



**ORIGINAL RESEARCH PAPER**

**Gynaecology**

**A COMPARATIVE STUDY OF EFFICACY OF LETROZOLE VERSUS CLOMIPHENE CITRATE IN OVULATION INDUCTION IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME**

**KEY WORDS:**

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**ABSTRACT**

Polycystic ovarian syndrome (PCOS) is a complex disorder with heterogeneous clinical and endocrine factors. Incidence in the reproductive age group is around 20 – 22%. Ovulation Induction refers to the therapeutic restoration of the release of one egg per cycle in the woman who either has not been ovulating regularly or has not been ovulating at all. In letrozole group, 52% of the cases developed single dominant follicle and 15% of the cases had developed two dominant follicles. In CC group only, 6% of the cases had monofollicular ovulation and 23% of the cases developed two follicles. Letrozol is more effective in inducing ovulation in patients with an ovulatory cycles than clomiphene citrate in terms of monofollicular ovulation and a better endometrial thickness than when compared with clomiphene citrate. Letrozole can be recommended as the first line drug for ovulation induction in an ovulatory patients with polycystic ovarian syndrome.

**Introduction**

Polycystic ovarian syndrome (PCOS) is a complex disorder with heterogeneous clinical and endocrine factors. Incidence in the reproductive age group is around 20 – 22%. Ovulation Induction refers to the therapeutic restoration of the release of one egg per cycle in the woman who either has not been ovulating regularly or has not been ovulating at all. Appropriate patient selection can be a significant determinant of the success of OI among PCOS patients. Induction Agents include SERMS (Clomiphene citrate) and Aromatase Inhibitors (Letrozole).

Clomiphene citrate is given in dose 50 mg / day. A baseline TVS performed on D1 to D3 to exclude ovarian cyst. Therapy is begun with in the first 5 days after the onset of a spontaneous or progesterone induced menses and continued for 5 days (D3 – D7 of cycle). US FDA recommends maximum dosage of 100 mg / day. Considerable clinical experience with CC indicates that a dosage up to 250 mg / d is safe. If ovulation does not occur after 3 cycles of therapy, further treatment with CC is not recommended and the patient should be re evaluated. The most serious Complication of Cc therapy is OHSS (ovarian Hyperstimulation syndrome. Set backs of Clomiphene include Discrepancy between ovulatory and pregnancy rates, poor endometrium 30% (peripheral anti estrogenic effect), decreased glandular density, decreased uterine blood flow, extended FSH window – Multifollicular ovulation and Clomiphene resistance (20 – 25% fail to ovulate). Letrozole is a third generation AI. It is highly selective and a highly potent inhibitor of Aromatase in vitro, in vivo in animals and in humans. In PCOS, it results in increased concentrations of both estradiol and inhibit which results in a normal negative feed back loop that limits FSH response, thereby avoiding the risk of high multiple ovulation and OHSS. It is given in dose 2.5 – 5 mg from D3 – D7 or Single dose 10 – 30 mg on D3 shows similar rate of ovarian stimulation.

**MATERIALS AND METHODS:** Cohort study, a prospective, randomized, parallel, multicentric comparative trial done over a period of one year at Department of fertility research clinic, IOG, Egmore. 100 women of age 21 – 35 years, after obtaining informed consent, with a period of infertility with normal male factor, bilateral tubal patency, with no other endocrine abnormalities were included in the study.

PCOS was diagnosed if 2 of the Diagnostic criteria were satisfied: 1. Oligomenorrhea / Amenorrhea, 2. Clinical evidence of Acne / hirsutism and 3. USG evidence of PCOS

**ARMS ASSIGNED INTERVENTIONS**

- 1. Experimental Drug:** Letrozole 2.5 mg OD for 5 days (D3 – D7)
- 2. Active Comparator Drug:** CC 50 mg OD for 5 days (D3 – D7)

Height, weight, BMI and waist (in cm) were measured. Clinical evidence of acne, hirsutism, acanthosis nigricans, hyper thyroidism and hypothyroidism were looked for in all patients enrolled in our study. Antral follicle count of at least 10 with size 2 – 9 mm. the ovarian volume = / > 10 ml was taken as USG evidence of PCOS. For

bilateral tubal patency – hysterosalpingography was performed.

**RESULTS AND ANALYSIS**

The selected randomized patients were allocated as Group L and Group CC of which Group L patients were administered Letrozole 2.5 mg OD from D3–D7 of the menstrual cycle and Group Cc patients were administered CC 50 mg OD from D3 – D7 of the menstrual cycle. Both the group of patients, was subjected to transvaginal ultrasonographic monitoring of number of follicles. Maximum diameter of the largest follicle and endometrial thickness from D11 onwards. The serum progesterone levels were measured on Day 21 which indicates the definite occurrence of ovulation. The treatment was discontinued in both the groups, if patients, developed ovarian enlargement.

The number of follicles, mean diameter of the largest follicle, ovulation rate, endometrial thickness and serum progesterone values were compared in the two groups. A group test or the students test was used to compare data as appropriate. A value < 0.05 was considered to be statistically significant.

