Original research article

Study of Clomiphene Citrate Vs Letrozole For Ovulation Induction in Infertile PCOS Women

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Abstract

Background: This study was conducted to compare Clomiphene Citrate Vs Letrozole for ovulation induction in infertile PCOS women.

Methods: This study includes 200 infertile PCOS women attending GOPD Department of Obstetrics and Gynaecology, NMCH from January 2021 to December 2022. The patients were divided in two groups. 100 women received 100mg CC once daily from D2-D6 of cycle. 100 women received 2.5 mg Letrozole once daily from D2-D6 of cycle – both groups for 3 cycles each. Follicular monitoring was done daily from D12-D16 of cycle. Inj HCG 5000IU was administrated IM when atleast one follicle with a mean diameter of more than equal to 18 mm was achieved. After 36 hours of HCG administration ovulation was confirmed on ultrasound.

Results : Both groups were comparable with respect to age, BMI and mean duration of infertility. Both groups were compared with respect to number of follicles, mean diameter of largest follicle, rate of ovulation, mean endometrial thickness and serum progesterone level on D21 of cycle. The number of mature follicle was significantly lower but but the endometrial thickness and ovulation rate was significantly higher in Letrozole group than CC group. **Conclusion:** My study showed that Letrozole has better ovulation rate than CC and should be considered as 1st line drug for ovulation induction in infertile PCOS women.

Keywords: PCOS, HCG

Introduction

Polycystic Ovarian Syndrome (PCOS) is a heterogenous, multisystem endocrinopathy affecting 5- 10% of reproductive age women[5]. It was first reported in modern literature by Stein and Leventhal in 1935. The development of PCOS has been linked to hereditary and environmental factors including genetics, insulin resistance and obesity[5]. The clinical presentation of PCOS varies widely. Women with PCOS often seek care for menstrual disturbances, clinical manifestations of hyperandrogenism and infertility. Menstrual disturbances commonly observed in PCOS include oligomenorrhea or amenorrhea. However, 15-40% of women with PCOS have normal menses[3]. Infertility affects 40% of women with PCOS[5]. PCOS is the most common cause of anovulatory infertility[5]. PCOS is diagnosed by ESHRE/ASRM (Rotter`dam criteria), 2003; which include two of the following : (a)Oligomenorrhea or amenorrhea , (b)Clinical and/or biochemical signs of hyperandrogenism , (c)Polycystic ovaries in USG.[11] Ovulation Induction refers to the therapeutic restoration of the release of one egg per cycle in the woman who either has not been ovulating regularly or has not been ovulating at all. Although it is usually acceptable for OI to result in the release of two eggs, one should avoid the ovulation of more than two eggs in an effort to minimize the risk of OHSS and multiple gestation. Appropriate patient

selection can be a significant determinant of the success of OI among PCOS patients. Once ovulation has been documented for a particular treatment, Patients should be mentally prepared to continue with that regimen for at least 3 cycles. Because for most treatment the rate of a pregnancy occurring per therapeutic cycle is the same for each of the first three cycles.

There are two main medications used for ovulation induction are clomiphene citrate and letrozole.[5] Clomiphene Citrate (CC) has been the most widely used drug for the treatment of infertility since its introduction into clinical practices in the 1960s. It is a non-steroidal selective estrogen receptor modulator that has predominant action resulting in long-lasting estrogen receptor depletion. CC has a long half life (2 weeks), and this may have a negative effect on the cervical mucus and endometrium, leading to discrepancy between ovulation and conception rates. CC induces ovulation in 80% cases and about 40-50% conceive. The risk of multiple ovulation and multiple pregnancies with CC is around 10%.[5] Letrozole (nonsteroidal aromatase inhibitor) acts by decreasing the conversion of andro-stenedione and testosterone to estrogen in the ovary. This decrease in circulating estrogen increases gonadotropin secretion. Multiple developing follicles appear from day 7, but because letrozole does not deplete estrogen receptors, normal negative feedback occurs centrally as the dominant follicle grows and the estrogen level increases. This results in follicle-stimulating hormone suppression and atresia of smaller follicles, and midcycle mono-ovulation occurs in most patients. It does not possess the adverse antiestrogenic effect of Clomiphene specially thinning of the endometrial lining and is associated with higher pregnancy rate than CC treatment in patients with PCOS. It has short half-life (50 hours)[5] thus it is rapidly eliminated from the body. This study was done to compare the efficacy of clomiphene citrate verses letrozole for ovulation induction in infertile PCOS patients.

