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COMPARING LETROZOLE AND CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN FEMALES WITH PRIMARY INFERTILITY DUE TO ANOVULATION.

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ABSTRACT

Context: CC was widely used for ovulation induction in women with anovulatory infertility; aromatase inhibitors like letrozole can be used for better pregnancy outcomes in these patients. **Aims:** To compare the effect of CC and letrozole on ovulation induction in females with primary infertility due to anovulation. **Settings and Design:** An Observational study at Tertiary Health care centre, at Department of Obstetrics and Gynaecology, AVBRH, DMIMS, Sawangi (Meghe), Wardha. **Methods and Material:** 120 patients were divided into two equal groups. Both CC and Letrozole were given from Day 3 to Day 7 of menstrual cycle. Folliculometry was done from Day 8 on alternate days till Day 16 or till atleast one follicle reaches ≥ 18mm. Inj hCG 10,000 was given. The treatment was given for three cycles in both the groups. Main outcome measures: Ovulation Rate, Pregnancy rate, Endometrial thickness. Statistical analysis used: SPSS 24.0 version and GraphPad Prism 7.0 version. **Results:** The mean age, Body Mass Index (BMI), duration of infertility in both CC and Letrozole groups were similar. Ovulation rate was 72.33% in letrozole group and 63% in CC, which was not statistically significant ($p=0.17$). There was statistically significant difference between Endometrial thickness (CC 8.29±0.73, Let 9.45±0.60, $p<0.05$, S).Monofollicular rate was more in Let than CC and this being statistically significant (Let-76.74%, CC- 51.24%, $p<0.05$,S). Let group had pregnancy rate as 43.33% as compared to 18.33% in CC group and this statistically significant ($p<0.05$,S). **Conclusions:** Present study showed that Letrozole had better pregnancy rates than CC. Letrozole can be used as a choice of drug for ovulation induction in females with infertility due to anovulation.

KEYWORDS : Letrozole, Clomiphene Citrate, ovulation induction, anovulation

INTRODUCTION

Ovulatory Dysfunction comprises of 30-40% of causes of infertility in women [1]. WHO classifies anovulation amongst various categories. It includes Class I- Hypogonadotropic hypogonadal anovulation. Class II- Normogonadotropic normoestrogenic anovulation, Class III- Hypergonadotropic anovulation. Hyperprolactinemia is considered as a separate entitiy [2]. Polycystic Ovarian Syndrome (WHO class II), is one of the leading cause and is responsible for 70- 85% of cases infertility due to anovulation [2]. Clomiphene Citrate (CC) has been widely used for ovulation induction since its introduction. It is administered orally and is readily available and economic to use. Eventhough the ovulation rate is under range of 70-80%, the pregnancy rate is quite lo i.e. around 30-40% [3]. CC being (SERM) Selective estrogen receptor modulator has adverse effects by blocking the estrogen receptors on endometrium and endocervical glands.

Letrozole is orally taken aromatase inhibitor. It prevents peripheral conversion of testosterone to estrogen. Thus it doesnot have affect the quality of endometrium and cervical mucus. It is short acting than CC and also does not lead to multiple pregnancy.

This study was carried out to compare the effect of CC and Letrozole when given to women with primary infertility due to anovulation in a rural tertiary health care centre in Central India.

MATERIALS AND METHODS

The study was conducted at a rural tertiary health care centre with an infertility clinic located in Central India. This observational study was carried between September 2017 and August 2019. The study protocol was approved by Institutional Ethics committee. Patients were included in the study after valid, informed consent. The inclusion criteria included patients in age group of 20-40 years with primary infertility having BMI≤ 30 kg/m^2 and had documented unilateral or bilateral tubal patency These patients had anovulation detected on folliculometry in menstrual cycle prior to the study. Patients with hyperprolactinemia, male factor infertility, thyroid disorder, endometriosis or PID, with pelvic pathology detected on USG, with prior treatment for infertility, diabetes or cardiovascular, liver or renal disease, unexplained infertility were excluded from the study. The patients were subjected to detailed history pertaining to duration of infertility, obstetric history, menstrual history, past medical illness or any surgical interventions, family history of any illness or hereditary disorders and details of any treatment taken in past for infertility management. The decision to give either clomiphene citrate or letrozole was taken by the consultant at the infertility clinic. In the 1st treatment cycle, Clomiphene citrate 50 mg OD and letrozole 2.5 mg OD were given from Day 3 to Day 7 of spontaneous menstrual cycle. The follicular monitoring was done on alternate days starting from Day 8 onwards either till Day 16 of menstrual cycle or at least till one dominant follicle ≥18mm (mean follicular diameter) in size is seen in either of the ovaries, which if found inj hCG 10,000 IU i.m. was given. Endometrial thickness (ET) was measured on the day of trigger. TVS was done 48 hours post trigger to detect ovulation. If ovulation, did not occur repeat scan was done after 72 hours to diagnose Luteinised Unruptured Follicles. Couples were advised for timed intercourse, 24-36 hours post Inj hCG. UPT was done if patient had missed period. Dose of the drug was increased in subsequent cycle, if patient did not respond to the given dose i.e. if patient had undeveloped follicles. The dose of CC was increased to 100 mg and 150mg OD in subsequent cycles. The letrozole was increased to 5 mg and 7.5 mg OD. The treatment was continued either till occurrence of pregnancy or for total three cycles if patient did not conceive in the current treatment cycle. Primary outcome measure was ovulation rate whereas secondary outcomes were pregnancy rate, endometrial thickness on day of trigger, multifollicular rate. Chi-square test and student's unpaired't'-test were used for statistical analysis. Results were expressed as mean and standard deviation of mean. A p value <0.05 was considered

