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Original Research Article

The effect of letrozole vs clomiphene citrate for ovulation induction in patients of infertility with polycystic ovarian syndrome

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ABSTRACT

Background: The overall prevalence of primary infertility in India is 3.9% to 16.8%. PCOS being a recognized cause of infertility, affects 8 to 13% of all reproductive-age women. Clomiphene citrate (CC) is most commonly used as first line drug for ovulation induction. CC is selective estrogen receptor modulator (SERM) and has adverse effect on cervical mucus and endometrial receptivity resulting in low pregnancy rates. Letrozole an aromatase inhibitor is considered as better alternative drug due to its benefits over CC. Thus, the aim of the present study is to assess the effect of letrozole and clomiphene citrate for ovulation induction in women with PCOS and compare the pregnancy rates.
Methods: This is a hospital based randomized controlled study conducted on 89 patients at Armed forces medical college in western Maharashtra from June 2019 to May 22. Women with infertility due to PCOS attending OPD/IPD who fulfilled the inclusion criteria were included in the study. The subjects were divided into two groups through computer generated randomization and Group A of 45 subjects received letrozole for ovulation induction while Group B with 44 subjects received clomiphene citrate (CC). Data was analyzed and comparison among the study groups was done with the help of unpaired t test or Mann-Whitney test.
Results: The number of mature follicles after treatment was significantly greater in clomiphene citrate group (1.59 ± 1.04) as compared to letrozole (1.02 ± 0.76). However, there was statistically significant greater mono ovulation with letrozole (55.2% vs 40.3%, p=0.03). After ovulation induction, the mean endometrial thickness was significantly greater in letrozole group as compared to CC (9.85±2.32 mm vs. 8.45±1.53 mm; p<0.05). Ovulation rate with letrozole was 42.5% vs 32.5% and pregnancy rate was letrozole 20% vs CC 7.5% which was statistically significant (p<0.05).
Conclusions: Letrozole is a better drug for ovulation induction in women with PCOS with an ovulatory cycles as pregnancy rates are higher and lesser chance of multiple pregnancy.

Keywords: Clomiphene citrate, Infertility, Letrozole, PCOS

INTRODUCTION

Infertility is a growing concern of the modern society. It is a unique condition that is not limited to an individual but affects the couple as such. The overall prevalence of primary infertility in India is between 3.9% and 16.8%.[1] Both the partners are equally responsible for the causes. The majority of causes in an infertile couple often includes a male factor, an ovulatory dysfunction or a tubal-peritoneal disease.[2]

Polycystic ovary syndrome (PCOS) is an endocrine disorder, commonly affecting 8 to 13% of all reproductive-age women and is a recognized cause of infertility due to

oligo-anovulation.[3] It is characterized by hormonal and metabolic disturbance in the body which manifests with numerous clinical presentations.[4] Typical features are ovulatory dysfunction, oligo/amenorrhea, features of hyperandrogenism such as hirsutism/acne/alopecia. Women with PCOS have insulin resistance with compensatory hyperinsulinemia and are at increased risk of type 2 diabetes, metabolic syndrome and cardiovascular disease.[5] PCOS is associated with impaired HPO feedback, increased LH secretion, aberrant oocyte maturation, and premature arrest of activated primary follicles affecting the ovulation.[6] Thus, ovulation induction is the main modality of treatment of infertility in women with PCOS.

