha campus for 12 months i.e., 1st February 2016 to 31st January 2017 after approval of the project (CPSP/REU/OBG-2013-183-5649). The sample size was calculated using the WHO sample size calculator. The required sample was obtained after calculation i.e., 164 (82 in each group for letrozole and clomiphene citrate) with a level of significance of 5% and power of test of 80%. P1 21.5%, P2 7.8%. Data was collected from Females of age 18-40 years irrespective of weight, years of marriage, and duration of sub-fertility with primary ovarian sub-fertility were included in the study. The patients with Primary sub-fertility due to male factors, tubal factors diagnosed (hysterosalpingography), and unexplained causes (no cause known) were excluded from the study. The data of 164 patients was collected from the OPD after taking informed consent. The patients were divided into two groups of 82 in the Letrozole group and 82 in the CC group using a lottery method (patients picked the chits labelled Group A or Group B). Group A received CC (50-100mg) and the next group B Letrozole (2.5-5 mg), both from days 3-7 of menstrual cycle, up to three cycles. Patients were followed for ovulation based on serial ultrasounds of the pelvis on day 12 of the menstrual cycle. A follicular size of >18mm was taken as positive and patients were advised of Intramuscular HCG(10,000 IU) to cause ovulation, followed by timed intercourse of 24 to 36 hours up to 3rd cycle. Then a urine pregnancy test was done after 5 weeks from the last menstrual period. All details were recorded in predesigned proforma by the researcher.

Statistical analysis was analyzed with SPSS version 20.0 software. Mean and standard deviation will be calculated for quantitative variables like age, years of marriage, and duration of sub-fertility. Frequency and

percentages (for both groups) were calculated for qualitative variables like efficacy (Yes/No), socio-economic status (Low, Middle, Upper), BMI, Education, and living with husband. The chi-square test was used for qualitative variables like the presence of mature follicles positive pregnancy test and BMI. A P-value of <0.05 is considered to be statistically significant. Confounders like; duration of sub-fertility, years of marriage, BMI, Education, Socioeconomic status, living with husband, and age were controlled through stratification.

Results

A total of 164 women were interviewed to know the outcomes of two different drugs. 82 women were given clomiphene citrate and 82 were treated with Letrozole. The mean age was found to be 28.48±4.12 in the clomiphene citrate group whereas 28.45±3.01 in the Letrozole group. Mostly Normal BMI was found in both groups 52 (63.4%), and 62 (75.6%) in Clomiphene Citrate and Letrozole groups respectively found to be significant at P<0.000 details were given in Table I.

There were 36 (43.9%) women who passed the secondary exam treated by Clomiphene Citrate drug while in the Letrozole group, 52 (63.4%) had secondary education. In both the groups' socioeconomic status was compared and assessed income, the data showed the middle and upper-income categories as Presented in Figure 1.

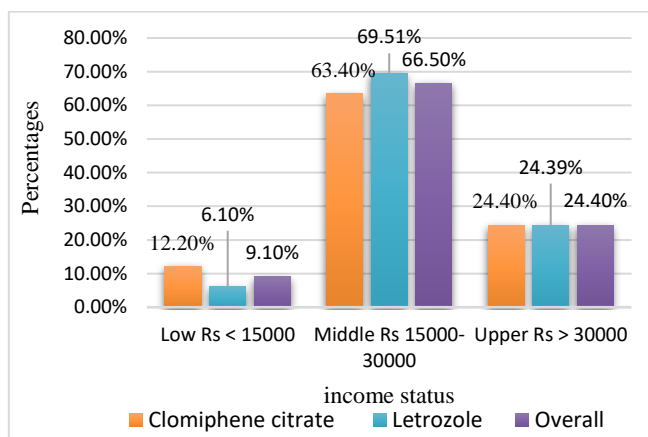


Figure no. 1 Socioeconomic status

When asked about living with their husband approximately all women responded yes they live with their husband. The Pregnancy results were noticed after being treated with Letrozole and Clomiphene Citrate, It was found that Letrozole is a powerful drug because in only 8 cases it gave no positive results while in the rest of the cases, it gave positive results as compared to Clomiphene Citrate drug.

