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RESEARCH ARTICLE

A comparative study of ovulation induction by clomiphene citrate vs letrozole

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ABSTRACT

Objectives: The present study was conducted to compare ovulation induction by clomiphene citrate and letrozole in women with ovulatory dysfunction. **Methodology:** In this open label comparative randomized clinical trial, patients aged 20 to 40 years with infertility diagnosed with ovulatory dysfunction were treated with either letrozole or clomiphene citrate in the Obstetrics and Gynecology OPD, of Dr. D. Y. Patil Medical College, Pune. Clomiphene citrate (CC) was administered as 50 mg once daily for five days, then increased by 50 mg per cycle up to maximum of 150mg, if ovulation did not occur. Letrozole was administered as 2.5 mg once daily for five days, and then increased by 2.5 mg per cycle up to maximum of 7.5 mg, if ovulation did not occur. **Results:** Mean age of the patients was 29.8 years and 31.44 years in letrozole and clomiphene citrate group respectively. Ovulation rate (83% vs 63%), endometrial thickness (8.8 ± 1.5 vs 7.1 ± 1.6 mm) and pregnancy rate (63% vs 47%) was found to be significantly higher among patients in letrozole group as compared to clomiphene citrate group. The mean numbers of follicles were significantly lower in the letrozole group. Side effect profile was similar in letrozole and clomiphene citrate group. **Conclusion:** Our findings show that individuals treated with letrozole had a better clinical outcome than those treated with clomiphene citrate, which has a comparable adverse effect profile.

Keywords: Letrozole, clomiphene citrate, infertility, ovulation induction.

The failure to conceive after 12months of regular, unprotected sexual activity is referred to as infertility. Couples with primary infertility have never been able to conceive, whereas couples with secondary infertility have been unable to conceive after an initial pregnancy. Infertility affects around 8% - 10% of couple's worldwide.[1]

A comprehensive history of the female and male partners should be taken. Couples experiencing infertility can be categorized into five groups - ovulatory problems, tubal infertility, male infertility, endometriosis, and unexplained infertility. Around 20% of women suffering from infertility have ovulation abnormalities.

Mono-follicular ovulation is the primary goal in anovulatory women. Clomiphene citrate (CC) is an anti-estrogenic synthetic non-steroidal medication. From 2nd-5th day of menstrual cycle (or withdrawal bleed), CC was administered as 50mg once daily and couples are encouraged to have scheduled intercourse commencing on 9th day of the cycle. In order to reduce the possibility of multiple pregnancy, TV scans are used to monitor follicular response. Midluteal levels of progesterone are also checked. Ovulation occurs in 80% of females, and pregnancy in 35 - 40%of those who take clomiphene.[2] Clomiphene resistance is seen in 20–25% of women.

Aromatase inhibitors decrease estradiol synthesis, diminish hypothalamus - pituitary estradiol feedback, and increase FSH production. Letrozole at doses of 2.5-7.5mg daily for 5 days has shown to stimulate ovulation. When compared to clomiphene or gonadotropin therapy, aromatase inhibitors raise FSH levels while blocking estradiol

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synthesis, resulting in folliculogenesis with lower levels of circulating estradiol. Letrozole may be an effective monotherapy choice for clomiphene resistant women.

A Cochrane systematic review of clinical trials comparing CC to letrozole was published by Franik et al.[3] Due to insufficient reporting of research methodology they determined that the quality of evidence in the assessed studies was low. One of the trials in that evaluation included a large number of severely obese women (BMI > 40kg/m2), which does not represent clinical practice in the majority of reproductive clinics throughout the world. Therefore, the findings are not generalizable. More study is needed to compare CC to letrozole as an ovulation induction agent, according to the authors of the cochrane review. Furthermore, regional, genetic, cultural and phenotypic variances in PCOS and disparities in therapeutic procedures in other regions of the world may restrict the ability to generalize the review findings in India. CC and letrozole have been compared in a small number of Indian individuals with ovulatory failure. In order to compare ovulation induction by CC and letrozole in women with ovulatory dysfunction, the current study was conducted.