Clomiphene citrate (CC) is the drug of choice for ovulation induction in polycystic ovarian syndrome.[7] CC is a selective estrogen receptor modulator (SERM) which competes for estrogen receptors and leads to an increased gonadotropin secretion. CC antagonizes the action of estrogen at receptor level in cervix and endometrium and therefore, affects the cervical mucus and endometrial receptivity resulting in low pregnancy rates.[8] CC also has side effects like mood changes, flushing, higher multiple pregnancy and clomiphene resistance.[9]

Letrozole is an alternative option for CC. It inhibits aromatase enzyme and decreases the production of estrogen in the periphery. Thus, releasing the pituitary and hypothalamus from the negative feedback effect of estrogen and thereby increasing the gonadotropins. A recent systematic review and meta-analysis, has shown that letrozole has higher ovulation rates and live births in women with PCOS as compared to CC.[10] Letrozole also offers benefit over CC as it reduces the risk of multiple follicle development and does not have any antiestrogenic effect on endometrial and cervical mucus.[11,12]

Thus, the aim of the present study is to assess the effect of letrozole and clomiphene citrate for ovulation induction in women with PCOS and compare the pregnancy rates.

METHODS

This was a hospital based randomized control study conducted in the department of Obstetrics and Gynecology of Armed forces medical college in western Maharashtra from June 2019 to May 2022. After a valid informed consent, 89 patients attending the OPD/IPD with primary infertility were included in the study.

All the women included in the study belonged to the age group ranging from 20 to 40 years with PCOS. PCOS was diagnosed when clinical evidence of hyperandrogenism like acne/ hirsutism/alopecia was present along with: oligomenorrhea, amenorrhea or USG evidence of polycystic ovaries. All the patients had at least one patent fallopian tube and a normal uterine cavity as determined by hysterosalpingography or hystero-laparoscopy. Women with uterine/adnexal pathology with medical co-morbidities were excluded from the study. The male partner was evaluated and had normal semen analysis as per WHO 2010 criteria.

A detailed history was taken using a piloted performa. A thorough physical examination was conducted and their weight, height, and body mass index (BMI) were recorded. Transvaginal ultrasonography (TVS) examination was performed to exclude any pelvic pathology before treatment. Randomization was done by computer-based randomization with allocation of 45 and 44 patients to group A and B respectively. Ovulation induction was started from D2 of cycle. Group A received letrozole 2.5mg/day for 5 days with stepwise increase in the dose up to 7.5mg in next cycle in absence of ovulation. Group B received clomiphene citrate 50mg/day for 5 days with incremental increase up to 150mg in subsequent cycles.

A baseline TVS was carried out on D2 of cycle before starting induction and then on alternate day from D9 to D16 of the cycle. When a matured follicle of size 18-22 mm was noted, ovulation trigger using HCG 10000 IU injection IM was given. Patients were then advised about timed intercourse for next 3-4 days. Patients were reviewed 48 hours after the trigger for confirming Ovulation. If no ovulation was noted, then she was reviewed after 24 hours and if still no ovulation, then it was considered a failed cycle. If there was no formation of dominant follicle, then it was considered as failed cycle. The patients with ovulation were reassessed whenever she misses her normal periods or on day 2 of next cycle. Confirmation of the pregnancy was done by UPT and TVS. All patients were offered maximum 3 cycles of OI (ovulation induction) + TI (timed intercourse).

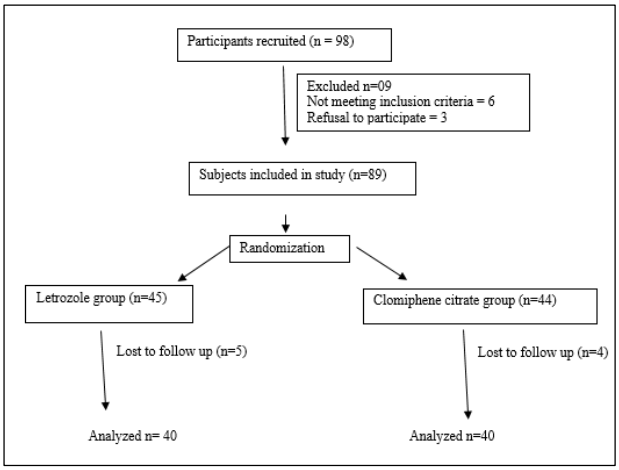

Figure 1: Study design.

