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Original Research Article

## Use of letrozole versus clomiphene citrate combined with gonadotropins for ovulation induction in infertile women with polycystic ovary syndrome: a pilot study

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### ABSTRACT

**Background:** The aim of the study was to evaluate the efficacy of letrozole and clomiphene citrate (CC) in gonadotropin-combined for ovulation stimulation in women with polycystic ovary syndrome (PCOS). It was a prospective pilot study.

**Methods:** This prospective trial included 124 patients of infertile women with PCOS. Letrozole dose of 5 mg/day (n = 65) or a CC dose of 100 mg/day (n = 59) was given on day 3 to day 7 of the menstrual cycle, combined with gonadotropin i.e. follicle stimulating hormone (FSH) at a dose 75 IU every day starting on day 7 and continued to day 9. Main outcome measures were occurrence of ovulation, number of mature follicles, serum estradiol (E2) and endometrial thicknesses on the day of human chorionic gonadotropin (hCG), and pregnancy rates.

**Results:** The clinical profile including mean age, duration of infertility, BMI, baseline FSH, LH and E2 of patients belonging to both groups were comparable. The numbers of mature follicles (4.3±0.3 vs. 2.9±0.7) were significantly higher in letrozole+FSH group. Serum E2 levels on the day of hCG (301.78±85.7 vs. 464.7±72.9 pg/mL) were significantly lower in the letrozole+FSH group. Significant differences were found in endometrial thickness measured on the day of hCG in letrozole+FSH group (p=<0.0001). The rate of ovulation was higher in letrozole+FSH group and it was marginally statistically significant (p=0.040). The rate of pregnancy was slightly greater in the letrozole+FSH group (17.85% versus 13.33%), although not statistically significant.

**Conclusions:** Letrozole in combination with FSH appears to be a suitable ovulation inducing agent versus CC with FSH in PCOS. This combination may be more appropriate in patients who are particularly sensitive to gonadotropin.

**Keywords:** Clomiphene citrate, Gonadotropin, Letrozole, Ovulation induction

### INTRODUCTION

It is now well known that polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age, with an estimated prevalence of 5%-10% of the general population, and by far the most common cause of an-ovulatory infertility.<sup>1</sup> Clomiphene citrate has been the most widely used drug for the treatment of infertility.<sup>2</sup> However, 20-25% of the

women are failing to ovulate due to CC resistant.<sup>3</sup> In such cases, the traditional alternative is to administer gonadotropins; however, it is associated with an enhanced risk of multiple pregnancies and ovarian hyperstimulation.<sup>4</sup> Gonadotropins (FSH/hMG) used in combination with CC decrease the dose required for optimum stimulation and make it more cost-effective in women who fail to react to CC treatment.<sup>5</sup> As of late, aromatase inhibitor has been explored as a potential

ovulation induction agent.<sup>6</sup> Because it does not reduce estrogen receptors in central and peripheral target tissues, it classically results in mono-ovulation, and it may have no adverse impact on endometrium and cervical mucus.<sup>7,8</sup> However, intra-uterine insemination (IUI) cycles sometimes need multiple follicular developments; therefore, aromatase inhibitor must be combined with exogenous gonadotropins for superovulation in IUI. Gonadotropin, either urinary or recombinant FSH, have been used to stimulate ovulation in women who fail to ovulate or get pregnant with CC.<sup>9,10</sup>

The superiority of aromatase inhibitor over CC has not been proven in gonadotropin-combined ART (assisted reproductive technology) cycles. Several previous studies were done, both controlled and non-controlled, comparing letrozole with CC alone or in combination with gonadotropins. However, still insufficient proof is available to recommend letrozole for routine use in ovulation induction. Most of these studies recommend that larger randomized studies are necessary to confirm the effectiveness of letrozole as an ovulation inducing agent in infertile women.<sup>11-14</sup>

The aim of this study was to evaluate the efficacy of letrozole or CC, in combination with FSH, in women with PCOS undergoing ovarian stimulation and to evaluate the pregnancy rate.

## METHODS

This prospective controlled clinical trial was conducted in a tertiary infertility care unit, MAGS Medical and Research Center, Kolkata, India. The work has approved by the local ethical committee. Informed consent was taken from all women who were included in this study. One twenty-four women with PCOS, diagnosed by the Rotterdam criteria, who had previously failed to conceive or ovulate, were included in the study.<sup>15</sup> At least one tubal patency was confirmed by hysterosalpingography in all subjects. Semen parameters were interpreted by the World Health Organization (2010) criteria. The patients were examined clinically. Their weight, height, body mass index was estimated. Transvaginal U/S examination was performed to exclude any pelvic pathology before treatment.

We excluded the female if age was >37 years old, had severe endometriosis (stage IV), or a basal serum FSH of >15 mIU/mL.

Randomization of recruited women was carried out using online software ([www.randomization.com](http://www.randomization.com)) to generate a random number table. The patients were randomly distributed into two groups. Letrozole, in a dose of 5 mg/day (n = 65), or CC, in a dose of 100 mg/day (n = 59), was given on day 3 to day 7 of menstrual cycle. In addition, gonadotropin either urinary or recombinant FSH 75 IU was administered every day on both groups, starting on day 7 and continued to day 9. When at least

one mature follicle (with a mean diameter  $\geq 18$  mm) was observed, 10,000 IU of hCG were given subcutaneously to trigger ovulation. Patients were asked for timed intercourse 36- 40 hours later. All women received 400 mg micronized progesterone intra-vaginally daily for 15 days for luteal support. All women continued received 500 mg metformin t.i.d.

