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Randomised controlled trial to study the difference in follicular growth in infertile patients receiving a prior cycle of oral contraceptive pills followed by letrozole vs letrozole alone

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Abstract
Background: Letrozole is widely used for ovulation induction in infertile women with normo-gonadotropic anovulation and polycystic ovarian syndrome (PCOS). Pretreatment with combined oral contraceptive pills (OCPs) may suppress the hypothalamic–pituitary–ovarian axis and potentially optimize follicular response, but the data on randomized controlled trials is limited in this regard.
Aim: To compare follicular growth and reproductive outcomes in infertile women receiving a prior cycle of OCPs followed by letrozole versus infertile women receiving letrozole alone.
Materials and Methods: This prospective, randomized, double-blind controlled trial was conducted over 24 months (August 2022–July 2024) in the Department of Obstetrics and Gynaecology at a tertiary care teaching hospital in western India. Adult infertile women (>18 years) with primary or secondary infertility and WHO Group II anovulation, including PCOS, with normo-gonadotropic normo-gonadism and patent tubes were enrolled. Women with male factor, endometriosis, genital Koch's, pelvic inflammatory disease, anatomical abnormalities, prior IVF/IUI or prior ovulation induction were excluded. A total of 180 women were randomized; 17 withdrew before treatment, leaving 82 in Group A (letrozole only: 5 mg once daily for 5 days from day 2) and 81 in Group B (one cycle of OCPs [Mala-D] followed by the same letrozole regimen). Baseline demographics, BMI, and day-2 FSH, LH, and TSH were recorded along with baseline TVS on Day 2 followed by follicular growth monitoring from day 9 onwards.
Results: Both groups were comparable in age, BMI, type of infertility, comorbidities, and basal hormonal profile ($p>0.05$). AFC did not differ significantly between groups. Group B had a higher mean number of follicles >18 mm (3.02±1.28 vs 2.20±1.1; $p<0.05$) and greater mean endometrial thickness (8.06±2.19 vs 7.4±2.20 mm; $p<0.05$). Time to LH surge was significantly shorter in the OCP+letrozole group ($p<0.05$). UPT positivity (12.5% vs 17.28%) and clinical pregnancy rates (10.97% vs 14.81%) were higher in Group B. Rates of ectopic pregnancy, multiple gestation, and weight gain were low and comparable between groups ($p>0.05$).
Conclusion: A prior cycle of OCPs followed by letrozole results in improved follicular maturity, better endometrial development, shorter time to LH surge, and higher pregnancy rates compared with letrozole alone, without increasing adverse outcomes. OCP pretreatment appears to be a useful strategy to enhance ovulation induction outcomes in infertile women with WHO Group II anovulation and PCOS.

Keywords: Infertility; Ovulation induction; Letrozole; Oral contraceptive pills; Follicular growth; Randomized controlled trial

Introduction

Fertility is the capacity to produce offspring, and a couple is considered to be infertile if they cannot conceive after 12 months of unprotected intercourse. A stricter definition of infertility is failure to achieve a pregnancy in a 12-month period for patients under 35 years of age and failure to conceive in a 6-month period for people after 35 years [1].

The prevalence of infertility worldwide is estimated to be one in seven to one in five (14-20%) couples in their reproductive age [2]. The causes of infertility can be male, female or a combination of both and include disorders of ovulation, tubal disease, endometriosis, chromosomal abnormalities, sperm factors and unexplained infertility. Majority of infertility cases are overcome through surgical and medical infertility treatment. Medical treatment options include assisted reproductive technology (ART) such as in vitro fertilization (IVF),

intracytoplasmic sperm injection (ICSI), and intrauterine insemination (IUI). Infertility treatment has been dramatically advanced in recent years; however, age related infertility remains as one of the most difficult challenges [2, 3].

Letrozole is a potent, reversible, and highly selective aromatase inhibiter (AI) that prevents conversion of androgen-to-estrogen, it increases follicle stimulating hormone (FSH) by decreasing the negative feedback of estrogens on the hypothalamus. Letrozole is considered ideal for ovulation induction, as it does not decrease estrogen receptors in target tissues and has less negative impact on endometrium and cervical mucus, thus typically favoring mono- follicular growth [4].

Unfortunately, randomized controlled trials (RCTs) that could provide high quality evidence on this issue are currently lacking. Therefore, this randomized controlled trial was designed to study the effectivity of pre-treatment with oral contraceptive pills before beginning ovulation induction with Letrozole.