Statistical analysis

The data was entered in MS Excel and analyzed using SPSS ver. 20. Quantitative data is presented as Mean and Standard deviation and qualitative data is presented with number and percentage. Comparison among the study groups is done with the help of unpaired t test or Mann-

Whitney test as per results of normality test. Association among the study groups is assessed with the help of Chi-Square test or Fisher test for small sample. A 'p' value less than 0.05 is considered as significant.

RESULTS

Total 98 patients with infertility due to PCOS were analyzed for recruitment during the study period. Out of which 89 subjects meeting the study criteria were included and randomized into two groups. 9 subjects dropped out of the study (5 in group A, 4 in group B), data of 80 patients were analyzed finally. There was no statistically significant difference between the two groups in terms of baseline characteristics like age, BMI, duration of fertility and baseline FSH, LH, TSH and prolactin levels (Table 1).

Following the ovulation induction protocol, there was statistically significant mono ovulation with letrozole (55.2%) when compared to clomiphene citrate (40.3%). Clomiphene citrate had significant multifollicular development (CC 47.9% vs 21.55%). The total number of follicles during the stimulation was significantly higher with clomiphene citrate (1.59±1.04 vs 1.02±0.76; P <0.0001). There was no statistical difference in the pretreatment endometrial thickness between the groups. However, the endometrial thickness just prior to the HCG trigger in the letrozole group (9.85±2.32mm) was significantly higher when compared to CC group (8.45±1.53mm) (Table 2).

Table 1: Baseline characteristics of the participants in both the groups.

Parameters	Letrozole group (n=40	CC group (n=40)	P value
Age	25.13±4.10	25.93±3.79	> 0.05
BMI	28.09±4.86	27.97±4.49	> 0.05
Duration of infertility (months)	23.75±6.68	24.93±6.94	> 0.05
FSH (IU/ml)	7.79±1.21	8.29±1.30	> 0.05
LH (IU/ml)	6.37±1.04	6.14±0.56	> 0.05
TSH (mIU/L)	3.41±0.63	2.89±0.25	> 0.05
Prolactin (ng/dl)	27.99±0.84	26.77±0.86	> 0.05
Data is presented as mean ± standard deviation			

Ovulation occurred in 17 (42.5%) patient in letrozole group and 13 (32.5%) patients in CC group, there was statistical difference between the groups (p value <0.05). The detailed ovulation rates with respect to cycles is shown in Table 3. 27 (67.5%) women did not ovulate with maximum dose of CC.

Pregnancy was confirmed in 8 patients (20%) in letrozole group. Out of which, one woman conceived with first cycle, 2 in second cycle and 5 pregnancies in third cycle. 3 (7.5%) pregnancies were noted in CC group, 1 with second cycle and 2 pregnancies in third cycle. The p value was <0.05, which was statistical.ly significant (Figure 2).

Table 2: Response to ovarian stimulation between both groups.

Parameters	Letrozole group (n=40)	CC group (n=40)	P value
Ovulation			
Mono ovulation	55.2 %	40.3%	0.03
Poly ovulation (≥ 2)	21.55%	47.9%	< 0.0001
Number of mature follicles	1.02±0.76	1.59±1.04	< 0.0001
Endometrial thickness before and after OI			
ET before treatment (in mm)	4. 33±2.48	4.52±2.32	>0.05
ET after treatment (in mm)	9.85±2.32	8.45±1.53	< 0.05

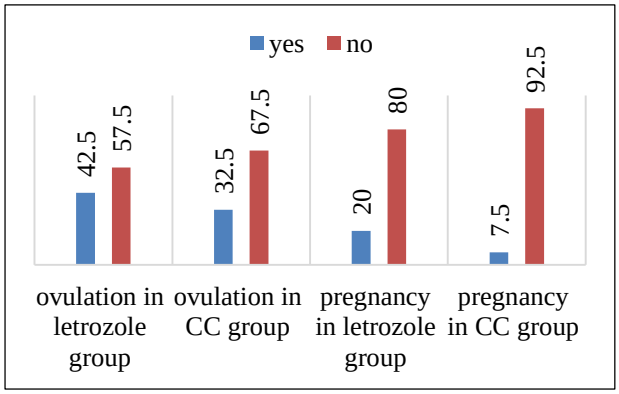

Figure 2: Comparison of ovulation and pregnancy rate between both the groups (in percentage).