The chemical pregnancy was done by testing  $\beta$ -hCG assay. The occurrence of ovulation, number of mature follicles ( $\geq 18$  mm diameter), serum E2 levels and endometrial thickness measured on the day of hCG administration.

## Statistical analysis

Data were analyzed with SPSS 20.0 (SPSS Inc., Chicago, IL). Data are expressed as mean  $\pm$  standard deviation (SD). The  $\chi^2$  test was used to compare proportions, and the Student's t-test to compare means. P value of less than 0.05 was considered statistically significant.

## RESULTS

Baseline characteristics among the two groups are summarized in Table 1.

**Table 1: Baseline characteristic of patients with infertility in both groups.**

Parameter(s)	Letrozole+FSH N=65	CC+FSH N=59	P value
Age (years)	27.3 $\pm$ 1.9	26.9 $\pm$ 2.1	0.267
Duration of mean infertility period	2.1 $\pm$ 0.9	2.3 $\pm$ 0.6	0.152
Height (cm)	162.07 $\pm$ 3.7	161.3 $\pm$ 3.2	0.219
Weight (kg)	74.8 $\pm$ 2.9	75.1 $\pm$ 3.3	0.591
Body mass index (Kg/m <sup>2</sup> )	27.9 $\pm$ 2.5	28.3 $\pm$ 2.3	0.357
Previous IUI trials	1.1 $\pm$ 0.9	0.8 $\pm$ 1.4	0.154
Pre-treatment endometrial thickness (mm)	4.7 $\pm$ 1.4	4.5 $\pm$ 0.7	0.323
FSH (IU/mL) on day 2/3 of cycle	7.7 $\pm$ 2.1	7.4 $\pm$ 1.7	0.386
LH (IU/mL) on day 2/3 of cycle	6.54 $\pm$ 1.4	6.17 $\pm$ 2.1	0.246
E2 (pg/mL) on day 2/3 of cycle	63.61 $\pm$ 0.5	63.72 $\pm$ 1.9	0.653
TSH (mIU/L) on day 2/3 of cycle	3.1 $\pm$ 1.3	2.94 $\pm$ 1.63	0.545
Prolactin (ng/dL) on day 2/3 of cycle	27.59 $\pm$ 6.72	26.83 $\pm$ 7.1	0.541

Data are expressed as mean $\pm$ SD.

No statistical difference could be detected for mean age, BMI, pre-treatment endometrial thickness (mm) among the two groups of patients. The duration of infertility was

not significantly different between the two groups. There was also no significant difference about baseline biochemical parameters such as FSH, LH, E2, TSH, and prolactin plasma levels. Although total doses of FSH were similar, the number of mature follicles on the day of hCG administration were significantly higher in the letrozole+FSH group ( $p < 0.0001$ ). No cancelled cycles occurred due to excessive stimulation or cases of ovarian hyperstimulation syndrome. Significant difference was found in endometrial thickness measured on the day of hCG administration (Table 2).

**Table 2: The outcomes of cycles using gonadotropin (FSH) combined with letrozole or clomiphene citrate.**

Parameter (s)	Letrozole+FSH N=65	CC+FSH N=59	P value
Days of hCG administration	11.5±1.3	12.1±1.5	0.018
Follicular development by day 14 (mm)	22.4±0.5	22.7±0.9	0.021
No. of follicles $\geq 18$ mm on day of hCG administration	4.3±0.3	2.9±0.7	<0.0001
Serum E2 (pg/ml)	301.78±85.7	464.7±72.9	<0.0001
Endometrial thickness (mm) on day of hCG	9.62±0.9	8.33±0.4	<0.0001
Serum progesterone (ng/mL)	10.09±1.01	9.55±0.92	0.002
Ovulation	28 (43.07%)	15 (25.42%)	0.040
Pregnancy	5 (17.85%)	2 (13.33%)	0.705

Data are expressed as mean  $\pm$  SD.

Ovulation rate was higher in letrozole+FSH group compare to CC+FSH group ( $p=0.040$ ). Chemical pregnancy rates were comparable in the two groups but it was not statistically significant ( $p=0.705$ ) (Table 2).

## DISCUSSION

Several smaller prospective randomized trials have also shown that letrozole may be an acceptable alternative to CC as an ovulation induction drug in women with PCOS.<sup>16-18</sup> The rate of mature follicular development was significantly higher when letrozole in addition with FSH. The regimen of letrozole addition with FSH was, therefore, more effective and safer than CC in addition with FSH for ovulation induction. These results support the concept that letrozole combined with FSH reduces the risk of hyperstimulation in patients who are particularly sensitive to gonadotropins.

One pilot study had been reported, and its results indicated that letrozole groups were associated with a significantly higher pregnancy rate and thicker endometrium in gonadotropin-combined IUI cycles.<sup>5</sup> The pregnancy rate in group Letrozole+FSH was observed to be slightly higher, though not statistically significant, as compared to group CC+FSH. Having unsuccessful to previous cycles of CC/Letrozole therapy, it is possible that CC/Letrozole alone is unable to produce an optimum amount of endogenous gonadotropin (FSH) necessary for the development of competent follicles and inducing ovulation. This supports our observations in the study.

## CONCLUSIONS

We found letrozole co-treatment with FSH achieved a higher rate of mature follicular growth and ovulation. However, considering the lower percentage of pregnancy in this study, it should be further investigated in larger populations to determine whether letrozole is more beneficial in certain subgroups of infertile patients.

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