

COMPARATIVE STUDY OF EFFECTIVENESS OF 2.5 mg VERSUS 5 mg DOSES OF LETROZOLE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Abstract

Background: Polycystic Ovarian Syndrome PCOS accounts for over 75% of anovulatory infertility. Letrozole is an effective alternative to clomiphene citrate as a first line drug for ovulation induction in women with PCOS. Letrozole has a definitive role in anovulatory women who have not responded to the clomiphene citrate therapy.

Aim: The objective of this study is to compare the safety and efficacy of two doses of Letrozole 2.5 mg and 5 mg as ovulation induction drug in infertile women with PCOS.

Materials and methods: This was a comparative observational study. After fulfilling the selection criteria, total 90 females of PCOS were enrolled and randomly divided into two equal groups. One is treated with Letrozole 2.5mg and other is 5mg, starting from the 2nd day of menses for 5 days. Socio-demographic parameters, duration of infertility, ovulation rate, number of matured follicles, endometrial thickness, primary and secondary outcome were measured

Results: There is no statistical significant difference found between Letrozole 2.5mg and Letrozole 5mg group in terms of socio-demographic and clinical characteristics ($P>0.05$). The ovulation rate was slightly higher in Letrozole 2.5mg group (96%) as compared to Letrozole 5mg group (92%), but not statistically significant ($p>0.05$). There was no significant difference in number of days to achieve follicular maturity and mean endometrial thickness at hCG administration between both groups ($p>0.05$). The common side effects of Letrozole therapy were nausea, dizziness and ovarian cyst formation

Conclusion: This study has shown that both the doses 2.5 mg and 5 mg Letrozole have equal effectiveness for ovulation induction and it recommends the use of 2.5 mg letrozole dose for initiation of ovulation induction in PCOS.

Keywords: Letrozole, Ovulation induction, polycystic ovary syndrome, dose, infertile women

INTRODUCTION

Infertility is a worldwide problem. Millions of women of reproductive age are affected by infertility worldwide. In India approximately 8% of currently married women suffered from infertility. Most of them (5.8%) are secondary infertile. For infertility, PCOS (Polycystic ovarian

syndrome) is the most common female endocrine disease and a frequent cause [1]. Characteristics of PCOS are anovulation, clinical or biochemical hyperandrogenism and presence of polycystic ovaries [2]. In the fertile age, it affects 5% to 10% [3], while as per recent studies reporting even higher rates [4]. Several methods have been effective for ovulation induction and fertility treatment in women with PCOS. These include weight reduction, exercise, lifestyle modifications, and drugs such as clomiphene citrate (CC), letrozole, metformin and gonadotrophins. Other measures include ovarian drilling and in-vitro fertilization (IVF) [5]. For over 40 years, CC which is a selective estrogen receptor modulator was considered the first-line drug in ovulation induction [5, 6]. It is however associated with a lower cumulative pregnancy rate of 40-45% despite an ovulation rate of about 70-80% after 6 months of treatment with its side effects. There is, therefore, a need for a simple, safe and effective alternative drug for ovulation induction particularly in patients with PCOS [7, 8]. Letrozole is a nonsteroidal third generation orally-active aromatase inhibitor, with good potential for ovulation induction. It has been in use for few years now, and numbers of researchers have studied this molecule as an option for ovulation induction [9]. Letrozole acts by reducing estrogen production by blocking androgens to estrogens conversion. Additionally, it has no adverse effect on endometrium and cervical mucus. In India, letrozole was approved for ovulation induction from 2006 to 2011 by the Drug controller general of India (DCGI). Letrozole has been shown to have good ovulation rate in CC-resistant PCOS women [10]. Indian PCOS women have high prevalence of insulin resistance [11] and thus are likely to have high CC resistance. Letrozole could prove to be a good alternative for ovulation induction in such women. **Aim:** To compare the effectiveness and safety profile of 2.5mg versus 5mg daily doses of oral Letrozole administered from 2nd to 6th day of the menstrual cycle for ovulation induction in infertile women with PCOS.

MATERIAL AND METHODS

This was a comparative observational study carried out in at Vardaan Diagnostics and Women Care Center Delhi India. A total of 90 women with PCOS who fulfilled the inclusion criteria attending our center during the study period were enrolled.

