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RESEARCH ARTICLE

Clomiphene citrate vs letrozole for ovulation induction in subfertile women with polycystic ovary syndrome: a randomized controlled trial

Nazmashamim, Lokeshwari K, Vinodkumarsuresh Basavaradder

Corresponding author: Dr. Lokeshwari K, Associate Professor, Department of OBGYN, Basaveshwara Medical College Hospital & Research Centre , Chitradurga, Karnataka, India; Email : lokeshwari.kannayan@gmail.com

ABSTRACT

Objectives: To compare the efficacy of letrozole and clomiphene citrate (CC) for ovulation induction, endometrial thickness and pregnancy rate in subfertile women with polycystic ovary syndrome (PCOS). **Material and methods:** A prospective randomized clinical trial was conducted from 1st October 2019 to 31st December 2020, in Basaveshwara Medical College Hospital and Research Centre, Chitradurga. A total of 63 participants were allocated into two groups. Group 1 (N=31) received clomiphene citrate 50 mg twice daily, and group 2 (N=32) received letrozole 2.5 mg twice daily. Both study groups were randomly administered CC or letrozole from day 2 to day 6 of a regular menstrual cycle. Transabdominal ultrasonography was done from day 10 till the dominant follicle appeared. Inj. hCG 5000 IU was administered within 24 hrs after the appearance of the dominant follicle. Parameters assessed were ovulation rate – the appearance of dominant follicles, endometrial thickness, and pregnancy rate. **Results:** Baseline characteristics were comparable between the two groups. The mean endometrial thickness of 7.2 ± 0.61 in the CC group as compared with the letrozole group was 8.06 ± 0.38 (P=0.000). Ovulation rate as assessed by the appearance of the dominant follicle was significantly higher in the letrozole group (22.45 ± 2.21) as compared with the CC group (19.98 ± 1.88). Analysis of pregnancy rate in the two groups showed a higher pregnancy rate of 81% in group 2 compared to 22% in group 1 (P=0.00). **Conclusion:** This study showed significant improvement in endometrial thickness and pregnancy rates in the letrozole group as compared to CC used for ovulation induction in infertile PCOS. Furthermore, we noted a substantially increased ovulation rate in the letrozole group (P<0.00).

Keywords: Polycystic ovary syndrome, infertility, clomiphene citrate, letrozole.

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of the reproductive age group and a frequent cause of anovulatory infertility [1]. PCOS is a syndrome that encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria like ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary morphology [2]. It is characterized by menstrual irregularities, anovulation, clinical or biochemical features of hyperandrogenism and the presence of polycystic ovaries. It affects 5 to 10% of women in the fertile age groups.

Since 80% of women with PCOS have anovulation or oligo-ovulation, ovulation induction is the cornerstone for the treatment of women with PCOS suffering from infertility [1]. Insulin resistance with compensatory hyperinsulinemia is a prominent feature of PCOS affecting approximately 65–80% of women. Hyperinsulinemia results in increased ovarian androgen biosynthesis in vivo and in vitro and decreased synthesis of sex hormone-binding globulin (SHBG) protein in the liver, leading to increased bioavailability of free androgens. This excess local ovarian androgen production

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augmented by hyperinsulinemia causes premature follicular atresia and anovulation resulting in impaired ability to conceive naturally [3].

PCOS is a complex reproductive metabolic disorder and the hypothalamic-pituitary axis has been the target of first-line ovulation induction therapy. Clomiphene citrate, a selective estrogen receptor modulator, antagonizes estrogen's negative feedback at the hypothalamus with a consequent increase in ovarian stimulation by endogenous gonadotropin and has been used for ovulation induction for decades. Clomiphene citrate (CC) has been the standard first-line ovulation induction (OI) agent in PCOS women with ovulation rates of ~85% and pregnancy rates of 35–40%. This discrepancy between ovulation and conception rates has been attributed to the peripheral anti-oestrogenic actions of CC on endometrial development and cervical mucus [4]. Clomiphene citrate leads to prolonged depletion of estrogens receptors associated with any anti-oestrogenic effects on the endometrium. This is supported by recent studies reporting adequate endometrial thickness during letrozole treatment [4].