Table 3: Comparison of ovulation and pregnancies with respect to number of cycles.

	Letrozole group (n=40) (%)	CC group (n=40) (%)
Ovulation		
I cycle	11 (27.5%)	6 (15%)
II cycle	7 (17.5%)	8 (20%)
III cycle	12 (30%)	9 (22.5%)
Total pregnancies	8 (20%)	3 (7.5%)
I cycle	1	0
II cycle	2	1
III cycle	5	2

DISCUSSION

In our study, 80 patients had ovulation induction for infertility. The mean age was 25 years with majority of them between 21-25 years. Both the group were comparable in terms of BMI, duration of fertility and hormone profile. In present study, the mean endometrial thickness was 9.85±2.32mm with letrozole and 8.45±1.53mm with CC. Letrozole had better endometrial stimulation when compared to CC. This is due to the fact that clinically available clomiphene has 2 isomers - En clomiphene and Zu clomiphene. En clomiphene is eliminated from the blood rapidly, whereas Zu clomiphene is not readily excreted from the body and is responsible for anti-estrogenic effect on cervix and endometrium[9]. These results were similar to a study from Turkey where the authors noted that letrozole resulted in significantly improved endometrial thickness in comparison to CC ($p<0.001$)[13]. Also, Mehnaz et at study showed mean endometrial thickness of 8.1±1.5 mm with letrozole vs. 6.8±1.9 mm with CC ($p=0.0022$).[14]

The ovulation rates were significantly higher with letrozole as compared to CC (42.5% vs 32.5%) and letrozole had 55.2% of mono ovulation. On other hand, CC had statistically significant multi-follicular development, thus increasing the risk of multiple pregnancy. Shavina et al study had cumulative ovulation rates of 86.7% and 85.2% with letrozole and CC respectively and 68.4% of mono-follicular development in letrozole group ($p = 0.000$).[15] A prospective, randomized clinical trial by Chakravorty et al reported that ovulation occurred in 25 subjects (37.87%) in the letrozole group and 13 subjects (19.67%) in the CC group, with a statistically significant difference between the two groups.[16] Furthermore, 15%-40% of women with PCOS do not ovulate with CC.[17] Clomiphene resistance, as per definition is failure to ovulate after receiving 150mg of CC daily for 5 days per cycle, for at least three cycles.[18] In our study, 27 (67.5%) women did not ovulate with first cycle of 150mg CC.

In our study, the pregnancy rate with letrozole group was 20% and significantly higher than the CC group. The anti-estrogenic effect of CC on endometrium leads to inappropriate development of endometrium and is associated with a low implantation rate and low conception rates. Wang et al study showed that clinical pregnancy and ongoing pregnancy rates of the LE group were significantly higher than that of the CC group (25.6% vs. 13.3%, 23.3% vs. 11.1%) ($P<0.05$). The study also concluded that endometrial receptivity during the implantation window of LE is superior to CC in PCOS women, which may be related to higher clinical pregnancy and ongoing pregnancy rates. Endometrial flow index examined by 3-D power Doppler, and integrin avb3 in uterine secretion during the implantation window, could be better and preferable non-invasive predictor markers for pregnancy.[19]

CONCLUSION

Although the study was done at a single centre with small sample size, we found letrozole to be a better option for women with PCOS with anovulatory cycles as pregnancy rates are higher and lesser chance of multiple pregnancy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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