Materials and methods

It was an open label comparative randomized clinical trial from October 2019 to September 2021 in the Department of Obstetrics and Gynecology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune, Maharashtra, India.

Inclusion criteria:

1. Patients between 20 to 40 years of age with infertility diagnosed with ovulatory dysfunction.
2. Patients in whom all other causes of infertility are ruled out.
3. Patients willing to comply with all study procedures and available for the duration of the study and willing to give written informed consent.

Exclusion criteria:

1. Females diagnosed with tubal dysfunction, endometriosis, uterine hypoplasia, congenital anomalies of the cervix and the vagina.
2. Couples diagnosed with not treatable male infertility.
3. Current use of hormonal contraception or hormonal implants within the past 3 months.
4. Contraindications to clomiphene citrate or letrozole or use of medications that are an absolute contraindication during pregnancy within the past 3 months.
5. Patients unwilling to give written informed consent.

Sampling and randomization: Total 60 patients with infertility diagnosed with ovulatory dysfunction were recruited in the study. The study carried out by Amer et al found that the average number of follicles in patients receiving clomiphene citrate group was 1.90 ± 0.77 and in the letrozole group was 1.17 ± 0.47.[4] On entering this data in WinPepi software, the minimum sample size came out to 24 that is, 12 in each group. However, we recruited total 60 patients (30 in each group) who fulfilled the study criteria. Patients were divided into the two treatment groups using computer generated random numbers (randomization allocation of 1:1).

Treatment protocol -

Clomiphene citrate group:Clomiphene Citrate (CC) was administered as 50 mg once daily for five days (days 2-6), if ovulation was not achieved, then increased by 50 mg per cycle until ovulation was achieved, up to a maximum of 150 mg in the following cycle.

Letrozole group: After spontaneous or progesterone-induced bleeding, Letrozole was administered as 2.5 mg once daily for five days (from day 2 to 6) and if ovulation did not occur, then increased by 2.5 mg per cycle until ovulation was achieved, up to a maximum of 7.5 mg in the following cycle.

Human chorionic gonadotropin (hCG) 5000 IU was administered intramuscularly as an ovulation trigger when the dominant follicle size reached >18 mm. Intercourse should be planned 24 to 36 hours after the hCG injection. TVS, 48 hours later to verify ovulation with or without day 21 serum progesterone was done.

Outcome variables -

The variables compared between the two treatment groups were:

1. On transvaginal sonography (TVS) endometrial thickness: On a mid-sagittal picture at fundus, it was measured across the endometrial cavity (from echogenic border to echogenic border). Between days 11 and 18, a consultant performed serial TVS using a diagnostic ultrasound system with a probe frequency of 6.5 MHz on alternate days.
2. Ovulation rate: Ovulation was defined as a collapsed follicle on TVS and the presence of free fluid in the pouch of Douglas, as well as a serum progesterone value of more than 3 ng/ml on day 21.

3. On cycle days 12 -14, on TVS, the size and number of developing follicles were measured.
4. Pregnancy rate is determined by detecting urine human chorionic gonadotropin (hCG) after 7 days of missing period or by ultrasound identification of the gestation sac.

Data collection: A Pre-designed and semi-structured study proforma was used for data collection. Baseline data such as age, menstrual history and obstetric history were noted down. General and systemic examination was performed and findings were noted. Patients were monitored by baseline infertility work up, hormonal assay, and folliculography. Patients were regularly followed up to note any side effects like ovarian hyperstimulation syndrome.

Statistical analysis: The analysis included comparing of patients in the two groups based on different demographic, laboratory and clinical parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data was expressed as absolute number and percentage. Cross tables were generated and chi square test was used for testing of associations and student t test was used for comparison of quantitative parameters. P - value < 0.05 is considered statistically significant. All analysis were done using SPSS software, version 24.0.