Pregnancy was positively found with 1st cycle, 2nd cycle & 3rd cycle in 2 (2.44%), 34 (41.4%) & 21 (25.6%) respondents respectively with Clomiphene Citrate. Whereas pregnancy was positive with 1st cycle, 2nd cycle & 3rd cycle in 20 (24.3%), 36 (43.9%) & 18 (21.9%) respondents respectively with Letrozole. (Table II)

Table I: Frequency Distribution of Demographic Status.

Parameters	Clomiphene Citrate-Group	Letrozole-Group	Overall	P-Values
Age	28.48±4.12	28.45±3.01	28.46±3.56	0.041
Years of marriage	3.15±1.47	2.82±0.82	2.98±1.14	0.016
Duration of sub-fertility	3.04±1.37	2.81±0.83	2.92±1.1	0.035
BMI	24.29±2.37	23.96±3.12	24.12±2.74	0.094

Table II: Comparative Pregnancy Results among 2 groups.

Comparative Pregnancies	Clomiphene Citrate		Letrozole		P-value
	N	(%)	N	(%)	
Pregnancy Results					
Pregnancy Positive in 1st cycle	2	2.44%	20	24.39%	0.001
Pregnancy Positive in 2nd cycle	34	41.46%	36	43.90%	0.041
Pregnancy Positive in 3rd cycle	21	25.61%	18	21.95%	0.035
No Positive Pregnancy till 3rd cycle	25	30.49%	8	9.76%	0.000
Total	82	100	82	100	

When the dosage was given with Clomiphene Citrate there were 28 (34.1%) cases found with no positive results after 100mg till 3rd cycle. Positive history was found when dosage was given with Clomiphene Citrate 100 mg till 1st cycle only 1 case observed, 50mg till 2nd cycle gives 33 respondents while 100mg with 3rd cycle positive history was found in 20 respondents. (Table III)

When the dosage was given with Letrozole there were only 6(12.5%) cases that found no positive results after 100mg till 3rd cycle. This tends a positive result with Letrozole. Better efficacy was also noticed in the Letrozole drug compared to Clomiphene Citrate. Efficacy was positively found with 1st cycle, 2nd cycle

& 3rd cycle in 2 (2.4%), 23 (28.05%) & 32 (39.02%) respondents respectively with Clomiphene Citrate. Whereas efficacy was positive with 1st cycle, 2nd cycle & 3rd cycle in 18 (21.9%), 34 (41.4%) & 24 (29.2%) respondents respectively with Letrozole.

Positive history was found when the dosage was given with Letrozole 2.5 mg till 1st cycle 16 cases were observed positive, 2.5 mg till 2nd cycle gives 36 respondents while 5.0 mg with 3rd cycle positive history was found in 24 respondents.

Table III: Dosage with drug Clomiphene Citrate.

Dosage with Clomiphene Citrate	(n)	(%)	Dosage with Letrozole	(n)	(%)
1st cycle					
100 mg Positive	1	1.22%	Letrozole 2.5mg Positive	16	19.51%
2nd cycle					
50 mg Positive in	33	40.24%	Letrozole 2.5 mg Positive in 2nd cycle	36	43.90%
3rd cycle					
100 mg Positive in	20	24.39%	Letrozole 5.0 mg Positive in 3rd cycle	24	29.27%
No Pregnancies in 3rd cycle					
100 mg Clomiphene	28	34.15%	No Positive results of Letrozole 5.0 mg till 3rd cycle	6	7.32%

Table IV: Efficacy of both Drugs with Duration of subfertility.

Parameter	Efficacy		P-value
	Yes	No	
Duration of Sub Fertility with Clomiphene	3.02±0.83	3.01±1.63	0.311
Duration of Sub Fertility with Letrozole	2.64±0.63	3.25±1.25	0.041
Stratification of Efficacy Concerning Living Status (Group A)	52	20	0.001
Stratification of Efficacy Concerning Living Status (Group B)	76	06	

Discussion

Clomiphene citrate (CC) has been proven to be the first line therapy among the women for the treatment of polycystic ovarian syndrome (PCOS). Clomiphene citrate is one of the effective drugs for ovulation since 1960.¹⁶ The present study was done to compare the role and effects of Clomiphene Citrate in ovulation induction with Letrozole for patients presenting with primary subfertility due to ovulatory factors. The Alternate Hypothesis was to see that Letrozole is more effective than Clomiphene Citrate in patients with

primary ovarian sub-fertility. A significant difference was found when treating women with these two drugs in primary sub-fertility cases.