MATERIALS AND METHODS

This study was carried on 200 infertile PCOS women attending GOPD Department of Obstetrics and Gynaecology, NMCH from January 2021 to Decenber 2022. Informed consent was obtained from all the patients. Inclusion criteria were age between 20-35 yeas, primary or secondary infertility specific to PCOS, Polycystic ovary diagnosed by ultrasound, bilateral patent tubes confirmed by HSG, normal Husband's Semen fluid analysis according to WHO criteria(2010). Exclusion criteria were age < 20 and > 35 years, gynecological disorders e.g. Fibroid, Ovarian cyst, Endometriosis, hyperprolactinemia, hypo or hyperthyroidism (endocrinological disorder), impaired hepatic or renal function, history of hypersensitivity to study drugs, female with bilateral tubal blockage and male infertility. Study population was divided in two groups. Group A- 100 women received 100mg CC once daily from D2-D6 of cycle. Group B- 100women received 2.5 mg Letrozole once daily from D2-D6 of cycle – both groups for 3 cycles each. Transvaginal ultrasonography scans were performed on day 12 of menstrual cycle and then daily until the mean diameter of largest follicle reached 18mm. At ultrasonographic scan, internal diameter of each visible follicle was measured in two dimensions and the average diameter was calculated. In addition, the endometrial thickness (in mm) was measured at the greatest diameter perpendicular to the midsagittal plane in the fundal region, including both layers of endometrial cavity.

Inj HCG 5000IU was administrated IM when atleast one follicle with a mean diameter of more than equal to 18 mm was achieved. After 36 hours of HCG administration ovulation was confirmed on ultrasound. On day21 serum progesterone level was measured. Women in

both the groups without evidence of ovulation and with negative pregnancy test were asked to follow the respective schedule of treatment in subsequent cycles.

Duration of treatment in both the groups was 3 months. Chemical pregnancy was assessed by serum level of beta hCG measurement once the patient missed her period. Documentation of at least one gestational sac in USG was confirmed as clinical pregnancy.

Statistical analysis :-
To deal with data, quantitative in nature, minimum and maximum values, mean and standard deviation along with percentage, if required are computed. To determine the significance of difference of mean, t-test for independent samples are applied. When handling qualitative data, contingency table are generated and percentage of cell frequencies and marginal totals are computed. For calculations SPSS software is used.

RESULT:
Total 200 patients were divided in two groups. CC stands for Clomiphene Citrate study group and L stands for Letrozole study group. In L group mean age was 25.71±3.67 years and in CC group mean age was 25.06±3.66. Difference was not statistically significant (P>0.05). Mean BMI in L group is 24.8840± 2.2543 kg/m² and mean BMI in CC group is 24.90±2.2469 kg/m². Both the groups are comparable with respect to BMI with P value >0.05 i.e. Not significant. Mean duration of infertility was 2.69±1.49 years in L group and 2.57±1.43 years in CC group which was statistically not significant (P>0.05).

Table1 :- Baseline demographic characteristics of patients of each group

No. of subjects	**L (100)**	**CC (100)**	**P-value**
Mean age (years)	25.71±3.6	25.06±3.6	>0.05
Mean BMI (kg/m²)	24.88±2.25	24.90±2.25	>0.05
Mean duration of infertility (years)	2.69±1.49	2.57±1.43	>0.05

86% of patients in L group had primary infertility and 80% in CC group had primary infertility (P>0.05 not significant).

In present study, Letrozole was given in 232 cycles of 100 patients, ovulation occurred in 178 (76.72%) cycles which was suggested by rupture of dominant follicle. In CC group clomiphene was given in 255 cycles of 100 patients and ovulation occurred in 132 (51.76%) cycles. Ovulation rate in L group was more and statistically highly significant (P<0.01) as compared to CC group.

