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Comparative study of fertility outcomes on ovulation induction with clomiphene citrate versus letrozole among anovulatory polycystic ovarian syndrome women

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Abstract: Objective: To evaluate fertility outcomes on ovulation induction with clomiphene citrate versus letrozole among anovulatory Polycystic Ovarian Syndrome (PCOS) women.
Material and Methods: This randomized controlled study was conducted in the infertility clinic of our institute between 2015 to 2018. 106 subjects from 18-39 years, BMI < 30 kg/m^2, anovulatory infertility, at least one patent fallopian tube, diagnosis of PCOS, and male partner sperm concentration of at least 15 million/ml were included. These subjects were randomly allocated into 2 groups. One group was given letrozole and the other group clomiphene citrate. Follow-up with serial transvaginal ultrasonography was done for follicular growth. Inj. Human chorionic Gonadotropin (hCG) was administered 36 hours prior to ovulation as predicted by folliculometry, and a check scan was done for ovulation. The result was evaluated in terms of the number of follicles, ovulation rate, endometrial thickness from D11 to D14, successful pregnancy outcome, complications, and failure.
Results: A total of 106 patients were included, 52 cases were treated with Letrozole and 54 cases with clomiphene. Most subjects in either group had oligomenorrhea (57.4% & 61.4%) with regular cycles. Ovulation occurred in 27 (51.9%) subjects with letrozole and 18 (33.3%) with clomiphene. Successful pregnancy outcomes were seen in 24 out of 52 (46.1%) with letrozole and 16 out of 54 (29.6%) with Clomiphene.
Conclusion: Successful pregnancy outcome was higher with letrozole despite a lesser number of mature follicles. Clomiphene citrate could be replaced by Letrozole as the key medication for chronic anovulation in PCOS.

Keywords: Anovulation; Clomiphene citrate; Letrozole; Infertility.

1. Introduction

Anovulation is a large spectrum in reproductive endocrinology [1]. The commonest cause being poly cystic ovarian syndrome (PCOS). There is a multiplex interaction of neuroendocrine and intra ovarian mechanisms that regulate the normal ovulatory cycle. This is controlled by the hypothalamo-pitutary ovarian axis. Interference at any level of this axis causes anovulation [2].

The overall incidence of PCOS varies from 8% to 10% [3]. In the PCOS population, infertility is seen in about 74% cases (50% with primary and 25% with secondary infertility) due to oligo/anovulation and the combined effects of multiple abnormalities like obesity, endocrine, metabolic and inflammatory on oocyte quality [4].

CC has been the standard medicine in order to induce ovulation in people with anovulatory cycles for many years [1]. It is a non-steroidal SERM. Despite having a miraculously high follicle growth & ovulation

rate, the pregnancy rates are quite low. There is also incidence of increased miscarriage rate than the general population as well as clomiphene resistance leading to failure of treatment [5].

Recently, it has been found that Letrozole has a good ovulation rate. It belongs to aromatase inhibitor class and has a short half-life resulting in shorter FSH window and hence mono-ovulation and so far no anti estrogenic effect have been found on cervical mucus and endometrium. Risks of conditions like hyperstimulation of ovary and multiple pregnancy along with a less incidence of side effects [6]. Clomiphene as well as letrozole are orally administered, have very few side effects, easily available but letrozole is expensive.

Researchers are conducting studies worldwide to find out which of the two drugs is better and safer: clomiphene or letrozole. This study was conducted to compare the follicular growth, ovulation rate, and change in endometrial thickness pregnancy rate & pregnancy outcomes in patients following Ovulation Induction by either of the two drugs.

2. Material and methods

This randomized comparative prospective study conducted at the Department of Obstetrics and Gynaecology of our institute from 2015 to 2018, after due approval from the institutional ethics and research committee. All infertile subjects aging 18 through 39 years with BMI < 30 kg per square metre diagnosed with anovulatory cycles radiologically by ultrasound and Polycystic Ovarian Syndrome (Rotterdam criteria) (1) having at least one patent fallopian tube, no uterine or tubal anomaly after doing hystersalpingography and having partner's sperm concentration of at least 15 million/ml were recruited in the study after taking written informed consent.

We excluded subjects with male factor infertility, patients who underwent Ovarian Induction within the last 6 months and patients with specific endocrine abnormalities. Patients having uncontrolled thyroid disease or hyperprolactinemia were also excluded.