Materials and Methods

This prospective, randomized, double-blind controlled trial was conducted over 24 months (August 2022–July 2024) in the Department of Obstetrics and Gynecology at a tertiary care teaching hospital in western India. Adult infertile women (>18 years) with primary or secondary infertility and WHO Group II anovulation, including PCOS, with normogonadotropic normogonadism and patent tubes were enrolled. Women with male factor, endometriosis, genital Koch's, pelvic inflammatory disease, anatomical abnormalities, prior IVF/IUI or prior ovulation induction were excluded. A total of 180 women were randomized; 17 withdrew before treatment, leaving 82 in Group A (letrozole only: 5 mg once daily for 5 days from day 2) and 81 in Group B (one cycle of OCPs [Mala-D] followed by the same letrozole regimen). Baseline demographics, BMI, and day-2 FSH, LH, and TSH were recorded along with baseline TVS on Day 2 followed by follicular growth monitoring from day 9 onwards.

Sample size

By keeping the confidence limits at 95% and power of study at 80%, to detect a minimum of 10% difference in proportion of effect, a total sample size of 162 patients was calculated, which was randomly divided into two groups with 81 patients each for better validity of results. A computer assisted randomization table into 2 groups of 81 subjects each fulfilling inclusion and exclusion criteria.

The sample size was calculated using formula;

n= [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)]

- Population size (for finite population correction factor or FPC) (N): 200
- Hypothesized% frequency of outcome factor in the population n 95%+/-(p): 5
- Design effect (for cluster surveys-DEFF): b1
- Confidence level (%): 95%
- Sample size: 30 (approximately)
- Result from open-Epi, version 3, open-source calculator-SS Proper
- Hence, a minimum sample size of approximately 81 cases in each group during study period was randomly selected and included in present study.

One hundred eighty adult women attending Gynecology OPD and ART Centre with infertility (one year of unprotected regular coitus), having regular or anovulatory cycles and confirmed tubal patency, in the absence of male factor and endometriosis (seen on TVS), meeting the inclusion and exclusion criteria were included in the present study. These women were randomized at the outpatient clinic based on a computer-generated list to no OCP pretreatment (non-OCP group A) group with 95 subjects; or OCP pretreatment (OCP group B) group with 85 patients.

Blood investigations like FSH, LH, PRL, TSH, Blood sugars were sent on D2. An informed consent was taken after patient selection. Seventeen patients (non-OCP group: n =13, OCP group: n = 04) did not start the treatment cycle after the initial consultation for personal reasons. So, 82 participants of group A (non OCP group) received T Letrozole 5 mg OD for 5 days. 81 participants of group B (OCP group) received Oral contraceptive pills (Mala- D) from D2 of periods. After 1 cycle of OC pills, group B received T Letrozole 5 mg OD for 5 days starting from 2nd day of next cycle. Baseline TVS was done for both the groups on day 2 for Antral follicular count and endometrial thickness. Participants of both the groups underwent follicular monitoring starting from D9 till follicle size reaches 18-20 mm. UPT was done after 21 days. A transvaginal sonography was done on day 35 to confirm intrauterine or extrauterine gestation.

Data analysis

Statistical data was collected by a blinded observer in the form of observation charts. Statistical analysis was done by using proportions and percentage for qualitative characters and chi-square or z-test was applied for quantitative type of data, mean & SD was calculated. Z-test & ANOVA was used wherever necessary. Data was compared and analyzed statistically for the significance of observed differences if any. Statistical analysis was done by using SPSS software and conclusions were drawn.

Results

Table 1: Demographic distribution of patients

Age (years)	Group A (Letrozole only)	Group B (OCP + Letrozole)	P value
21-25	32	30	0.78 (NS)
26-30	44	46	
>30	06	05	
Total	82	81	
Mean age (years)	27.28 ±8.73	28.03 ±9.12	

The above table shows age distribution among both groups. The mean age in group A was 27.28 ±8.73 years and group B was 28.03 ±9.12 years. There was no significant difference in age distribution in two groups. (p>0.05). Out of total 162 patients, there were 39 (47.56%) and 40 (49.38%) overweight patients among Group A and Group B respectively. The mean BMI in group A was 26.68 ±3.21 and group B was 27.11 ±3.42 Kg/m^2. There was no difference when two groups were compared statistically with respect to BMI. (p>0.05). Out of total 162 patients, there were 12 (14.81%) and 11 (13.58%) Impaired Glucose tolerance patients among Group A and Group B respectively. The menstrual irregularities were seen in 29 (35.80%) and 32 (40%) patients among Group A and Group B respectively. There was no difference when two groups were compared statistically with respect to diabetes mellitus, hypertension and other co- morbidities. (p>0.05)

Table 2: Type of infertility

Type of infertility	Group A (Letrozole only)	Group B (OCP + Letrozole)	P value
Primary	68	72	0.45 (NS)
Secondary	14	09	
Total	82	81	

The above table shows co-morbidities among both groups. Out of total 162 patients, there were 68 (82.92%) and 72 (88.89%) patients of primary infertility among Group A and Group B respectively. There was no difference when two groups were compared statistically with respect to type of infertility. (p>0.05).