Ethical statement: The study protocol conforms to the Declaration of Helsinki and was approved by the Institutional Ethics Committee before commencement. Written informed consent was taken from all patients. No harm is intended for the subjects. A prick pain was experienced during the withdrawal of the blood sample. The same was explained to the participants before consenting. The participants were not subjected to any extra cost because of the study.

Results

It was observed that ovulation occurred in 83% of the letrozole group patients, which was significantly higher as compared to 63% in the group who received CC (p value < 0.05) (table 1).

Mean number of follicles were 1.8 ± 0.5 in the letrozole group, which were significantly lower than that of 2.3 ± 0.4 in the group who received CC (p value < 0.05). It was observed that 63% of the patients in the letrozole group secreted one follicle while only 27% of the patients in the group who received CC secreted one follicle (table 2).

Mean endometrial thickness in the letrozole group was 8.8 ± 1.5 mm, ranging from 6 to 14.8 mm, while it was 7.1 ± 1.6 mm, ranging from 4.4 to 13.4 mm in the group who received CC. We observed the mean endometrial thickness to be significantly higher in the letrozole group as compared to clomiphene citrate group, p value < 0.001 (table 3).

Table 1: Comparison of ovulation between letrozole and clomiphene group

Parameters	Treatment group			
	Letrozole		Clomiphene citrate	
	N	%	N	%
Ovulation occurred	25	83%	19	63%
Ovulation did not occur	5	17%	11	37%
Total	30	100%	30	100%
P value < 0.05				

Table 2: Comparison of number of follicles between letrozole and clomiphene group

Parameters	Treatment group			
	Letrozole		Clomiphene citrate	
Number of follicles	N	%	N	%
1	19	63%	8	27%
2	4	13%	11	37%
3	5	17%	6	20%
4	2	7%	5	17%
Total	30	100%	30	100%
	P value < 0.05			
Mean number of follicles	1.8 ± 0.5		2.3 ± 0.4	
	P value < 0.05			

Table 3: Comparison of mean endometrial thickness between letrozole and clomiphene group

Categories	Treatment group				P value
	Letrozole		Clomiphene citrate		
	Mean	SD	Mean	SD	
Endometrial thickness (mm)	8.8 (Range 6 to 14.8)	1.5	7.1 (Range 4.4 to 13.4)	1.6	< 0.001

Table 4: Comparison of pregnancy rate between Letrozole and clomiphene group

Parameters	Treatment group			
	Letrozole		Clomiphene citrate	
	N	%	N	%
Pregnancy conceived	19	63%	14	47%
Pregnancy did not conceive	11	37%	16	53%
Total	30	100%	30	100%
	P value < 0.05			

Table 5: Comparison of adverse drug reaction between letrozole and clomiphene group

Adverse drug reactions	Treatment group				
	Letrozole		Clomiphene citrate		
	N	%	N	%	P value
Headache	2	7%	3	10%	0.76
Hot flashes	1	3%	2	7%	0.45
Abdominal bloating	1	3%	2	7%	0.14
Abdominal pain	1	3%	1	3%	0.67
Nausea	2	7%	1	3%	0.88

We observed that patients conceived in 63% of the letrozole group, which was significantly more than that in the group who received CC (47%), p value < 0.05 (table 4).

We observed headache, hot flashes, abdominal bloating, abdominal pain and nausea in 7%, 3%, 3%, 3% and 7% of the patients in letrozole group respectively. Similarly, in the group who received CC headache, hot flashes, abdominal bloating, abdominal pain and nausea in 10%, 7%, 7%, 3% and 3% respectively. The adverse drug reaction profile was similar between the patients in the two treatment groups (table 5).