Table 2 :- Comparison of outcome (ovulation rate, number of follicles, size of follicles, Endometrial thickness and pattern between L and CC group

	L	**CC**
Ovulation		
Occurred	178 (76.72%)	132 (51.76%)
Not occurred	54 (23.27%)	123 (48.23%)
Total	232 (100%)	255 (100%)
No of follicles	**L**	**CC**
0	2 (0.86%)	6 (2.35%)

1	188 (81.03%)	74 (29.01%)
2	28 (12.06%)	130 (50.98%)
≥3	14 (6.03%)	45 (17.64%)
Total	232 (100%)	255 (100%)
Size of follicles (mm)	**L**	**CC**
18-18.9	6 (2.58%)	48 (18.82%)
19-19.9	10 (4.31%)	112 (43.92%)
20-20.9	28 (12.06%)	45 (17.64%)
21-21.9	38 (16.37%)	28 (10.98%)
≥22	150 (64.65%)	22 (8.62%)
Total	232 (100%)	255 (100%)
Endometrial thickness (mm)	**L**	**CC**
5-5.9	6 (2.58%)	60 (23.52%)
6-6.9	30 (12.93%)	116 (45.49%)
7-7.9	50 (21.55%)	36 (14.11%)
8-8.9	94 (40.51%)	22 (8.62%)
9-9.9	28 (12.06%)	18 (7.05%)
10-10.9	16 (6.89%)	3 (1.17%)
≥11	8 (3.44%)	0 (0%)
Endometrial pattern	**L**	**CC**
Trilaminar	178 (76.72%)	132 (51.76%)
Non trilaminar	54 (23.27%)	123 (48.23%)
S. Progesterone (Day21)	**L**	**CC**
ng/ml	17.18±1.57	12.30±1.87

In L group out of 232 cycles, 188 (81.03%) had 1 number of dominant follicle. Mean number of dominant follicle in L group was 1.23±0.56. In CC group out of 255 cycles, 130 (50.98%) had 2 number of dominant follicles. Mean number of dominant follicles in CC group was 1.84±0.73. Letrozole treated cases had better monofollicular development rate than CC treated group.($P<0.01$) – highly significant. Mean diameter of largest follicle in L group was 21.76±1.75mm and in CC group mean diameter was 19.97±1.17mm. P value <0.001 – highly significant.

In L group endometrial thickness was 8-8.9mm in 40.15% of cycles.Mean endometrial thickness was 8.31±1.28mm. In CC group ET was 6-6.9mm in 45.49% of cycles. mean endometrial thickness was 6.83±1.20mm. This difference in thickness of endometrium was highly significant ($p<0.001$).

In L group 76.72% of cycles showed trilaminar pattern while 23.27% had non-trilaminar pattern of endometrium. In CC group 51.76% cycles showed trilaminar pattern while 48.23% had non-trilaminar pattern ($p<0.001$). Mean value of serum progesterone on day21 ofcycle in L group was 17.18±1.57ng/ml and in CC group was 12.30±1.87 ng/ml.

Table3 :- Comparison of ovulatory cycles and conception in both group

	L	**CC**
Number of ovulatory cycles	178/232 (76.72%)	132/255 (51.76%)
Number of pregnancy	54/100 (54%)	26/100 (26%)
Pregnancy rate per cycle	54/232 (23.27%)	26/255 (10.19%)

L group had 76.72% ovulation rate per cycle and in CC group 51.76% ovulation rate per cycle. P value<0.001- highly significant. Among 100 patients in L group 54 became pregnant and among 100 patients in CC group 26 became pregnant. P value<0.001- highly significant.