The enrolled patients were systematically randomized and allocated into two groups. All odd number patients received clomiphene citrate and were allocated to Group "C" and all even number patients received letrozole and were allocated to Group "L".

The principal investigator was responsible for enrolment, allocation to either group, or assignment of intervention to the patients. It was a single blinded trial in which the subjects were blinded. The prescribed drug was given to the subject in a secured envelope with the mode of administration and the analysis was conducted by an independent analyser.

Thorough history elicited to exclude complaints suggestive of thyroid abnormalities, history of pain during menstruation, any discharge from the breast, features pointing towards possibility of hyperandrogenisation syndrome, hyperinsulinemia, etc. A meticulous general and gynaecological examination was conducted which included biochemical and radiological workup which included Complete hematogram, LFT, KFT, Thyroid function tests, Prolactin, FSH/LH, serum Testosterone, and DHEAS. Prior to the start of treatment, a baseline transvaginal ultrasound was done to check for signs of polycystic ovaries. Following the examination, patients were prescribed exercise, lifestyle changes, folic acid, and metformin for three months. These patients were downregulated with 10 mg of medroxyprogesterone acetate for induced bleeds and asked to return on day two of their cycles. Group C patients were given 50mg clomiphene citrate tablet twice day for five days after reporting back. The tablet letrozole 2.5mg was given twice daily for five days to the subjects in group L.

Serial transvaginal ultrasonography was done to look for dominant follicle, endometrial thickness and number of follicles.

TVS was used to monitor follicular development on D 10 followed by D 12, D 14, and D 16 of cycle until a mature follicle measuring 14–18 mm or larger was discovered (by taking average of the inner 2 diameters of follicle). A single dose of Injection hCG 10,000 IU Intramuscular given when minimum 1 follicle measured more than 14 mm and ET measured minimum 8 mm. After 48 hours of hCG injection, a second TVS was performed to confirm the release of the egg, which was confirmed by the collapse of the follicle and the presence of fluid in the Douglas pouch. If the follicle remained unruptured after 72 hours, a third TVS was performed to look for a luteinized unruptured follicle. Trilaminar ET of 8 mm regarded as good outcome when the plane of measurement of ET was through central longitudinal axis of uterus at most distant points between

echogenic surfaces of diameter. After 36 hours of hCG, two days of scheduled intercourse were recommended, with the luteal phase supplemented with micronized progesterone. The study's key outcome indicators were the rate of ovulation and the number of pregnancies. For pregnancy, three cycles of the same dosage of the prescription medicine were observed. The cycle was terminated if follicular development was poor. In such circumstances, patients in Group C received 100mg clomiphene and patients in Group L received 5mg letrozole in the following cycle. The protocol was repeated, with group clomiphene which received 150mg and letrozole group which received 7.5mg. These subjects were evaluated for follicle count per cycle , successful follicular maturation, failure of follicular maturation, endometrial thickness before & after administration of Injection HCG, no. of cycles after which pregnancy occurred, positive urine beta-hCG test for pregnancy with gestational sac detection on TVS, rate of pregnancy & abortion, multiple pregnancy if any, live birth and complications or side effects if any.

2.1. Statistical Methods

All statistical analysis was done using the SPSS-20 software.

3. Results

There were 106 patients who qualified for the study. Of these, 54 patients were allotted in the clomiphene citrate group and 52 were prescribed tablet Letrozole. These patients were comparable to each other in terms of age, ethnicity and BMI, (Table 1).

The participants in these 2 groups were compared regarding mean period of infertility, age, clinical features of menstrual flow and regularity, and hyperandrogenic features when the baseline characteristics were compared. The majority of the participants in both groups experienced oligomenorrhea with regular cycles (57.4 and 61.4 percent, respectively). Hyperandrogenism was reported in 81.4 percent (n- 44) of Clomiphene Group patients compared to 80.7 percent (n- 42) of Letrozole Group patients. The mean BMI for the two groups was 27.5 and 27.9, indicating that the majority of the patients were overweight. 87.0(n-47) percent of patients in Group C USG characterised polycystic ovaries, compared to 84.8(n-44) percent in group letrozole, with a statistically significant p value. In the group Clomiphene, data suggestive of hyperandrogenism were seen in roughly 27.7% (15) of patients, compared to 26.9% (n-14) in the Group Letrozole, which was insignificant statistically.