Table 3: Basal hormonal profile

Basal hormonal profile (day 2)	Group A (Letrozole only) (n=82)	Group B (OC pills followed by Letrozole) (n=81)	P value
FSH (IU/mL)	8.1 ± 4.3	7.9 ± 3.7	>0.05 (NS)
LH (IU/mL)	5.1±6.9	5.7 ±15.9	>0.05 (NS)
TSH (µIU/ml)	2.61 ± 1.1	2.38 ± 4.44	>0.05 (NS)

The above table shows basal hormonal profile among both groups. The mean FSH in group A was 8.1 ±4.3 and group B was 7.9 ±3.7. There was no significant difference in FSH levels in two groups. (p>0.05). Similarly, LH and TSH levels shows no significant difference in both groups at baseline. (p>0.05)

Table 4: Follicular and endometrial factors

Variables	Group A (Letrozole only) (n=82)	Group B (OC pills followed by Letrozole) (n=81)	P value
Antral follicle count (AFC)	3.79±1.08	4.18 ±1.19	>0.05 (NS)
No. of follicles >18 mm	2.20±1.1	3.02 ±1.28	<0.05 (S)
Endometrial thickness	7.4 ± 2.20	8.06 ± 2.19	<0.05 (S)

The mean Antral follicle count (AFC) in group A was 3.79 ±1.08 and group B was 4.18 ±1.19. There was no significant difference in Antral follicle count (AFC) in two groups. (p>0.05). The mean number of follicles >18mm in group A was 2.20 ±1.1 and group B was 3.02 ±1.28. There was significant difference in number of follicles >18mm in two groups. (p<0.05). The mean endometrial thickness in group A was 7.4 ± 2.20 and group B was 8.06 ± 2.19. There was significant difference in endometrial thickness in two groups. (p<0.05). It took 15.08±22 days and 14.11±28 days to reach LH surge by women in Group A and Group B respectively. There was significant difference in number of days to reach LH surge in the two groups. (p<0.05). Urinary pregnancy test was positive in 10 patients (12.5%) in Group A and 14 patients (17.28%) in Group B. Urinary pregnancy test positivity was significantly more in group B. Similarly, there were 09 (10.97%) and 12 (14.81%) clinical pregnancy among Group A and Group B respectively. Clinical pregnancies were also seen more in patients with OCP pretreatment.

Table 5: Complications

Complications	Group A (Letrozole only) (n=81)	Group B (OC pills followed by Letrozole) (n=81)	P value
Ectopic Pregnancy	02	01	>0.05 (NS)
Weight gain	22	18	>0.05 (NS)
Multiple gestations	02	02	>0.05 (NS)

The above table shows complications among both groups. Out of total 162 patients, there were 22 (27.16%) and 18 (22.22%) patients had weight gain among Group A and Group B respectively. There was no significant difference when two groups were compared statistically with respect to weight gain. (p>0.05). Similarly, there was no difference when two groups were compared statistically with respect to complications like ectopic pregnancy and multiple gestations. (p>0.05).

Discussion

A total of 180 infertile women in their reproductive age group and who are keen to conceive, attending gynecology OPD and ART center meeting the inclusion and exclusion criteria are included in the present study. These women were screened for tubal disease, endometriosis, male factor infertility. Out of the selected patients, 17 women opted out before initiation of therapy, for personal reasons. So, the study was carried out with remaining 163 patients, 82 in group A (non OCP pre-treatment) and 81 in group B (OCP pre-treated).

In the present study, the mean age in group A was 27.28 ±8.73 years and group B was 28.03 ±9.12 years. There was no significant difference since the two groups were comparable. In a study by Salama *et al*[5] on combined oral contraceptive premedication before letrozole ovulation induction observed the mean age in letrozole only and letrozole with oral contraceptive pills group was 27.9 ± 4.29 and 27.8 ± 2.04 years respectively. There was no statistically significant difference in both groups with respect to age. This finding was similar to present study.

