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Original Research Paper

Gynaecology

A STUDY TO COMPARE THE EFFECTS OF LETROZOLE AND CLOMIPHENE CITRATE ON LIVE BIRTH RATE IN INFERTILE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME (PCOS) UNDERGOING INTRAUTERINE INSEMINATION

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ABSTRACT

INTRODUCTION

In patients suffering from Polycystic Ovarian Syndrome (PCOS) Clomiphene Citrate (CC) has been used for the past 50 years as the first line of drug for ovulation induction (1). But it binds and blocks estrogen receptors and exerts antiestrogenic effect on the endometrium and cervical mucus which adversely affects the pregnancy rate.

Letrozole does not block the estrogen receptors and thus has no antagonistic effect on endometrium(2). Letrozole is also associated with monofollicular growth and ovulation thus preventing complications like hyperstimulation and multiple pregnancies(2,3) .

AIM

This study was done to compare the effect of letrozole and CC on parameters related to ovulation, pregnancy rate and live birth rate in infertile women with PCOS undergoing intrauterine insemination (IUI).

MATERIALS AND METHODS

A retrospective analysis of the effect of CC and letrozole on the cycle characteristics and outcome of PCOS women undergoing ovulation induction was done at Gynaecworld, Mumbai, a centre of women's health and fertility.

One hundred primary infertility patients with PCOS were evaluated in this study and divided into CC (Group A, n = 50) and Letrozole (Group B n = 50). Group A received 100 mg of CC and Group B 5mg of Letrozole per day from day 3 to day 7 of menses.

In both groups transvaginal sonography was done on day 2 of the cycle (baseline), followed by follicular monitoring till ovulation. Number of follicles, endometrial thickness, pregnancy rate, abortion rate and live birth rate were compared between the two groups.

RESULTS

The mean age in group A was 31.2 years and 29.9 years in group B (p=0.1025). There was no significant difference between the basal levels of FSH and LH between the two groups. BMI, Antral Follicle Count (AFC), and ovarian volume in both the groups were comparable.

Letrozole group showed lower preovulatory estrogen levels as compared to that of clomiphene group which was statistically significant (p=0.0004). The difference in endometrial thickness and pregnancy rates were statistically significant, with group A having a lower pregnancy rate (P=0.012, P=0.032, respectively). There was no abortion in group A and 2 abortions in group B.

CONCLUSION

Our study shows that letrozole was associated with monofollicular growth, better endometrial thickness and pregnancy rates in infertile women with PCOS compared to clomiphene citrate. However, the live birth rates in letrozole and CC groups were not statistically significantly different.

KEYWORDS : letrozole, clomiphene citrate, Indian study, IUI, Endometrial thickness, PCOS.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most common female endocrine disorder which affecting 5-10% of women in reproductive age group. It is associated with 75% of all anovulatory disorders causing infertility.(1)

Clomiphene citrate (CC) is considered to be the first line treatment for ovulation induction in PCOS patients.(2) It is a selective estrogen receptor modulator (SERM) with a structure which binds to hypothalamic estrogen receptors, causing estrogen receptor replenishment in the hypothalamus, resulting in increased pituitary FSH(1). Increased FSH drives folliculogenesis at the level of pituitary.(2) However, due to CC resistance, 20-25% women fail to ovulate.(3)

Another drawback of CC is its long half-life and causing accumulation in the body. CC remains bound with the estrogen receptors and causes long-lasting depletion of the estrogen receptors(4).

Endometrial thickness (ET) is one of the most important factors for conception. ET of less than 6-8 mm can cause low pregnancy rates (5). ET facilitates embryo implantation and thus increases the chances of pregnancy and decreases the chances of abortion. It is seen that CC causes adverse effects on ET(6) and cervical mucus due to its antiestrogenic effect.(7)

Letrozole which is a 3rd generation aromatase inhibitor has been in use for ovulation induction for the past few years (8,9,10). Letrozole suppresses estrogen biosynthesis by blocking the action of aromatase enzyme which converts androstenedione to estrogen (1). Since letrozole does not block the estrogen receptors, normal central feedback mechanism remains intact. Therefore, the growing dominant follicle increases estrogen levels by negative feedback mechanism, decreases FSH and monofollicular growth occurs (7,11). Letrozole has been observed to be effective in induction of ovulation in anovulatory and ovulatory infertile women with inadequate response to CC (11, 12). It reduces the risk of multiple pregnancy and ovarian hyperstimulation syndrome since it induces monofollicular growth. (7,13). Letrozole also results in reduction of total circulating estrogen as a result of inhibition of aromatase enzyme. Preovulatory estrogen levels are low in case of letrozole as compared to clomiphene citrate. (10)

Letrozole is also used as a chemotherapeutic agent and this has raised concerns regarding its potential teratogenic risk of cardiac malformations. An abstract which was presented in ASRM (American Society For Reproductive Medicine) led to its ban in India

in 2011. In the later years, after various studies proved beyond doubt that letrozole is not associated with any teratogenic risk the ban was lifted (14,15).