Letrozole an aromatase inhibitor, which blocks estrogen synthesis, directly affect hypothalamic–pituitary–ovarian function and might increase pregnancy rates with lower multiple-pregnancy rate through single-follicle recruitment, a better side effect profile [5,6]. Presently available literatures comparing clomiphene citrate and letrozole as first-line therapy for women with anovulation is conflicting in nature and inconclusive. There is a need for randomized trials to establish the true potential of letrozole.

Material and methods

This prospective randomized clinical trial was performed on 63 patients diagnosed with primary and secondary infertility with PCOS from 1st October 2019 to 31st December 2020. Institutional ethical committee clearance was (approval number was BMC&H/IEC/2020-2021/60) obtained. All eligible participants were informed and written consent was taken. Sixty-three patients who met the inclusion criteria were selected. No patient was lost during follow-up. The sample size was estimated by assuming an alpha error of 5% and power of 80%. All cases with the polycystic ovarian syndrome with primary and secondary infertility were included in the study. Female infertility due to other causes and infertility caused due to male factors were excluded from the study.

Demographic characteristics like age, body mass index, drug history and menstrual history were noted. Randomization of recruited patients was carried out using a random number table. All patients were randomized to receive either one of the two drugs over the next 3 months. Randomization codes (1,2) were packed into sealed opaque envelopes by an individual not involved in enrolment, treatment and follow-up of patients to ensure concealment of allocation. Another individual had the responsibility for dispensing the trial drugs to the patient based on the unique randomization code. At the end of allocation, the individual provided us with a randomization list. Group 1 (N=31) received clomiphene citrate (CC) 50mg twice daily and group 2 (N=32) received letrozole 2.5mg twice daily. Both study groups were randomly administered CC or letrozole from day 2 to day 6 of the regular menstrual cycle. Transabdominal ultrasonography was done from day 10 till the dominant follicle appeared. Inj. hCG 5000 IU was administered within 24 hrs after the appearance of the dominant follicle. Parameters assessed were ovulation rate as assessed by the appearance of dominant follicles, endometrial thickness, and pregnancy rate.

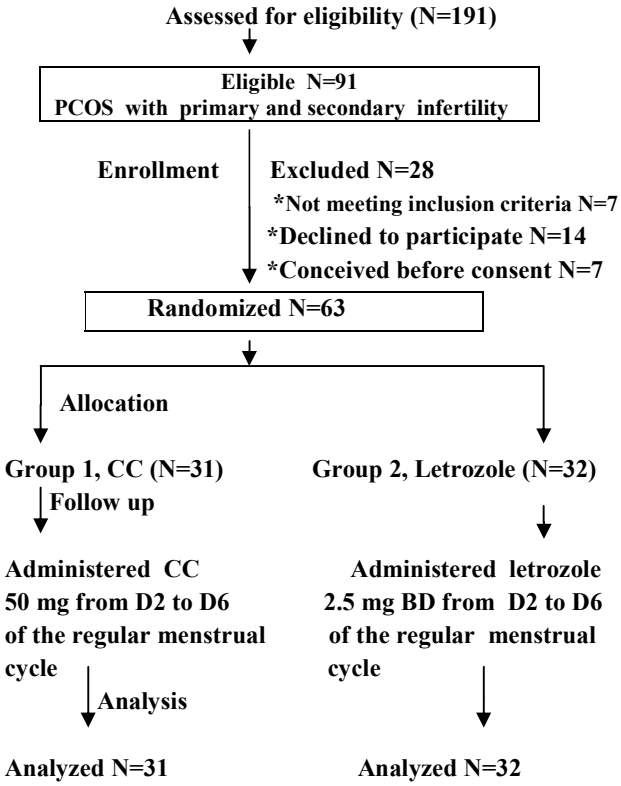

Figure 1: Flowchart showing the recruitment of participants in the study

The mean ± standard deviation (SD) was calculated for quantitative variables. Qualitative variables are presented as

frequencies. The Student's t-test and Mann–Whitney U test was performed to compare continuous variables with and without a normal distribution in the two groups. The student's t-test was performed for variables with a normal distribution (age, BMI). The proportional data were compared using a chi-square test and fisher's exact test. A p-value of < 0.05 was considered statistically significant.