Discussion

We observed that the mean age of the patients was 29.8 years and 31.44 years in letrozole and group receiving CC respectively, with no significant difference between them (p value = 0.18). In anovulatory women with PCOS, Amer et al investigated whether letrozole, as a primary ovulating induction drug, would result in greater conception rates than CC.[4]Patients in letrozole and group receiving CC had mean age of 28.3 and 28.1 years, respectively, in their study. The average age of the patients in Liu et al and colleagues' research was 27 years for letrozole group and 26.8 years for group receiving CC.[5] Without statistical significance, Jain and colleagues found that the mean age in Letrozole group was 27.34 ± 4.38 years while the mean age in group receiving CC was 27.16 ± 4.14 years.[6] Elsemary et al compared the results of ovulation induction with clomiphene citrate and letrozole in PCOS patients.[7] The average age of the patients in letrozole and group receiving CC was 31.1 years and 32.5 years, respectively, with no statistical significance. In the research by Mejia et al, the average age of the patients in letrozole and letrozole +CC was 31 years and 30 years, respectively.[8] Bansal et al investigated ovulation induction in infertile women with PCOS with letrozole and clomiphene citrate in a randomized trial.[9] The average age of the patients in their trial was 27 and 26 years, respectively, with no significant difference between letrozole and group receiving CC.

We observed that mean BMI was 27.1 and 26.2 kg/m2 in letrozole and group receiving CC respectively, with no statistical difference between them (p value = 0.35). We also observed that 37% in letrozole group and 33% in group receiving CC had the infertility for less than 2 years respectively. The patient groups had similar levels of mean FSH, LH, LH/FSH ratio, testosterone and prolactin. In our study, menstrual history parameters were also similar between the two study groups. The mean BMI in the randomized trial by Amer et al was 27.3 kg/m2 in letrozole group and 27.7 kg/m2 in group receiving CC, respectively.[4] In both research groups, the average duration of infertility was 1.5 years. The mean LH, FSH, and testosterone levels in letrozole and group receiving CC were identical, confirming our findings. The mean BMI of the patients in letrozole and group receiving CC was 20.8 and 21.1 kg/m2, respectively, in a comparable research by Liu et al. In both research groups, the median duration of infertility was one year.[5] The letrozole and group receiving CC had mean LH of 11.6 mIU/ml and 12.4 mIU/ml, respectively, and average FSH of 6.7 mIU/ml and 6.6 mIU/ml respectively. In a comparable research, Jain et al discovered that the mean BMI in letrozole group was 22.90 ± 2.00kg/m2 and 23.06 ± 2.04kg/m2 in group receiving CC, with no statistical significance.[6] In addition, the average duration of infertility in the current research was 4.58 ± 2.68 years for letrozole group against 5.62 ± 3.47 years for clomiphene group. In the research by Elsemary et al, the median duration of infertility was 4 years in letrozole group and 5 years in group receiving CC.[7] The letrozole and group receiving CC had mean BMIs of 32.1 and 34.2 kg/m2, respectively. Patients in letrozole and letrozole +CC had mean BMIs of 33 and 34 kg/m2, respectively, according to Mejia et al [8]. In a comparable trial, Bansal and colleagues found that the average infertility duration was 3.9 years in letrozole group and 3.4 years in group receiving CC, with no significant difference.[9]

In the present study, we observed that ovulation occurred in 83% of letrozole group patients, which was significantly higher as compared to 63% in group receiving CC (p value < 0.05). Ovulation rates were similar in letrozole (84%) and CC (80%) groups in a randomized trial by Amer et al (80 percent), with a p value of 0.5.[4] Liu et al discovered that letrozole therapy (73.3%) had a greater ovulation rate than CC treatment (52.7%) (p<.001).[5] Women who got letrozole + CC had a greater ovulation rate than women who received letrozole alone (77 percent vs 43 percent, p value 0.01), according to Mejia et al.[8] Ovulation took place in 86.73 percent of cycles induced with letrozole compared to 85.21 percent of cycles induced with clomiphene citrate, according to Bansal et al (p= 0.751).[9]