Our study aims to compare the effect of letrozole and clomiphene citrate on ovulation, ET, pregnancy rates and live birth rate in women with PCOS undergoing intrauterine insemination (IUI).

MATERIALS AND METHODS

A retrospective study was conducted on PCOS women with primary infertility who had undergone ovulation induction and IUI at Gynaecworld, Mumbai in 2018.

One hundred PCOS women with primary infertility who had no major medical disorders were retrospectively analysed.

Rotterdam's criteria was used to diagnose PCOS. Women fulfilling at least 2 of the following criteria were selected (oligomenorrhea/ amenorrhea, clinical or biochemical hyperandrogenism, sonographic findings of ≥12 follicles per ovary with <10mm size or increased ovarian volume >10 cm3 or both). At least one patent fallopian tube and normal uterus were confirmed by hysterosalpingography or laparoscopy.

Male partner parameters including physical examination and semen analysis in all patients were normal.

Women were divided into 2 groups. Group A consisted of 50 women (n = 50) who received 100 mg of CC from day 3 to day 7 of menstruation. Group B consisted of 50 women (n = 50) who received 5mg letrozole from day 3 to day 7 of menstruation.

In both groups ET was measured by transvaginal sonography (TVS) before and during stimulation and on the day of human chorionic gonadotropin (hCG) trigger injection by the same fertility specialist using a single sonography machine. Intramuscular hCG 10,000 IU trigger was given when the lead follicle size reached >18 mm. Single IUI was done 36 hours after the hCG trigger injection after confirming ovulation sonographically. All the patients were on luteal phase progesterone support from the day of IUI. Pregnancy rate and outcome of pregnancy were studied.

STATISTICAL ANALYSIS

For variables such as age, years of infertility, hormonal levels, endometrial thickness, unpaired t-test was used. For other variables, Chi- square test and Fischer exact test were used. The significant level of p value was <0.05.

RESULTS

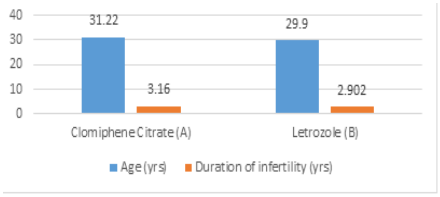
The mean age of group A was 31.2 and group B was 29.9 years (p = 0.1025). Duration of infertility in group A and group B were 3.16 and 2.9 years respectively (p = 0.5854). Age and duration of infertility were not statistically significant.

Basal hormonal levels of FSH, LH, estrogen (E2) and AFC were not found to be statistically different between the two groups (Table 1). In letrozole group, E2 levels on the day of trigger were lower than that of CC group (p = 0.0004), which was statistically significant.

Table 1:

Groups	Clomiphene Citrate (A) N = 50	Letrozole (B) N = 50	P-value
Age (Years)	31.22 ± 4.26	29.90 ± 3.73	0.1025(NS)
Duration of infertility (years)	3.160 ± 2.33	29.02 ± 2.38	0.5854(NS)
BMI	28.30 ± 4.40	27.08 ± 4.59	0.1709(NS)
Basal LH mIU/ml	4.51 ± 2.25	4.47 ± 1.91	0.926(NS)
Basal FSH mIU/ml	6.27 ± 1.99	6.068 ± 2.653	0.736(NS)
Basal E2 pg/ml	36.12 ± 13.15	34.86 ± 11.45	0.6124(NS)
Pre-ovulatory E2 pg/ml	382.68 ± 155.68	287.78 ± 130.41	0.0013(S)
AFC	14.65 ± 9.04	17.29 ± 12.46	0.2282(NS)

(S-Significant, NS- Not Significant)

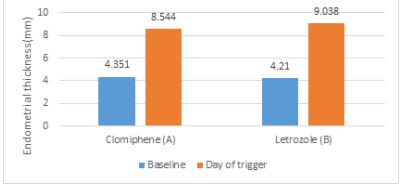


The mean ET on day 2 of menses was 4.351 mm for group A and 4.210 mm for group B, with no statistical difference in basal ETs between the two groups (p = 0.4549). On the day of hCG trigger, the mean endometrial thickness was 8.544 mm TL in group A and 9.038 mm TL in group B, which was statistically significant. (p=0.0124). (Table 2)

Table 2 :

ET (mm)	Clomiphene (A) N=50	Letrozole (B) N=50	P-value
Baseline	4.351 ± 0.9313	4.210 ± 0.9479	0.4549
Day of trigger	8.544 ± 0.820	9.038 ± 1.099	0.0124 (S)

(S-Significant, NS-Not Significant)



Letrozole group showed monofollicular growth in 56% patients compared to 24% in CC group, which are statistically significant.(P=0.00109) (Table 3).