Results

Sixty-three patients were enrolled in the study and allocated randomly into two groups. Figure 1 depicts the flow of participants in the study. Group 1 was induced with CC and group 2 was induced with letrozole. The baseline characteristics of participants in the two groups were comparable (table 1). The distribution of primary and secondary infertility cases in each group was shown in table 2.

Table 1 : Baseline characteristics of participants in the study groups

Variables	Group 1 (CC) N=31	Group 2 (Letrozole) N=32	P Value
Age (years)	27.39 ± 4.45	28.34 ± 3.99	0.85
BMI (kg/m^2)	24.8 + 3.13	24.62 + 3.13	0.58
Duration of infertility (years)	3.6 ± 2.2	3.2 ± 1.8	0.45

Endometrial thickness was significantly higher in the letrozole group compared to the CC group. Ovulation rate as assessed by the appearance of dominant follicles was significantly higher in the letrozole group. The pregnancy rate was also significantly higher (81%) in the letrozole group (table 3).

Table 2: Distribution of primary and secondary infertility cases

Variables	Group 1 (Clomiphene citrate group) N (%)	Group 2 (Letrozole group) N (%)
Primary infertility	28 (90.3)	11 (34.4)
Secondary infertility	3 (9.7)	21 (65.6)
Total	31 (100)	32 (100)
χ^2 value=20.9 , DF=1, P=0.01		

Table 3: Primary outcome measures in study groups

Parameters	Group 1 (Clomiphene citrate group) N=31	Group 2 (Letrozole group) N=32	P value
Endometrial thickness (mm) Mean ± SD	7.2 ± 0.61	8.06 ± 0.38	0.000 (S)
Ovulation rate (Appearance of dominant follicles) Mean ± SD	19.98 ± 1.88	22.45 ± 2.21	0.000 (S)
Pregnancy rate (%)	22	81	0.000 (S)

Discussion

The results of the present study showed a significantly higher ovulation rate, and pregnancy rate in the letrozole group compared to the CC group. There was also significantly higher endometrial thickness in the letrozole group.

For ovulation induction in PCOS commonly prescribed drugs are clomiphene citrate and letrozole. For anovulatory cycles, CC gives a high rate of ovulation than letrozole, despite better ovulation pregnancy rate per cycle remains relatively low due to the antiestrogenic effect of CC, produced on cervical mucus thickening and thinning of endometrium. It has been noted that 15-50% of women on CC develop a thin endometrium <8mm with a tendency toward a nontrilaminar pattern at midcycle [7]. As letrozole was used for ovulation induction reported 75% success was studied by Mitwally and Casper [8]. By keeping this concept, this study aimed to compare the efficacy of letrozole and CC for ovulation induction in infertile women with PCOS and also study done to compare the effects of letrozole and clomiphene citrate on the development of dominant follicles, endometrial thickness and pregnancy rate.

Clomiphene citrate is a standard drug used for ovulation induction in PCOS women for more than 6 decades. Around 20 to 25 % of patients developed resistance to clomiphene probably due to hyperinsulinemia associated with PCOS [9]. Anti-estrogenic effect of clomiphene leads to prolonged depletion of estrogen receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus. This is responsible for the difference between ovulation and pregnancy rate[10].