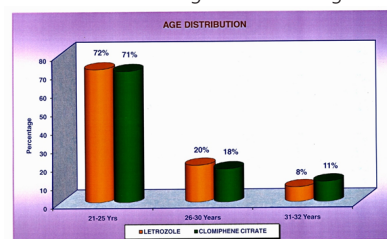
**AGE GROUP – CROSS TABULATION**

Age Group		Group		Total
		L	CC	
21 – 25 Yrs.	Count % within Group	72 72.0%	71 71.0%	143 71.5%
26 – 30 Yrs.	Count % within Group	20 20.0%	18 18.0%	38 19.0%
31 – 35 Yrs.	Count % within Group	8 8.0%	11 11.0%	19 9.5%
Total	Count % within Group	100 100.0%	100 100.0%	200 100.0%

**GROUP STATISTICS**

Age Group	N	Mean	Std. Deviation	Std. Error Mean
L	100	24.8800	3.18862	0.31886
CC	100	25.1600	3.32338	0.33234

The table shows the mean, standard deviation, in both groups L & CC with respect to age the mean age in Group L is 24.8 years. The mean age in Group CC is 25.1 years. Both groups are comparable, by applying the chi-square test, chi-square value 0.586 and p-value 0.746 are obtained. P value being > 0.05 is not significant.



**CROSS TAB**

Oligo Menorrhoea		Group		Total
		L	CC	
No Oligo Menorrhoea	Count % within Group	74 74.0%	73 73.0%	147 73.5%
Oligo Menorrhoea	Count % within Group	26 26.0%	27 27.0%	53 26.5%
Total	Count % within Group	100 100.0%	100 100.0%	200 100.0%

**AMENORRHEA GROUP CROSS TAB**

Amenorrhoea		Group		Total
		L	CC	
No Amenorrhoea	Count % within Group	83 83.0%	77 77.0%	160 80.0%
Amenorrhoea	Count % within Group	17 17.0%	23 23.0%	40 20.0%
Total	Count % within Group	100 100.0%	100 100.0%	200 100.0%

17% of the cases in Group L had clinical evidence of hirsutism. 22% of the cases in Group CC had hirsutism.

36% of the cases in Group L and 27% of the cases in Group CC had Oligomenorrhoea.

17% of the cases in Group L and 23% of the cases in Group CC has history of amenorrhoea.

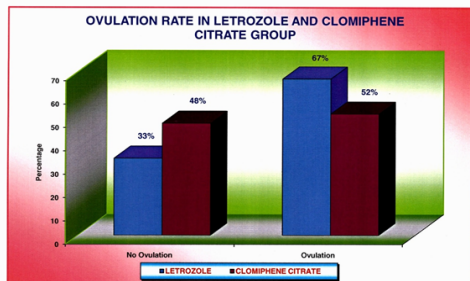
After excluding pregnancy by urine gravindex method, these patients were subjected to the study after progesterone withdrawal bleed.

**OVULATION GROUP**

Ovulation		Group		Total
		L	CC	
No Ovulated	Count % within Group	33 33.0%	48 48.0%	81 40.5%
Ovulated	Count % within Group	67 67.0%	52 52.0%	119 59.5%
Total	Count % within Group	100 100.0%	100 100.0%	200 100.0%

**CHI-SQUARE TESTS**

	Value	Df	Asymp. Sig. (2 sided)	Exact Sig. (2 – sided)	Exact Sig. (1 – sided)
Person Chi-square	9.778	1	0.002		
Continuity Correction	8.909	1	0.003		
Likelihood Ratio	9.862	1	0.002		
Teacher's Exact Test				0.003	0.001
Linear-by-Linear Association	9.729	1	0.002		
N of valid cases	200				



The ovulation response group tabulation shows that of 100 patients in L group, 67% ovulation occurred. 52% ovulation rate occurred in CC group. By applying chi-square tests, chi-square value 8.909 p value 0.003 (< 0.05) = Significant. This shows that there is statistically significant difference in ovulation induction

rate between the group of patients treated patients with L and CC. Letrozole treated patients had better ovulation rates than CC.

**NUMBER OF FOLLICLES IN L & CC GROUP**

Number of follicles		Group		Total
		L	CC	
No Follicle	Count % within Ovulation	33 33.0%	48 48.0%	81 40.5%
One Follicle	Count % within Ovulation	52 77.6%	6 11.5%	58 29.0%
Two Follicles	Count % within Ovulation	15 22.4%	23 44.2%	38 19.0%
Three Follicles	Count % within Ovulation	0 0.0%	23 44.2%	23 11.5%
Total	Count % within Ovulation	67 100.0%	52 100.0%	200 100.0%

**CHI-SQUARE TESTS**

	Value	Df	Asymp. Sig. (2 sided)
Person Chi-square	100.000 <sup>a</sup>	3	0.000
Likelihood Ratio	138.469	3	0.000
Linear-by-Linear Association	84.366	1	0.000
N of Valid Cases	100		

a. 2 cells (25.0%) have expected count less than 5. The minimum expected count is 2.88.