As seen in the Table 2, the mean of follicular number developed in Group CC calculated as 5.02 and in group L was 3.54 which was significant statistically ($p < 0.001$). Ovulation was observed in only 33.3% (n=18) patients in group C and in 51.9% (n=27) in the group L (p=0.052). However monofollicular development was seen to have significant value in the letrozole group ($p< 0.0001$). The mean ET also varied statistically between the Group CC and Group L ($p < 0.001$). A positive pregnancy outcome was seen in 29.6% (n=16) patients of group C and 46.2% (n=24 in group L patients, this difference was not significant (p=0.060). An insignificant difference according to statistics was found between the Group CC and Group L regarding live births & miscarriage. Though the failure to treatment with clomiphene was more as compared to letrozole but the difference seemed to be statistically insignificant.

4. Discussion

The subjects in the study had PCOS and anovulation. The research question was whether letrozole is superior to clomiphene for ovulation induction, resulting in higher ovulation rates, pregnancy rates, and live births, and obtaining a clear answer to this could have far-reaching implications in clinical practise. In our study it was observed that both groups were equivalent in terms of baseline clinical, radiological and biochemical characteristics, duration of infertility, body mass index. It was observed that oligomenorrhea, with acne, hirsutism and raised BMI was commoner presentation among both groups.

In our study, mean follicular growth was 5.02 in the Group C and 3.54 in Group L, which was statistically significant with a p value of< 0.001. Al Fouzan et al., in their study the letrozole group performed better than the clomiphene citrate group in terms of total quantity of advancing and mature follicles [7], but ovulation was only observed in 33.3 percent (n=18) patients in Group C and 51.9 percent (n=27) patients in Group L (p=0.052), which was statistically irrelevant. In the two groups, there was no statistically relevant difference in the mean frequency of cycles required to achieve pregnancy. As a result, the larger follicular development in

Table 1. Patient Baseline Characteristics

	Variable	**Clomiphene Citrate (N=54)**	**Letrozole (N=52)**
1	Mean Age (Years)	28.9	29
2	Infertility Duration (Mean)	2.5(2-3) (Years)	3.0(2.5-3.5)
3	Menstrual Charcteristics		
3a	Oligomenorrhea	31(57.4%)	32(61.5%)
3b	Cycle Duration(Mean)	29.5days	31.3 days
3a	Regular Cycles	43(79.6%)	42(80.7%)
3b	Irregular Cycles	11(20.37%)	10(19.2%)
3	Body Mass Index (Bmi) (Kg/M^2)	27.5(25.2-30.4)	27.9(25.4-32.1)
6	Hyperandrogenic Features (Clinically)		
6a	Present	44(81.4%)	42(80.7%)
6b	Absent	10(18.5%)	10(19.2%)
7	Ultrasound Features Of Pcos	47(87.0%)	44(84.8%)
7a	Antral Follicular Count(Afc)	16.4(14- 18)	18.4(16-20)
7b	Right Ovarian Volume (Ml)	11.20(9.8-12.3)	11.40(9.8-12.7)
7c	Left Ovarian Volume (Ml	11.4(10.3-12.4)	11.3(9.9-12.2)
	Lab Abnormalities (Hyperandrogenic) Yes No	15(27.7%) 39(72.2%)	14(26.9%) 38(73.03)%

Table 2. Ovulation and Pregnancy Outcomes

Induction of Ovulation & Characteristics	**Group CC (N=54)**	**Group L (N = 52)**	**p Value**
1) Number of Follicles	5.02(3-11)	3.54(2-5)	<0.0001
2) Monofollicular Development>18mm	15(21.7%)	41(78%)	<0.0001
2) Mean Ovulations Per Cycle	18(33.3%)	27(51.9%) 72_	0.052
3) Mean Endometrial Thickness (Mm)	8.55(7.9-10.3)	9.98(8.6-11.3)	<0.0001
Mean Number Of Cycles To Achieve Pregnancy	3(_+1.01)	2.92(_+ 0.89)	0.36
4)Positive Pregnancy Outcomes	16(29.6%)	24(46.2%)	0.060
5)Live Birth	14(25.9%)	22(46.2%)	0.029
5) Miscarriage	2(12.96%)	2(3.84%)	0.092
6) Failure To Treatment	38(66.7%)	28(48.1%)	0.028

the clomiphene group did not lead to a greater reproductive efficiency. A positive pregnancy result was found in 29.6 percent (n=16) of patients in group C and 46.2 percent (n=24) of patients in group L.