There were significantly higher ovulation rates in the letrozole group compared to the CC group. Richard et al [5] did a comparative study of letrozole versus clomiphene in PCOS and concluded that the cumulative ovulation rate was higher with letrozole than with clomiphene ($P<0.001$). They concluded that as compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with polycystic ovary syndrome. But a study conducted by Kar S [11] found no statistically significant difference in ovulation rate between the letrozole and clomiphene groups. This may be explained by the fact that letrozole creates an estrogen-deficient environment by inhibiting the conversion of androgens to estrogens. This releases the pituitary from negative feedback of estrogens and releases FSH. Also, an added positive effect is increased follicular sensitivity to FSH receptor gene expression.

Endometrial thickness was measured by the maximal thickness of the endometrial lining in the plane through the central longitudinal axis of the uterine body. In the present study mean endometrial thickness was significantly higher in

the letrozole group compared to the CC group. This was supported by a study done by Mitwally and Casper [8]. This suggests that endometrium is one of the most important targets of the antiestrogenic effect of clomiphene and explains the lower pregnancy rate and possible higher miscarriage rates with clomiphene.

Letrozole is a third generation aromatase inhibitor that acts by inhibiting the conversion of androstenedione and testosterone to estrogen in the ovary. This releases the hypothalamic/pituitary axis from estrogenic negative feedback, and the resultant increase in gonadotropin secretion leads to a rise in follicle stimulating hormone, stimulating ovarian follicular development. The pharmacodynamic properties of letrozole like a shorter half-life, as it does not deplete estrogen receptors, and an intact hypothalamoovarian axis provides a better rate of successful monofollicular ovulation, improved endometrial thickness and better quality and quantity of cervical mucus, which is important for embryo implantation and minimizing risk of Ovarian Hyper Stimulation Syndrome (OHSS) [12]. All these factors lead to a higher pregnancy rate and a greater likelihood of singleton pregnancy [13].

Since CC has a long half-life (2 weeks) accumulates in the body, whereas letrozole because of its short half-life (45hrs) is rapidly eliminated leading to a late follicular rise in circulating oestrogen thereby enhancing endometrial development with a subsequent increase in the chances of pregnancy. The rising oestrogen levels may also result in a shorter FSH window (mimicking the physiological cycle) with subsequent mono-ovulation and a lower risk of multiple pregnancies. As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with polycystic ovary syndrome [14-16]. Failure to achieve a good endometrial thickness and reduced pregnancy rates with CC may be attributed to its antiestrogenic effect on the endometrium.

The pregnancy rate per cycle was significantly higher in the letrozole group (81%) compared to the CC group (22%). Roque et al [17] did a systematic review of letrozole versus CC in PCOS and found a significant increase in the live birth and pregnancy rates in the letrozole group compared to the CC group. This may be due to lower mid-luteal serum estradiol levels and higher progesterone levels due to sustained aromatase inhibition in the luteal phase.

The limitation of the present study was an estimation of relevant hormones could not be done because of resource limitations. However clinical trials with large meta-analysis are needed to conclude the true potential benefits of letrozole.

Conclusion

This randomized trial showed that letrozole was superior to clomiphene citrate for the treatment of anovulatory infertility in women with PCOS. There was a significant improvement in endometrial thickness, ovulation rate and pregnancy rates in the letrozole group as compared to CC. Hence letrozole is a better alternative to CC for ovulation induction in anovulatory PCOS, and it may be considered a first-line drug for ovulation induction in PCOS women.

Conflict of interest: None. **Disclaimer:** Nil.

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Nazmashamim [1], Lokeshwari K [2], Vinodkumarsuresh Basavaradder [3]

[1] Assistant Professor, Department of OBGYN, Basaveshwara Medical College Hospital & Research Centre , Chitradurga, Karnataka, India; [2] Associate Professor, Department of OBGYN, Basaveshwara Medical College Hospital & Research Centre , Chitradurga, Karnataka, India; [3] Senior Resident Department Obgyn, BMCH, Chitradurga, Karnataka, India.