significant.

RESULTS

The study comprised of 120 patients, 60 in each group which received CC and letrozole. Age, BMI, duration of infertility and menstrual cyclicity and characteristics were similar in both the groups. (Table 1)

In CC group, 60 patients completed 168 cycles whereas letrozole was administered in total 159 cycles. During the 1st treatment cycle, both groups had received minimal dosage, i.e. CC- 50 mg OD and Letrozole- 2.5 mg OD. During the 2nd treatment cycle, 100 mg CC was given in 23 cycles out of total 56 cycles (41.07%), whereas letrozole 5 mg OD was given in 16 cycles out of total 54 cycles (29.62%). In the 3rd treatment cycle, 14 cycles (26.92%) out of total 52 cycles received CC-150 mg OD and 8 cycles out of 45 cycles (17.78%) received letrozle 7.5 mg OD.

In CC group, of total 168 cycles, successful ovulation occurred in 106 cycle, 15 cycles had LUFS i.e. Luteinised unruptured follicles, and 47 cycles had undeveloped follicles. In letrozole group, 115 cycles had ovulation, 14 cycles had LUFS whereas 30 cycles had undeveloped follicles.

The cycles on basis of number of dominant follicles were divided as with monofollicular and multifollicular growth. 76.74% cycles (99 cycles) in letrozole group had monofollicular growth as compared to 62 cycles (51.24%) in CC group. This difference was statistically significant ($p<0.05$).

The difference in the mean endometrial thickness measured on the day of trigger was statistically significant [CC- 8.29±0.73 mm, Let- 9.45±0.60 mm, $p<0.05$, S].

The pregnancy rate in letrozole group was 43.33% and in CC group was 18.33%, this difference being statistically significant ($p<0.05$, S) [Table 2].

Table 1: Patient charactersitics in both the groups.

Variable	Letrozole (n=60)	Clomiphene Citrate (n=60)	P value
Age (years)	28.15±4.57	28.56±4.33	p=0.61, NS
BMI (kg/m2)	25.34±2.16	24.93±2.08	p=0.29,NS
Duration of infertility (years)	3.36±2.21	3.63± 2.35	P=0.52,NS
Irregularity	30(50%)	38(63.33%)	p= 0.14, NS
Oligomenorrhoea	35(58.33%)	33(55%)	p= 0.73, NS

Table 2: Outcome of ovarian stimulation

	Letrozole (n=60)	CC (n=60)	p value
Mono follicular development	99(76.74%)	62(51.24%)	<0.05, S
Multi follicular development	30(23.26%)	59(48.76%)	<0.05, S
Mean day of trigger	15.04±0.84	14.77±0.88	0.12, NS
Mean day of ovulation	16.97±1.03	16.80±0.89	0.38, NS
Endometrial thickness	9.45±0.60	8.29±0.73	<0.05, S
Ovulation rate	72.33%	63.10%	0.17, NS
Pregnancy rate	26(43.33%)	11(18.33%)	<0.05, S
Pregnancy rate per cycle	16.35%	6.55%	<0.05, S

DISCUSSION

Clomiphene citrate was used previously on a wide scale for ovulation induction. CC being antiestrogenic causes long acting estrogen receptor (ER) depletion [4]. As a result, it has negative effect on cervical mucus[5] and endometrial thickness[6]. Letrozole, an aromatase inhibitor, has been used as an alternative drug for ovulation induction. Although many researches have suggested its use but the evidence is still confilting.