Discussion :-

Clomiphene citrate is the most commonly prescribed agent for ovulation induction. Unfortunately, despite high rate of ovulation, pregnancy rate per cycle remain relatively low. Present study compares CC with letrozole for ovulation induction in infertile PCOS patients[3]. Demographic profile should be comparable between L and CC group to reduce bias. In present stud, demographic characteristics of participants i.e., age, BMI, mean duration and type of infertility were comparable similar to study done by **Atay et al** who reported mean age of 27.2±0.9 years in L group (n=51) Vs 26.2±1.1 years in CC group (n=55).[2] The present study showed better ovulation rates in L group as evidenced by 76.72% as compared to 51.76% in CC group which were comparable with studies conducted by **Atay et al** (82.4% in L and 63.6% in CC group)[2] and **Mitwally et al** (75% in L and 44.4% in CC group).[8,9] In the present study the ovulation rate in Letrozole group was more and statistically highly significant (P<0.001). Present study showed that 81.03% of cycles in L group had monofoliicular development which is very much as compared to CC group which had only 29.01% of cycles had one number of dominant follicle. Among CC group majority of cycles i.e. 50.98% had two number of dominant follicles. Multifollicular development was statistically significantly higher in CC group. Similar results were in the study by **Sujata Kar et al, 2012**, in which 79.49% in L group and 54.85% in CC group had monofollicular development. Mean number of dominant follicle in present study among L group was 1.23±0.56 which is less than CC group i.e. 1.84±0.73 which was similar to study by **Atay et al, 2006**, with Mean number of dominant follicle in L group was 1.2 and in CC group was 2.4. Similar results were in **Sammour et al, 2001** in which Mean number of dominant follicle in L group was 1 and in CC group was 2.[13] Number of follicles in letrozole group as compared to clomiphene citrate was less and statistically very highly significant (P<0.001) Present study showed that mean diameter of largest follicle in L group was 21.76±1.75mm and in CC group was 19.97±1.17mm. Similar results were in study by **Ratnabali Chakravorti et al, 2016** in which mean diameter of largest follicle in L group was 23.4mm and in CC group 22.7mm.[10] Endometrial thickness was as the maximal thickness of the endometrial lining in the plane through the central longitudinal axis of the uterine body. Present study showed distribution of cases according to endometrial thickness, mean endometrial thickness in L group was 8.31±1.28mm and in CC group was 6.83±1.20mm and this was very highly significant (P<0.001). Similar results were in the study by **Atay et al,2006** in which mean ET in L group was 8.4mm and in CC group was 5.2mm. It was also similar to study by **Mitwally & Casper et al, 2001** in which mean ET in L group was 8mm and in CC group was 5mm.[4] The above results consolidate the belief that endometrium is one of the most important targets of the antiestrogenic effect of CC and may explain a large part of the lower pregnancy rate and possible higher miscarriage rate with CC. However, in general an endometrium that is less than 5 or 6 mm is usually associated with significant likelihood of failure to conceive. In addition, successful implantation requires a receptive endometrium, with synchronous development of glands and stroma. **Present study** showed trilaminar pattern of endometrium at the midcycle was seen in 76.72% of letrozole treated patient while only in 51.76% of CC group (p<0.001). These results are comparable to **Fisher et al, 2002** who also demonstrated 71% of letrozole treated patients with trilaminar pattern of endometrium as compared to 44% of CC group. This concluded that letrozole provides a

better uterine environment. Present study showed that mean serum progesterone level on day 21 of cycle in L group was 17.1834±1.57 ng/ml and in CC group was 12.3037±1.87 ng/ml. Similar results were in study by **Ratnabali Chakravorty et al, 2017** in which mean serum progesterone level on day 21 of cycle in L group was 18.4 ng/ml and in CC group was 14.0 ng/ml.[10] This study showed pregnancy rate achieved after ovarian stimulation was 54% in letrozole and 26% in clomiphene. An almost two-fold increase in pregnancy rate was observed in patients who received letrozole. The results were better than studies conducted by others like 21.6% in Letrozole versus 9.1% in clomiphene citrate by **Atay V et al, 2006**. 16.7% in letrozole vs. 5.6% in clomiphene citrate by **Sammour et al, 2001**[13] and 11.5% in Letrozole versus 8.9% in clomiphene citrate by **Al Fozan et al, 2004**[1] In this study pregnancy rate per cycle in letrozole was much better than CC group (23.27% in L verses 10.19%in CC) and this result was comparable to **Mitwally & Casper et al, 2001** (25% in L verses 10% in CC), **Atay et al, 2006** (21.6% in L verses 9.1% in CC), **Sohrabvand et al, 2006** (19% in L verses 7% in CC)[14].

Conclusion:-

Letrozole is more effective in inducing ovulation in patients with infertile PCOS women than clomiphene citrate in terms of monofollicular ovulation and a better endometrial thickness than when compared with clomiphene citrate. The mean diameter of the largest follicle and the serum progesterone level studied showed letrozole was superior than clomiphene citrate in inducing ovulation. Hence Letrozole can be recommended as the first line drug for ovulation induction in anovulatory patients with polycystic ovarian syndrome.

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