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A randomized clinical study to compare the outcome of two different ovulation induction regimes among PCOS patients

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Abstract
Aim: Study to compare the two different drug regimes in treatment of infertility among PCOS patients.
Materials and Methods: The present Randomized control trial was conducted in the Department of Obstetrics and Gynaecology, among PCOS patients diagnosed on the basis of revised Rotterdam 2003 criteria. In this clinical trial out of 120 patients, 60 patients received Clomiphene Citrate 100 mg (group A) and rest 60 patients received Letrozole 5mg (group B) daily since day 2-6 or 3-7 of menstrual cycle.
Result: Monofollicular development was statistically significantly, greater in the group B. There was also statistically significant difference between the two groups in endometrial thickness (CC 7.15±1.15mm, Let 9.31±2.15mm). Similarly, the ovulation rate was 88%% in group A and 92% in group B. The pregnancy rate was 23% in group A and 37% in group B.
Conclusion: The present study concluded that though Clomifen Citrate group showed good ovulation rate but final outcome was poor which can be due to anti-estrogenic effect resulting poor endometrial response and negative effect on cervical mucus.

Keywords: Infertility, letrozole, clomifen, PCOS

Introduction
Ovulation induction is the mainstay of treatment for infertile couple after primary evaluation and failure of medical method seeks surgical intervention.
Clomiphene citrate is considered as the drug of choice for first line treatment of anovulatory dysfunction for a variety of reasons. It is orally administered, has few side effects, is easily available and is inexpensive. Although ovulation rates are in the range of 70-80% the actual pregnancy rates are significantly lower at around 30-40% [1, 2]. However, clomiphene has certain well-defined disadvantages. Treatment with CC is associated with discrepancy in ovulation and pregnancy rates (60-85%; 10-20%). Miscarriage rate is higher than general population [3, 4], and 20-25% PCOS women are resistant to clomiphene [5, 6]. The desire for an effective alternative persists.
Letrozole, an aromatase inhibitor, was introduced into infertility practice in the year 2000 and is regarded as a second line treatment option, particularly in women with clomiphene resistance [7, 8]. Letrozole has found acceptance in various clinical situations and the indications for use have expanded [9, 10]. However, clomiphene has certain well-defined disadvantages. Treatment with CC is associated with discrepancy in ovulation and pregnancy rates (60-85%; 10-20%). Miscarriage rate is higher than general population [3, 4], and 20-25% PCOS women are resistant to clomiphene [5, 6].
The most often asked question of whether Letrozole is better than clomiphene as a first line treatment option remains unanswered and a clear answer would have important clinical implications for infertility specialists. Hence the present study was conducted to compare the outcome of two different ovulation induction regimes in an Indian setup.

Materials and methods
Study Design
The present Randomized control trial was conducted in the Department of Obstetrics and Gynaecology, among PCOS patients diagnosed on the basis of revised Rotterdam 2003 criteria [11].

Ethical approval and Informed consent
The study protocol was reviewed by the Ethical Committee of the Hospital and granted ethical clearance. After explaining the purpose and details of the study, a written informed consent was obtained.

Inclusion Criteria
- Patients of anovulatory PCOS
- Patients between 20-35 years of age
- Patients having infertility for more than one year
- Patients who has signed the informed consent

Exclusion criteria
- Patients who has not signed the informed consent
- Patients having any kind of acute and chronic systemic illness