Inclusion criteria

- Infertile women between the ages of 18-35 years
- Women diagnosed with PCOS
- Women who provided written informed consent for the study

Exclusion criteria

- Women with other infertility factors like: submucous uterine fibroid or cervical stenosis
- Women with infertility due to bilateral tubal blockage
- Women with other causes of anovulation such as hyper prolactinaemia and thyroid dysfunction
- Women whose husbands have any infertility factor
- Women with allergies or contraindications to Letrozole use
- Women who not provided consent and refused for TVS.

The diagnosis of PCOS was made up mainly by clinical and ultrasound findings in keeping with 2003 Rotterdam criteria [12].

All study women were randomly assigned and divided into two equal groups (45 each):

- Group 1: Received Letrozole (2.5 mg daily), started from day 2 to day 6 of the menstrual cycle and up to 5 consecutive days
- Group II: Received Letrozole (5 mg daily), started from day 2 to day 6 of the menstrual cycle and up to 5 consecutive days

All patients’ socio-demographic data were recorded , full history was taken , clinical examination and fertility workup (Transvaginal Scan, Seminal fluid Analysis) was done.

Complete blood count, random blood sugar, renal function test and liver function test done in all patients.

A baseline transvaginal ultrasonography (TVS) was done in both the group on the second day & 10th day of their menstrual cycle to measure the number, size, and location of the follicles on each ovary as well as endometrial thickness (ET) and to ensure the absence of ovarian cysts before starting treatment.

Primary Outcomes: Comparison of ovulation rates per cycle following administration of oral Letrozole 2.5mg versus 5mg for 5 days from day 2 to day 6 in infertile women with PCOS.

Secondary Outcomes: Comparison of the numbers of days to achieve matured follicles, the number of matured follicles, endometrial thickness at hCG administration, sides effects and complications between the two groups.

Statistical analysis: Data were analyzed using statistical package for social sciences version 22.0 (IBM Corporation). Continuous data were analyzed using the student t-test, while Chi-square(x2) test and Fischer's exact test was used for categorical data. A p value <0.05 was considered to be statistically significant.

RESULTS

There were ninety women with ovulatory dysfunction and PCOS were equally randomized into letrozole 2.5mg and letrozole 5mg group. Majority of the patients (60% & 75.6%) were 30-35 years age group with overall mean age was 29.86±2.34 years. Most of the patients,(66.7% & 60%) belonged to rural area of residence and lower socio-economic class. 60% of group I and 62.2% of group II women had education upto secondary school. Overall, mean BMI (kg/m2) was noted to be 24.25±2.36. There is no statistical difference was found (p>0.05) among socio-demographic characteristics between both study groups.

Table 1: Socio-demographic characteristics of PCOS patients for each group

Socio-demographic variables		Letrozole (2.5mg) (n=45)	Letrozole (5mg) (n=45)	P Value
Age (In year)	<30	18 (40%)	11 (24.4%)	0.114
	≥30-35	27 (60%)	34 (75.6%)	
Marital status	Married	44 (97.8%)	44 (97.8%)	1.00
	Unmarried	1 (2.2%)	1 (2.2%)	
Area of Residence	Rural	15 (33.3%)	18 (40%)	0.511
	Urban	30 (66.7%)	27 (60%)	

Educational status	Primary education	8 (17.8%)	9 (20%)	0.288
	Secondary education	27 (60%)	28 (62.2%)	
	Graduate	10 (22.2%)	8 (17.8%)	
Socio-economic class	Lower	21 (46.6%)	20 (44.4%)	0.328
	Middle	14 (31.2%)	13 (28.9%)	
	Upper	10 (22.2%)	12 (26.7%)	
BMI (kg/m ²)	Underweight	2 (4.4%)	1 (2.2%)	0.381
	Normal	15 (33.3%)	9 (20%)	
	Overweight	16 (35.6%)	17 (37.8%)	
	Obese	12 (26.7%)	18 (40%)	