In their study Atay V et al. enrolled 106 women with polycystic ovaries (55/51) and randomly assigned them to Group letrozole (2.5 mg/day) or Group CC (100 mg/day) in another trial. The Group letrozole's rate of ovulation (82.4 percent and 63.6 percent, P = 0.01) and rate of clinical pregnancy (21.6 percent and 9.1 percent, P = 0.03), both found to be greater significantly than the Group clomiphene [8]. His findings are nearly identical to those of our study, in which the no. of pregnancy achieved were somewhat greater in the letrozole group but not statistically relevant (p=0.060). Many additional studies have found similar outcomes. In their study Bayer et al enrolled 74 women and Zeinalzaden et al enrolled 107 women, both reported somewhat higher rate of pregnancy with Group letrozole; nonetheless, they found statistically irrelevant difference between the two groups in ovulation or pregnancy [9,10]. Begum et al. found similar results (letrozole 62.55 percent, clomiphene 37.5 percent, p 0.05) [11].

In our investigation, there was statistically irrelevant variance in mean ET between the 2 groups (p 0.001). The endometrium is amongst the most prime target antiestrogenic effect of Group CC, and Letrozole had a similar effect in a study conducted by Mitwally and Casper, which could clarify majority portion of lower pregnancy rate and higher miscarriage rate with CC [12]. Cortinez et al demonstrated typical morphological aspects of endometrium and adequate pinopodes expression in Group Letrozole during the implantation window [13]. Other studies, found insignificant difference in the outcome of either medicament seen in the endometrium.

Also, Anti-estrogenic effect on the endometrium and cervical mucus is seen with Clomiphene, which helps in explaining the difference in ovulation and conception rates [14]. Aromatase inhibitors, unlike clomiphene, do not consume oestrogen receptors, hence physiological central feedback mechanisms are not disrupted. Negative feedback occurs when there is growth of dominant follicle grows and oestrogen level rises, causing suppression of Follicle- stimulating Hormone and developing follicular atresia. Letrozole should result in a one dominant follicle development and mono-ovulation among majority of cases. In a research by Badawy et al, 438 women reported a slightly higher rate of pregnancy the Group CC (15.1 percent in the group Letrozole and 17.9 percent in the Group CC, p=0.72) [15].

In his study, Gonen et al. reported that the difference in rate of pregnancy between Group CC and Group L receiving letrozole and clomiphine was statistically insignificant (p=0.118), despite a two-fold increase in rate of pregnancy in the Group Letrozole (24 percent in Group letrozole & 12 percent in the clomiphene group), but he also observed that the endometrial thickness was less than the required level for implantation in 30% of women who received clomiphene which could be the result of protracted receptors of estrogen decrement in endometrium [16].

In a study conducted by Nejad and Bedaiwy et al. [17,18], it was reported that serum Estradiol level and mature follicular count on Injection hCG administration day was lower in the Group Letrozole than the Group CC which was statistically significant.

According to Nejad and Bedaiwy et al. [17,18], the serum Estradiol level and mature follicular count on the day of administration of hCG were lower in the Group letrozole than in the Group CC, which was statistically significant.

Statistically insignificant difference between the Group letrozole and Group CC as per live births (25.9 percent vs 46.2 percent in clomiphene vs letrozole, p value of 0.029%) and miscarriage. Failure to receive clomiphene treatment was higher in group C (66.7 percent) than in group L (48.1 percent), but this difference was not statistically significant. Badawy and colleagues, [18] with 438 women, the clomiphene group had a slightly higher pregnancy rate (15.1 percent in letrozole and 17.9 percent in CC, p=0.72), though this was not statistically significant.

5. Conclusion

To summarise, letrozole was found to be superior to clomiphene as observed in women with PCOS and women taking letrozole reported a higher Ovulation rate, conception, pregnancy, and live birth. The rate of pregnancy loss and cycles in which there is a successful pregnancy were comparable between the two groups. Main drawback of clomiphene therapy was its antiestrogenic effect on endometrial thickness and hence despite ovulation pregnancy outcome was poor.

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