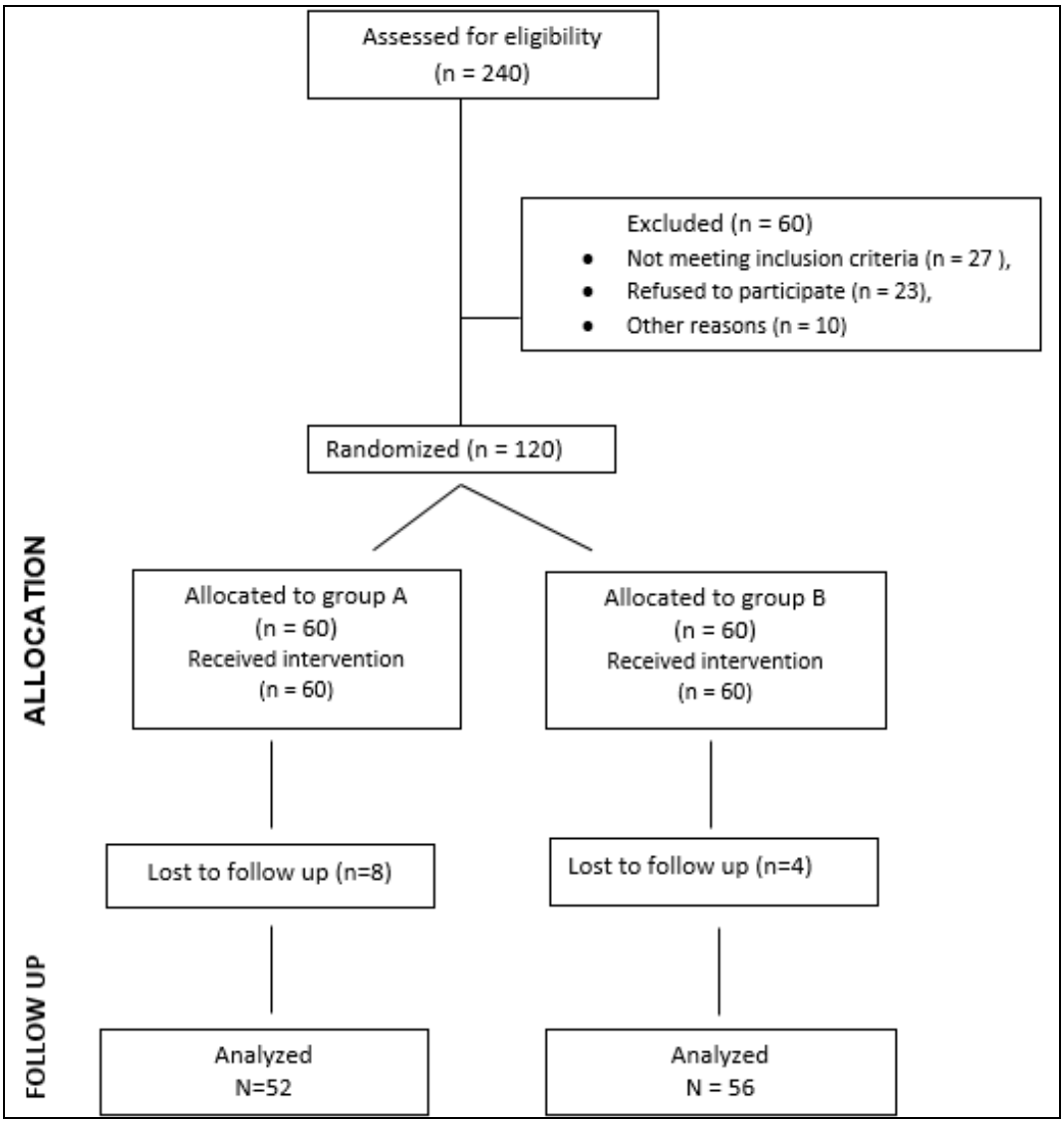
Sample Selection
60 subjects in each arm to achieve 80% power of study and level of significance 0.05 were recruited for the study.
The minimum sample size for each group was calculated using the formula:

$n = (Z_{\alpha/2}+Z_{\beta})^2 *2*\sigma^2 / d^2$,

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$, Z_{β} is the critical value of the Normal distribution at β, σ^2 is the population variance, and d is the hypothesized difference between the two study groups. Assuming equal group sizes to achieve a power of 80% and a two-sided confidence level of 95%, the study required a sample size ranging from 16 to 50 for each group. Assuming a non response rate of 10%, the minimum required sample size was 52. Therefore, a sample size of 60 for each group was included in the study.

Groups
Group A: Infertile patients with PCOS received 100 mg Clomifen Citrate
Group B: Infertile patients with PCOS received 5 mg Letrozole

Study protocol
In this trial 120 infertile patients with PCOS received either 100 mg Clomifen Citrate (n=60) or 5 mg Letrozole (n=60) daily since day 2-6 or day 3-7 of cycle. Serial follicular measurements were done by same observer from day 9 onwards and Human chorionic gonadotrophin was administered at a dose of 5,000 IU when at least 1 mature follicle (18-22 mm) was detected. Timed intercourse was advised to the patients after 24-36 hrs of hCG. Then the number of follicles, endometrial thickness, ovulation rate & pregnancy rate were measured in both groups.