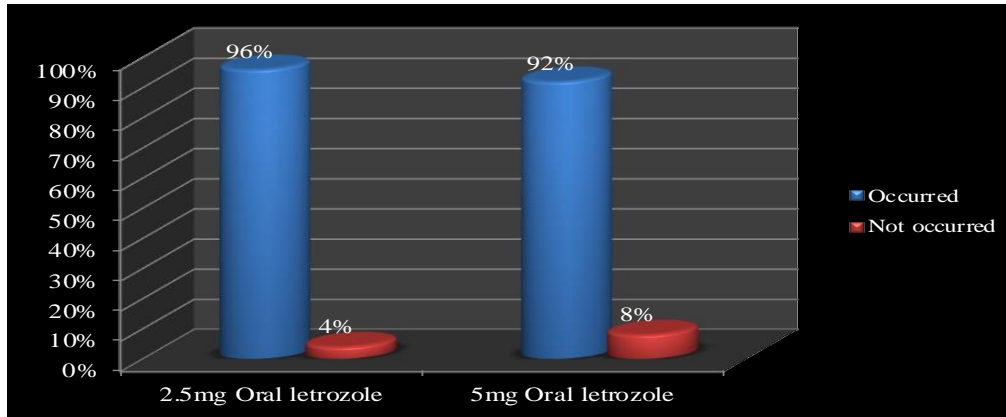
Majority of the patients had spontaneous menstrual cycle; 82.2% in letrozole 2.5mg group and 80% in letrozole 5mg group. The regular pattern of menstrual cycle was found in 55.6% in letrozole 2.5mg group and 51.2% in letrozole 5mg group. Most of them have secondary infertility (66.7% & 75.6% respectively) and the infertility duration were <3 years in 73.4% in letrozole 2.5mg group and 71.2% in letrozole 5mg group. There was no statistically significant difference was shown in clinical characteristics between the groups (P<0.05).

Table 2: Clinical characteristics of PCOS patients for each group

Clinical characteristics		Letrozole (2.5mg) (n=45)	Letrozole (5mg) (n=45)	P Value
Menstrual cycle	Spontaneous	37 (82.2%)	36 (80%)	0.787
	Induced	8 (17.8%)	9 (20%)	
Pattern of menstrual cycle	Regular	25 (55.6%)	23 (51.2%)	0.274
	Irregular	20 (44.4%)	22 (48.8%)	
Parity	0	27 (60%)	20 (44.4%)	0.139
	≥1	18 (40%)	25 (55.6%)	
Type of fertility	Primary	15 (33.3%)	11 (24.4%)	0.352
	Secondary	30 (66.7%)	34 (75.6%)	
Duration of Infertility	<3 years	33 (73.4%)	32 (71.2%)	0.314
	≥3 years	12 (26.6%)	13 (28.8%)	

Ovulation rates were higher in letrozole 2.5mg group as compared to letrozole 5mg group, but not significant statistically (p>0.05)

Graph 1: Comparison of ovulation rates per cycle among the study groups



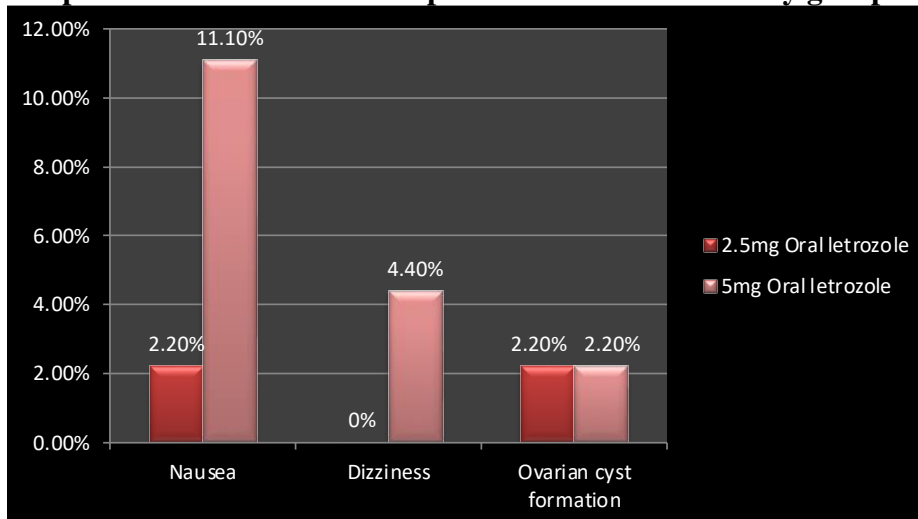
The mean number of days to achieve follicular maturity was 11.25 ± 1.62 for 2.5mg Letrozole group and 11.54 ± 1.81 for the 5mg Letrozole group, statistically not significant ($p > 0.05$)
 The mean number of matured follicles in the 5mg Letrozole group was higher (1.46 ± 0.78) when compared with the 2.5mg Letrozole group (1.31 ± 0.32). The difference was statistically not significant ($p > 0.05$). The mean endometrial thickness at hCG administration was 8.68 ± 1.34 and 9.03 ± 1.95 for 2.5mg and 5mg Letrozole group respectively. This was not statistically significant between both groups ($p > 0.05$).