Letrozole was seen associated with similar ovulation rates i.e. 73.08% however in comparison to the clomiphene citrate group it showed 60.78% of cases with comparatively higher rates of pregnancies and birth rates. The cases of pregnancies among PCOS patients targeted 750 infertile women and compared the birth rates among the Letrozole group. Letrozole gives better results as compared to Clomiphene citrate. A study conducted recently showed the results of clomiphene and Letrozole among patients and results of ovulation showed no significant increase in the ovulation cycle and pregnancies.¹⁹⁻²⁰

In the present study, When the dosage was given with Clomiphene Citrate there were 25 (48.1%) cases found with no positive results after 100mg till 3rd cycle. Positive history was found when dosage was given with Clomiphene Citrate 100 mg till 1st cycle only 1 case observed, 50mg till 2nd cycle gives 10 respondents while 100mg with 3rd cycle positive history was found in 16 respondents similar results found in the previous study.¹⁷

In this study, Pregnancy results were noticed after treated with Letrozole and Clomiphene Citrate, It was found that Letrozole is a powerful drug because in only 6 cases it gave no positive results while in the rest of the cases, it gave positive results as compared to clomiphene citrate drug. Pregnancy was positively found with 1st cycle, 2nd cycle & 3rd cycle in 2 (2.44%), 34 (41.4%) & 21 (25.6%) respondents respectively with Clomiphene Citrate. Whereas pregnancy was positive with 1st, 2nd & 3rd cycle in 20 (24.3%), 36 (43.9%) & 18 (21.9%) respondents respectively with Letrozole the outcomes of study were compared with the similar studies showed no significant difference in ovulation induction.²¹⁻²²

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positive result with Letrozole. Positive history was found when the dosage was given with Letrozole 2.5 mg till 1st cycle 16 cases were observed positive, 2.5 mg till 2nd cycle gives 36 respondents while 5.0 mg with 3rd cycle positive history was found in 24 respondents. While other studies^{17,23} showed that Letrozole, the most commonly used aromatase inhibitor for ovulation induction, is administered in doses between 2.5–7.5 mg per day for 5 days starting on day 3 of the menstrual cycle. Putative advantages of letrozole include its lack of antiestrogenic effects on the endometrium, 104 shorter half-lives when compared to clomiphene, and a higher rate of monofollicular ovulation.²⁴

In the present study, Better Efficacy was also noticed in the Letrozole drug as compared to Clomiphene Citrate. Efficacy was positively found with 1st cycle, 2nd cycle & 3rd cycle in 2 (2.4%), 23 (28.05%) & 32 (39.02%) respondents respectively with Clomiphene Citrate. Whereas efficacy was positive with 1st cycle, 2nd cycle & 3rd cycle in 18 (21.9%), 34 (41.4%) & 24 (29.2%) respondents respectively with Letrozole.^{17, 25}

Alternate protocols for ovulation induction in women failing to conceive with Clomiphene Citrate are more often randomly used with unpredictable outcomes. A clinical/biochemical parameter is expected to help in selecting a specific type of ovulation induction protocol most suitable for achieving improved ovulation and pregnancy rates in such women. It is also suggested that ovulation induction efficiency might improve if patient subgroups with altered chances for clomiphene Citrates or complications with new or conventional techniques could be identified.^{26,27}

It has been proven from the present study that letrozole has a better ovulation and pregnancy rate as compared to Clomiphene Citrate in patients with PCOS compared to two different published research. Several smaller prospective randomized trials have also shown that letrozole may be an acceptable alternative to clomiphene citrate as an ovulation induction drug in women with PCOS, an ovulation rate of 54.6% and pregnancy rate of 25% with letrozole induction in Clomiphene Citrate-resistant women with PCOS is reported²⁸⁻²⁹

Conclusion

Letrozole appears to be a suitable ovulation-inducing agent in women with primary ovarian subfertility who fail to conceive with Clomiphene Citrate. The dosage of

Letrozole is much lower with effective pregnancy results as compared to Clomiphene Citrate.

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