In the present study, the ovulation rate was 63.10% in CC whereas it was 72.33% in letrozole, and this difference was statistically insignificant (p= 0.17, NS). Similar results were found in studies by Kar et al. (2012) [7](p= 0.39, NS) and Roy et al. (2012)[8] (p=0.712, NS) which stated that ovulation rate in CC and letrozole was comparable. Amer et al. (2017)[9], in their study stated that ovulation rate per cycle in letrozole (75%) was significantly more than that in CC (67%) (p= 0.045, S). Hussain et al. (2013)[10], stated in their study that rate of ovulation in letrozole group (78.7%) was significantly greater than the CC group (53.3%) (p=0.001, S). Clomiphene citrate and letrozole both act by removing the negative feedback effect of estrogen on the hypothalamo-pituitary axis. This leads to pulsatile GnRH release, which in turn increases FSH levels and results in follicle development. Letrozole and CC groups both had nearly similar cumulative ovulation rate.

In the current study, 76.74 % cycles in letrozole group had single dominant follicle formation as compared to 51.24% cycles in CC group. Multifollicular development was seen in 48.76% of cycles where CC was given, in comparison with only 23.26% cycles of letrozole group. This difference was found to be statistically significant (p=0.0001, S). Kar et al. (2012)[7], had similar results showing 79.49% monofollicular development in Letrozole group in comparison to 54.85% in CC therapy group, the difference being statistically significant (p=0.027, S). Letrozole, being aromatase inhibitor, it reduces serum estrogen levels by preventing peripheral conversion of testosterone to estrogen. This removes the negative feedback of estrogen and leads to hypothalamic gonadotropin release, which stimulates growth of follicle. But unlike CC, letrozole does not reduce the estrogen receptors and also due to its short half-life (approx. 45 hours), the normal negative feedback of estrogen resumes as dominant follicle grows and estrogen level increases. This leads to further FSH suppression and atresia of remaining follicles leading to monofollicular growth [11]. In ovary, follicular sensitivity to FSH is increased by letrozole by accumulating intraovarian androgens. Estrogen levels rise as the dominant follicle grows in size, the regular negative feedback resumes, which further suppresses FSH secretion and causes atresia of the other smaller follicles. A single dominant follicle formation is most likely to take place[12]. Amer et al. (2017)[9] found comparable mono-follicle rate in both the groups i.e. 83.1% and 85.1% in CC and letrozole can be due to maximum dosage used in their study was 100 mg CC and 5 mg letrozole respectively (p= 0.723, NS). Monofollicular growth by letrozole prevents multiple pregnancy and has less predisposition to OHSS.

In the present study, the mean ET in letrozole group was 9.45± 0.60 mm in comparison to 8.29±0.73 mm in the CC group, where the difference was statistically significant (p=0.0001, S). Roy et al. [8] had similar results which found the difference in endometrial thickness to be statistically significant[CC- 6.3±1.1 mm, Let- 9.1±0.3 mm, p=0.014,S]. Whereas, Kar et al.[7] in their study found the ET in both the study groups to be comparable [CC- 7.61±1.96 mm, Let- . 7.65±2.10 mm, p=0.91, NS].

In the current study, the pregnancy rate in letrozole group was 43.33% as compared to 18.33% in CC group, the difference being statistically significant (p=0.0001, S). The pregnancy rate per cycle in letrozole group was 16.35% as compared to 6.55% in CC group and the difference was statistically significant (p=0.046, S). Kar et al. (2012)[7], reported that, pregnancy rate in letrozole group was 21.56% in comparison with 7.84% in CC group, this difference was found to be statistically significant (p=0.0125,S). Roy et al. (2012)[8], had

similar results, 43.8% pregnancy rate in letrozole group as compared to 26.4% in CC group, the difference being statistically significant (p=0.041,S). Although, the pregnancy rate per cycle, in both the groups was comparable being 14.6% and 8.8% in letrozole and CC groups respectively (p=0.061, NS). Badawy et al. (2009)[13], in their study reported that the pregnancy rate in CC was 17.9% as compared to 15.1% in letrozole therapy group. The difference among them was insignificant (p=0.72, NS).

CONCLUSION

In patients with similar demographic characteristics and clinical presentation, letrozole had more ovulation rate than clomiphene citrate, although the difference was not stastistically significant. Monofollicular development was profound in letrozole group, suggestive of fewer chances of multiple pregnancy and OHSS in these patients. Endometrial growth significantly differed in patients of both the groups. This signifies the side effect that clomiphene citrate has on endometrium due to its long standing antiestrogenic effect. Rate of pregnancy was higher in the letrozole therapy group, thus emphasizing on the importance of well-formed trilaminar endometrium required for proper implantation.

A number of factors are associated with the etiopathogenesis of anovulatory infertility. Proper selection of patients should be done. Based on the above observations, letrozole can be preferred drug over clomiphene citrate in women with infertility due to anovulation. The findings of this study will contribute to existing literature and will also throw a light on the response of these drugs in Indian women. More studies in a larger population can be useful in supporting our findings.

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