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Original Research Article

Letrozole versus Clomiphene Citrate for Ovulation Induction in Anovulatory Infertility: A comparative study

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Abstract

Background: The multifaceted health issue of infertility has negative societal and economic effects. Ovulatory abnormalities are the most prevalent recognisable female factor, and female factors still account for 40% to 55% of all causes. One of the most effective treatments for infertility brought on by anovulation is ovulation induction. The study's objective was to contrast the results of ovulation induction with letrozole and clomiphene citrate (CC) in females with anovulatory infertility.

Methods: 40 infertile women with anovulatory infertility were randomised to receive either letrozole or CC for ovulation induction at incremental doses for a maximum of three cycles in this assessor-blinded randomised controlled experiment. Endometrial thickness, ovulation frequency, pregnancy frequency, and rate of mono-follicular formation were the main outcomes examined. Both groups received 10,000 IU of human chorionic gonadotropin (hCG), timing of sexual activity was suggested, and ultrasound monitoring continued until the dominant follicle achieved a diameter of less than 18 mm.

Results: In both groups, the mean age, length of infertility, BMI, and endocrine status were comparable at the outset. In the letrozole group, 18 participants (90.0%) and in the CC group, 14 subjects (70.0%) experienced ovulation; this difference was statistically significant (P=0.0471). In the letrozole group, mono-follicular development was observed in 12 (60.0%) of ovulatory cycles as opposed to 5 (25.0%) in the clomiphene group (p=0.001). In the letrozole group, seven women (35%) and in the clomiphene group, five women (25%) both became pregnant (p=0.230). When hCG was administered, there was no statistically significant difference in the thickness of the endometrium between the two groups (9.69±1.22 mm vs. 9.80±1.05 mm with letrozole and clomiphene, respectively; p = 0.650).

Conclusion: In comparison to CC, letrozole impact demonstrated a higher ovulation rate and mono follicular development. Patients with anovulatory infertility may benefit from letrozole as a first-line treatment.

Keywords: Clomiphene Citrate, Letrozole, Anovulatory Infertility , PCOS, Pregnancy.

Introduction

A major issue that accounts for 40% of female infertility cases is ovulatory dysfunction. With painless periods, it presents as amenorrhea, oligomenorrhea, or polymenorrhea.[1] Ovulatory dysfunction has been linked to a large increase in the number of women who appear with chronic anovulation in recent years. The most frequent cause of infertility brought on by persistent anovulation is PCOS.[2] Using the Rotterdam criteria, it is simple to make a clinical diagnosis of PCOS, and treatment can usually be started after a few simple investigations and the exclusion of other female and male variables that may be contributing to infertility.[3] Another frequently occurring factor in anovulation and infertility is hypothyroidism.[4,5] Hyperprolactinemia, pituitary and hypothalamic disorders, obesity, early ovarian failure, strenuous exercise, and other factors are additional causes of anovulation.[6]

Patients with amenorrhea, oligomenorrhea, and persistent anovulation make up a sizable portion of those seeking care. The purpose of ovulation induction is the therapeutic restoration of a woman who has either not been ovulating regularly or not at all to the release of one egg every cycle. For example, clomiphene citrate (CC), letrozole (let), human menopausal gonadotropin (HMG), follicle stimulating hormone (FSH), gonadotropin releasing hormone (GnRH) agonists, etc. are some of the medications used to induce ovulation.[7] Gonadotropins are more efficient than CC, but they are also more expensive and linked to a higher risk of multiple pregnancies and ovarian hyperstimulation syndrome. The use of simple-to-use, less expensive, and effective medications like clomiphene and letrozole is preferred in fertility therapy due to the cost and potential side effects of gonadotropins.[8] The long-established standard medication for ovulation induction, clomiphene citrate (CC), is still regarded as the first-line ovulation induction choice. It is delivered orally, causes less side effects, is simple to find, and costs little. Clomiphene citrate therapy, however, is linked to disparity in ovulation and pregnancy rates (60–85%; 10–20%). A greater percentage of PCOS women miscarry than the general population, and 20–25% of them are clomiphene resistant. The prolonged depletion of oestrogen receptors caused by clomiphene citrate's anti-estrogenic action adversely affects endometrial development as well as the quantity and quality of cervical mucus. [9,10]