Table 3: Comparison of USG findings between letrozole 2.5mg and letrozole 5mg groups

USG findings	Letrozole (2.5mg) Mean \pm SD	Letrozole (5mg) Mean \pm SD	P Value
Number of days to achieve follicular maturity	11.25 ± 1.62	11.54 ± 1.81	0.078
Number of matured follicles	1.31 ± 0.32	1.46 ± 0.78	0.051
Endometrial thickness at hCG administration	8.68 ± 1.34	9.03 ± 1.95	0.323

The common side effects of Letrozole therapy were nausea, dizziness and ovarian cyst formation [Graph: 2]. There was no statistically significant difference between the two groups in terms of the side effects ($P > 0.05$).

Graph 2: Side effects and complication between the study groups



DISCUSSION

Clomiphene citrate is the most commonly prescribed drug for ovulation induction among PCOS women, but due to its poor efficacy rates, higher chances of multiple pregnancy and major side effects, Letrozole has been explored as a good alternative for treatment of PCOS. Letrozole as an aromatase inhibitor induces ovulation in women with PCOS without having antiestrogenic effects on the endometrium. Furthermore, Letrozole has a short half-life (45 hr), therefore, it is rapidly eliminated from the body [13].

In this study there was no statistically significant difference found ($p>0.05$) between Letrozole 2.5mg group and Letrozole 5mg group in terms of socio-demographic characteristics, similar results observed by Irowa O, et al [14] and Gharib MN, et al [15].

In the present study the ovulation rate was slightly higher in 2.5mg Letrozole group than the 5mg Letrozole group, however, statistically not significant difference ($p>0.05$), in agreement with the Guo, et al [16] and Badawy A, et al [17]. Letrozole was reported to be significantly better for ovulation induction in females who were resistant to the Clomiphene Citrate. Hyperinsulinemia, which is significantly related to the PCOS, is considered as the major contributory risk factor for resistance against Clomiphene Citrate [18].

This therefore implies that the 2.5mg oral daily doses of Letrozole and 5mg oral daily doses of Letrozole have similar effectiveness for ovulation induction in infertile women with PCOS. Current research demonstrated that the mean number of days to achieve follicular maturity was almost similar in the 2.5mg Letrozole and in 5mg Letrozole groups, these finding consistent with the Al-Fadhli, et al [19].

We have reported that the number of matured follicles was slightly higher in the 5mg Letrozole group as compared to 2.5mg Letrozole group, but this difference was not statistically significant ($p>0.05$), our findings supported by Yang MQ, et al [20] and Pandya MR, et al [21], Contrary to this study, Badawy MD, et al [22] found the mean number of matured follicles higher in the 2.5mg Letrozole group compared to the 5mg Letrozole group. This may be due to differences in the treatment protocols.

The mean endometrial thickness was on hCG administration slightly higher in 5mg Letrozole group as compared to 2.5mg group, our findings comparable with the Ramezanzadeh F, et al [23] and Rahmani E. et al [24].

The common side effects and complications noted in this study were nausea, dizziness and ovarian cyst formation. These side effects and complications were not statistically significant between the two Letrozole groups; this finding collaborates with the study done by Zakaria MMN, et al [25].

CONCLUSION

We have concluded that there were no statistically significant differences in the ovulation rates, number of days to achieve follicular maturity, number of matured follicles and endometrial thickness at hCG administration between the Letrozole 2.5mg group and Letrozole 5mg group.

Also shown there were minimal side effects and complications among both the groups. Therefore, this study has demonstrated that 2.5mg dose of Letrozole is safe and effective for ovulation induction and should be used as the ideal dose for initiation of ovulation induction in infertile women with PCOS.

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