Table 3:

Follicular Development	Clomiphene Citrate (A) N = 50	Letrozole (B) N = 50	P-value
Monofollicular development	24% (12)	56% (28)	0.00109

(S-Significant)

The total number of pregnancies was 6 in group A and 18 in group B which was statistically significant (p = 0.038). The total number of live births were 6 in group A and 16 in group B, this difference did not achieve statistical significance. There were no abortions in Group A and 2 abortions in Group B (Table 4).

Table 4:

Groups	Clomiphene Citrate(A) N=50	Letrozole(B) N=50	P-value
Pregnancy	12% (6)	36% (18)	0.038(S)
Abortion	0	4% (2)	1
Live birth	12% (6)	32% (16)	1

(S- Significant)

DISCUSSION

Our study shows that letrozole is associated with more frequent mono-ovulation and also the endometrial thickness and pregnancy rates with letrozole are significantly more than that of CC. However, despite a higher pregnancy rate in Group B, no statistical difference

was observed in live birth rates between the two groups.

Letrozole predominantly shows monofollicular development as compared to CC which induces multifollicular development. Hence chances of multiple pregnancies and ovarian hyperstimulation are more with CC. Similar result has been shown by Sujata Kar(3).

A double blind controlled trial by Legro RS et al compared letrozole vs CC in infertile PCOS women and concluded that letrozole was associated with higher ovulation and birth rates (16).

A randomized controlled trial by Ganesh A, et al compared the efficacy of letrozole with gonadotropins and CC- gonadotropin combination for ovulation induction in 1387 PCOS patients after CC failure and concluded that ovulation and pregnancy rate with letrozole were significantly higher as compared to CC-gonadotropin combination(79.30% vs 56.95%,

p value<0.0001 and 23.39% vs 14.35%, p-value <0.0001 respectively)(17). Our study shows significantly more pregnancies with letrozole (18) as compared to CC (6), (p-value: 0.038).

ET on the day of trigger was more in letrozole group (mean 9.038mm) as compared to CC group (mean 8.544 mm). Palihawadana et al also observed that letrozole showed better endometrial growth (9.89 mm) than clomiphene citrate (8.58 mm) and monofollicular development(18).Mitwally and Casper also reported that letrozole was associated with greater endometrial thickness than clomiphene citrate.(9)

Similar results have been reported by Mitwally & Casper, Baruah J, et al and Seyedoshohadaei et al. (9,2,19)

One study evaluated the molecular analysis of endometrium in PCOS patients and showed that Letrozole positively influences several markers of endometrial receptivity as compared to Clomiphene citrate. (20) Another study on endometrial and subendometrial vascularity showed that letrozole improves the endometrial receptivity as compared to clomiphene citrate in women with PCOS. (13)

Consistent with the findings of higher pregnancy rates in Letrozole group in our study, another meta-analysis of four randomized studies also reported significantly higher pregnancy rate in women treated with letrozole as compared to CC (22).

In 2015, 4999 cycles were meta-analysed by Roque M et al, which confirmed higher birth rates and pregnancy rates in PCOS patients with letrozole than with CC. However, no differences in ovulation, miscarriage or multiple pregnancy rates were observed (22).

Nahid et al studied 100 PCOS patients and showed no significant difference between pregnancy rates with letrozole as compared to clomiphene citrate, and also reported endometrial thinning with CC(23).

In our study preovulatory estrogen levels were low in letrozole group as compared to clomiphene group which is like other studies(23). Letrozole results in reduction of total circulating estrogen because of inhibition of aromatase enzyme.

In our study no abortions were seen with CC and 2 were seen with letrozole. Due to small sample size, no conclusion can be made. According to the study conducted by Seyedoshohadaei et al, no abortions were seen in CC group and 5 were seen in letrozole group which was not significant (2).

CONCLUSION

Our study suggests that pregnancy rates and ET are higher in patients treated with letrozole as compared to clomiphene citrate. The chances of multiple pregnancies and ovarian hyperstimulation is also reduced with letrozole. It can be concluded that administration of letrozole is effective in infertile patients with PCOS. However, we did not observe any difference in live birth rate and we suggest that a larger, randomized controlled trial be performed to get a clearer picture.

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