Similar findings were seen in study by Rachel B. Mejia *et al*. [6] where age among both groups shows no statistical difference. This shows that the prevalence of infertility was more in higher age group patients.

In the present study, out of total 163 patients, there were 39 (47.56%) and 40 (49.38%) overweight patients among Group A and Group B respectively. The mean BMI in group A was 26.68 ±3.21 and group B was 27.11 ±3.42 Kg/m^2. There was no difference when two groups were compared statistically with respect to BMI. (p>0.05). In a study by Salama *et al*. [5] observed no statistically significant difference in both groups with respect to BMI. This finding was similar to present study. Similar findings were seen in study by Rachel B. Mejia *et al*.

Many domestic and foreign reports have revealed a positive

correlation between the prevalence of infertility and age.[7] Out of total 163 patients, there were 68 (82.92%) and 72 (88.89%) patients of primary infertility among Group A and Group B respectively. There was no difference when two groups were compared statistically with respect to type of infertility. (p>0.05) It took 15.08±22 days and 14.11±28 days to reach LH surge by women in Group A and Group B respectively. There was significant difference in number of days to reach LH surge in the two groups. (p<0.05). The mean endometrial thickness in group A was 7.4 ± 2.20 and group B was 8.06 ± 2.19. There was significant difference in endometrial thickness in two groups. (p<0.05)

In my study there were 10 (12.5%) and 47 14(17.28%) pregnancy test positive among Group A and Group B respectively. There was significant difference when two groups were compared statistically with respect to pregnancy test positivity. (p<0.05). Similarly, there were 09 (10.97%) and 12 (14.81%) clinical pregnancy among Group A and Group B respectively. There was significant difference when two groups were compared statistically with respect to clinical pregnancy. (p<0.05). In a study by Salama *et al* [5] comparison between group (A) of Oral contraceptive pills followed by letrozole and group B (letrozole alone)regarding cycle outcomes showed ovulation was significantly higher in group (A) than in group (B) (p=0.003), Pregnancy rate per patients and cumulative pregnancy rate per cycles were significantly higher in group (A) than in group (B) (p=0.003 and 0.02 respectively).

Study by Branigan *et al* [] showed that the suppression of the hypothalamic- pituitary ovarian axis with OCs pre-treatment results in an excellent rate of ovulation and pregnancy compared with repeat CC-only treatment in patients who previously had not achieved ovulation on maximal doses of CC. Zhihua Chen *et al*[70] in a study observed LE in combination with low-dose intramuscular injection of HMG has high clinical pregnancy rate, which is promising for treating patients with PCOS infertility. A recent RCT by Legro *et al*[9] in women with PCOS demonstrated that those receiving Letrozole had significantly higher low birth rate (27.5%).

Letrozole is a targeted aromatase inhibitor which has primarily been used in post- menopausal women with breast cancer. Recently, it has been utilized in infertile pre- menopausal women because of its ability to enhance FSH production for ovulation induction. However, the ovarian follicle's response to FSH is only a part of the endocrine events occurring in a developing follicle. The health of the small antral follicles is driven primarily by androgens, which contribute to granulosa cell mitosis, sensitivity to FSH, and resistance to atresia. In contrast, elevated androgens in the late antral to pre-ovulatory follicle have a negative impact on follicle health and lead to atresia and cystic follicle formation. This ovarian physiologic data suggests that current applications of letrozole to infertility may be squandering some of the primary benefits available in using letrozole to promote follicle development [9, 10]. The present study showed that the combination of letrozole and OCP was superior to letrozole alone for inducing ovulation in the setting for infertility treatment in women with infertility.

Conclusion

The present study concludes that the combination of letrozole and OCP was superior to letrozole alone for inducing ovulation in the setting for infertility treatment in women with infertility.

This study showed that the suppression of the hypothalamic-pituitary-ovarian axis with OCs followed by Letrozole treatment results in an excellent rate of ovulation, takes less time for follicular maturation and has more chances of pregnancy compared with Letrozole-only treatment. Use of ovulation detection (urinary LH) kits can reduce the number of visits to the clinic required during a treatment cycle without affecting the pregnancy rate achieved.

In conclusion, where available transvaginal sonography combined with a urinary LH kit should be the method of choice for timing insemination. The current applications of letrozole to infertility may be squandering some of the primary benefits available in using letrozole to promote follicle development along with OC pills.

Conflict of Interest: Not available

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