The cross tabulation shows that of 100 patients studied in Letrozole group, 52% of the cases developed single follicle, 15% of the cases developed two follicles. 33% of the cases did not ovulate with Letrozole.

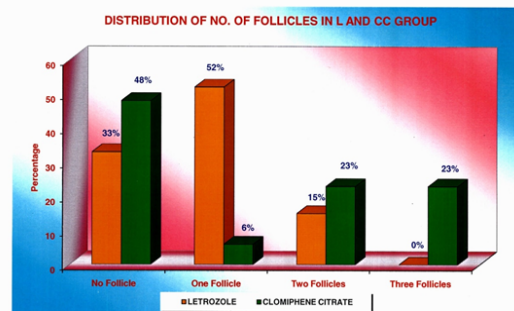
Of 100 patients in CC group, 6% of the cases the developed single follicle, 23% of the cases developed two follicle, 23% of the cases developed three follicles. 48% of the cases did not ovulate with CC therapy. By applying the chi-square tests, chi-square value 63.945 and p value =.000 (<0.05) highly significant.

Letrozole treated cases had better monofollicular ovulation rates than CC treated group.

**GROUP STATISTICS**

Size of Follicle	Group	N	Mean	Std. Deviation	p Value
	L	67	21.1560	2.40499	<0.05
	CC	52	18.7635	2.35614	

The table shows the mean diameter of largest follicle in L group is 21.15 mm with a S.D. of 2.404. In CC group, the mean diameter is 18.76 mm with a S.D. of 2.356 p value of 0.000 (<0.05) obtained which is highly significant.



**GROUP STATISTICS**

Endometrial Thickness	Group	N	Mean	Std. Deviation	p Value
	L	67	8.6090	0.43753	0.000 (<0.05)
	CC	52	7.1115	0.60929	

The table shows the mean endometrial thickness in L group is 8.60mm with a S.D. of 0.437.

In CC group the mean Endometrial thickness is 7.11 m with a S.D of 0.609 P value obtained is 0.000 (<0.05) = High Significant.

**GROUP STATISTICS**

Serum Progesterone Level	Group	N	Mean	Std. Deviation	Std. Error Mean
	L	67	13.4164	1.57688	0.000 (<0.05)
	CC	52	12.2788	1.87191	

The table shows the mean serum progesterone level in L group is 13.41 ng/ml CC group is 12.27 ng/ml. p value of 0.000 (<0.05) = Highly Significant.

**DISCUSSION**

In our study 17 % of cases in L group and 22 % of cases in CC group had hirsutism. 17% of cases in L group and 23% of cases in CC group had a history of amenorrhea. After excluding pregnancy for these patients by performing an urine gravindex method, these patients were included in our study after progesterone withdrawal bleed.

Both group were compared with respect of number of follicles, mean diameter of largest follicle, mean endometrial thickness and serum progesterone levels. The patients enrolled in both groups had no complications pertaining to L and CC during our period of study. In our study, the ovulation rate in L group was 67% and that of CC group 52%. In our study, 52% of the cases had monofollicular ovulation in L group where .as in CC group only 6% of the cases developed single follicle and 23% of the cases developed two follicles. In our study, the mean endometrial thickness was better in Letrozole group than CC group (8.6 mm vs 7.1 mm)

The mean endometrial thickness (7.1 mm) in CC group indicates the adverse effects of CC on the endometrial growth that is thought to be due to depletion of the endometrial receptors.

In our study the mean diameter of largest follicle was greater in L group than CC group (21.15 mm Vs 18.76 mm). The serum progesterone levels measured on D21 indicated the definite occurrence of ovulation was 13.41 ng/ml in L group and 12.27 ng/ml in CC group.

**CONCLUSION**

In the patients recruited in this study, mean age in L group was 21.8 yrs and In CC group 25.1 years. The mean duration of infertility in L group was 24.3 years and in CC group 24.4 years. In Letrozole group, the ovulation rate was 67% and in CC group 52%. In letrozole group, 52% of the cases developed single dominant follicle and 15% of the cases had developed two dominant follicles. In CC group only, 6% of the cases had monofollicular ovulation and 23% of the cases developed two follicles.

The mean diameter of largest follicle in L group is 21.15 mm and in CC group 18.76 mm. The mean endometrial thickness is L group is 8.6 mm and in CC group 7.1 mm. The serum progesterone level in L group is 13.41 ng/ml and CC group is 12.27

Letrozol is more effective in inducing ovulation in patients with an ovulatory cycles than clomiphene citrate in terms of monofollicular ovulation and a better endometrial thickness than when compared with clomiphene citrate. The mean diameter of the largest follicle and the serum progesterone level studied showed letrozole was superior than clomiphene citrate in inducing ovulation. Hence Letrozole can be recommended as the first line drug for ovulation induction in an ovulatory patients with polycystic ovarian syndrome.