In the present study, the average numbers of follicles were 1.8 ± 0.5 in letrozole group, which were significantly lower than that of 2.3 ± 0.4 in patients who received clomiphene (p value < 0.05). In a comparable trial, Jain et al found that the mean number of follicles in letrozole group was 1.17 ± 0.47, compared to 1.90 ± 0.77 in patients who received clomiphene, with a p value of 0.001.[6] This remark was backed up by our findings. Mono-follicular growth was seen in 68.47 percent of cycles induced with letrozole as

compared to 44.8 percent of cycles induced with clomiphene citrate in Bansal et al's study, and the difference was very significant (P<0.000).[9]

We observed that the mean endometrial thickness in letrozole group was 8.8 ± 1.5 mm, ranging from 6 to 14.8 mm, while it was 7.1 ± 1.6 mm, ranging from 4.4 to 13.4 mm in group receiving CC. We observed the mean endometrial thickness to be significantly higher in letrozole group as compared to group receiving CC, p value < 0.001.Jain et al found that letrozole group had a mean endometrial thickness of 7.55 ± 1.12mm, while group receiving CC had a mean endometrial thickness of 6.06 ± 0. 87mm, p<0.01.[6]Contrary to our findings, Elsemary et al discovered no statistically significant difference in endometrial thickness determined by TVS at the time of hCG administration between the two groups (7.8 ± 2.2 mm in the letrozole group and 8.1 ± 1.2 mm in the patients who received clomiphene).[7]The average endometrial thickness was 9.86 ± 2.32 mm in letrozole group and 9.39 ± 2.06 mm in patients who received clomiphene, according to Bansal et al, however the difference was not statistically significant (p= 0.751).[9]

We observed that 63% of the patients receiving letrozole conceived which was significantly more than that in the group receiving CC (47%), p value < 0.05.Pregnancy rates were found to be considerably greater in the letrozole group (61%) than in the patients who received clomiphene (43%) in a study similar to ours, with a p value of 0.01.[4] The conception rate (52.1 percent vs. 39.7%) and live birth rate (35.3 percent vs. 26.4 percent) were greater in letrozole therapy than in CC treatment, according to Liu et al, however there was no statistical significance (p>.05).[5] In another research by Jain et al, 48 percent of women in the letrozole group conceived, whereas only 16 percent of women in the group receiving CC conceived, a statistically significant difference (p <0.05).[6]According to Bansal et al, conception rates were 42.2 percent in letrozole group and 20.0 percent in clomiphene group, with a statistically significant difference (p =0.04).[9]

We observed headache, hot flushes, abdominal bloating, abdominal pain and nausea in 7%, 3%, 3%, 3% and 7% of the patients in letrozole group respectively and in 10%, 7%, 7%, 3% and 3% of the patients in the group receiving CC respectively. Severe adverse events included two cases of haemorrhagic cysts (one in each study group) and one case of acute cholecystitis (group receiving CC) that required hospitalization, according to Amer et al.[4] Cyst development (n = 3), diarrhea, nausea, and vomiting (n = 2), hot hands, heavy leg, headache, neck discomfort, skin spots and urinary tract infection were all reported by 12 people on letrozole. Minor side effects seen by 11 women using clomiphene citrate included cyst development (n = 3), hot flushes (n = 3), migraine, depressed mood, skin rash, and increased lever enzymes. Hot flushes were reported by 13 percent of letrozole patients and 31 percent of letrozole +CC patients in the study by Mejia et al, headache by 41 percent of letrozole patients and 28 percent of Letrozole +CC patients, and nausea by 9 percent of patients in each study group.[8]

Conclusion

Based on the results of this study, we conclude: 1) Ovulation rate, endometrial thickness and pregnancy rate was found to be significantly higher among patients in letrozole group as compared to group receiving clomiphene citrate (CC). The mean numbers of follicles were significantly lower in the letrozole group; 2) Side effect profile was similar in letrozole and group receiving CC.

Our findings show that individuals treated with letrozole had a better clinical outcome than those treated with clomiphene citrate, which has a comparable adverse effect profile.

Conflict of interest: None. **Disclaimer:** Nil.

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