Statistical analysis

The data was entered in the form of a data matrix in Microsoft Excel® and analysed statistically using IBM® SPSS® version 20.0.0. Descriptive statistics were calculated as frequencies for categorical variables and means and standard deviation for continuous variables. The association between the categorical variables was explored using Pearson chi-square test. The difference of continuous variables, among two groups was explored using student t-test. P-value of <0.05 was considered statistically significant for the purpose of the study.

Results

Table 1: Demographic profile

Variables	Group A	Group B	*p*-value
Age (Years)	26.89±2.01	26.43±2.13	≥0.05
BMI	25.91±2.23	26.21±2.81	≥0.05
Mean Infertility Duration (Years)	5.82±1.77	5.97±1.72	≥0.05

Test applied: student t-test

Table 2: Comparison of outcome of ovarian stimulation

Variables	Group A	Group B	*p*-value
Mean Endometrial Thickness (mm) on the day of hCG administration	7.01±1.15	9.31±2.15	≤0.05
Mean No. of Follicles>18mm on the day of hCG administration	1.82±0.71	1.77±0.69	≥0.05
Mono follicular (%)	61.7	88.6	≤0.05
Multi-follicular (%)	35.3	11.4	

Test applied: chi-square test

Table 3: Comparison of treatment outcome

Variables	Group A	Group B
Number of cycles (N)	218	192
Ovulation rate (%)	88.0	92.0
Pregnancy rate (%)	23.0	37.0
Multiple pregnancy (N)	31	2
Number of Miscarriage	7	3

Discussion

For many years, Clomifen Citrate has been used as the first treatment of choice for patients with PCOS. It is generally accepted that Clomifen Citrate reduces uterine receptivity, and thus reduces the chances of conception. It is associated with endometrial thinning in 15–50% of patients, probably due to estrogen receptor depletion. Furthermore, the use of CC may block estrogen receptors in the cervix, producing a negative effect on the quality and quantity of cervical mucus. Inappropriate development of the endometrium is associated with low implantation rate and early pregnancy loss due to luteal phase defect [12-14].

Aromatase inhibitors are non-steroidal compounds that suppress estrogen biosynthesis by blocking the action of the enzyme, aromatase, which converts androstenedione and testosterone to estrogens. Letrozole is a potent reversible oral aromatase inhibitor, which has been widely used in post-menopausal women with metastatic breast cancer [15]. It is given in a dose of 2.5–5 mg/day and has been shown to achieve optimal suppression of serum estrogen level and is almost free of side effects [15-17]. The efficient estrogen-lowering property of letrozole could be utilized to temporarily release the hypothalamus from negative feedback effect of estrogen and thereby inducing an increased discharge of FSH. With letrozole, estrogen production is eventually advanced by the induced FSH discharge, but in contrast to the use of CC, the hypothalamus is able to respond to estrogen feedback with a negative feedback mechanism [16]. This helps in modulating an overzealous discharge of FSH, which in turn is more likely to result in a mono-follicular ovulation with moderate estrogen concentration.

Table 4: RCTs comparing letrozole versus clomiphene

Sl. No.	Authors	Study design	Treatment arms	Endometrial thickness (mm)	Ovulation rates (%)	Pregnancy rates (%)
	Present study	RCT	Letrozole 5 mg vs. Clomiphene 100 mg	9.31±2.15 vs. 7.01±1.15	92.0 vs. 88.0	37.0 vs. 23.0
1	Badawy A *et al*. [18] Egypt, 2009	RCT	Letrozole 5 mg vs. Clomiphene 100 mg	8.1±0.2 vs. 9.2±0.7	67.5 vs. 70.9	15.1 vs. 17.9
2	Kar S [19] India, 2012	RCT	Letrozole 5 mg vs. Clomiphene 100 mg	7.65 vs. 7.61	73.08 vs. 60.78	21.56 vs. 7.84
3.	Chakravorty R *et al*. [20] India, 2016	RCT	Letrozole 5 mg vs. Clomiphene 100 mg	9.82 vs. 8.13	37.87 vs. 19.67	24.0 vs. 15.38

Conclusion

The present study concluded that though Clomifen Citrate group showed good ovulation rate but final outcome was poor which can be due to anti-estrogenic effect resulting poor endometrial response and negative effect on cervical mucus. However there is need for larger well designed randomized trials to generate robust data in order to establish the true potential of letrozole

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