Concerns include clomiphene citrate resistance as well as adverse effects such multiple follicle development, poor endometrial growth, and cyst formation. The need for a workable substitute never goes away. Letrozole, an aromatase inhibitor, was first used in infertility treatment in 2000 and is recommended as a good ovulation induction treatment choice, especially for women who are clomiphene resistant. As it works, letrozole prevents the enzyme aromatase from converting testosterone into oestrogen.[11]

The indications for use have increased as a result of its acceptance in a variety of clinical settings. Letrozole, unlike clomiphene, causes a mono follicular response at the recommended dose of 2.5–5 mg and has no negative effects on the endometrium or the cervical mucus since it has no effect on peripheral oestrogen receptor. Clomiphene citrate and letrozole were compared in this study for ovulation induction in ovulatory infertile women.

Materials and Methods

From July 2021 to December 2022, a hospital-based double-blinded prospective study was carried out in the Obstetrics and Gynaecology Department of Darbhanga

Medical College and Hospital, Laheriasarai, Bihar. A total of 63 patients who visited OPD for infertility during the research period were screened. Out of which, 21 patients did not match the requirements for inclusion, and a total of 42 patients did, and they were enrolled in the study. 42 patients were involved, and 2 patients were lost to follow-up. Thus, the final analysis involved 40 research participants data in all.

Complete blood counts, liver, thyroid, and renal function tests, prolactin, FSH/LH on day 3 of menstruation, among other tests, were performed as part of a thorough medical and gynaecological evaluation. On the initial appointment, a baseline transvaginal sonogram was performed to determine the antral follicle count (AFC).

After counselling, patients were randomised into two groups, A and B. The lowest dose of Clomiphene citrate 50 mg or Letrozole 2.5 mg was prescribed to begin on any day between days three and five of menstruation. On day 9 of the cycle, TVS began to monitor the follicles until a mature follicle measuring 18 to 20 mm or greater was found.

If at least one follicle was 18 to 20 mm and the endometrial thickness was at least 8 mm, a single 10,000 IU IM injection of hCG was administered. After 24 to 48 hours of hCG, a second TVS was performed to watch the release of the egg. A third TVS was performed to check for an unruptured luteinized follicle 72 hours after the hCG injection if the follicle was discovered to be intact. By spotting the collapsed follicle and fluid in the Douglas pouch, TVS was used to detect ovulation.After measuring the endometrial thickness, a trilaminar diameter of >/=8 mm was deemed to be a satisfactory result. Intercourse should be timed to occur 24 to 48 hours following hCG on two consecutive days, and micronized progesterone should be added to the luteal phase.

Women in group A were given the lowest dose of clomiphene citrate—50 mg—for their first cycle, followed by 100 mg if ovulation induction wasn't induced by 50 mg CC, then 125 mg CC for one cycle, and another cycle with 125 mg CC if that didn't work—for a total of four cycles. For group B Letrozole, a similar protocol was used, consisting of 2.5 mg for one cycle, 5 mg for the following cycle in the event of failure, 7.5 mg for the following cycle, and another cycle with 7.5 mg in the event of failure, for a total of four cycles with each drug.

If no follicle formed, the cycle was stopped, and a new cycle with a higher dose of the same medication was begun. Patients were instructed to take the same dose for a total of three cycles after ovulation was confirmed for a specific dose of the medication.

Statistical Package for Social Sciences (SPSS) version 22 was used to conduct the statistical analysis. The effectiveness of letrozole and clomiphene citrate (CC) for ovulation induction in women with anovulatory infertility was compared using the Student t-test (independent t-test).

To determine the relationship between result and demographic factors, the Chi-square test was used. It was created to create the Receiver Operating Curve (ROC). For all statistical analyses, $p < 0.05$ was considered significant, and $p < 0.001$ was considered highly significant.

Results

A total of 63 patients were examined for recruitment throughout the study period. 40 patients enrolled and finished the study because 21 patients did not match the inclusion criteria and 2 patients were lost to follow-up during the study. In Table 1, participants' baseline characteristics are compared. Age, infertility duration, BMI, and endocrine state did not statistically differ between the two groups at the baseline level.

Table 1: Baseline traits of the primary infertility patients in both groups

Variables	Clomiphene Citrate (n-20)	Letrozole (n-20)	p value
Age (years)	28.99±4.72	27.92±3.68	0.169
Duration of mean infertility period (years)	3.79±2.48	3.59±2.32	0.789
Body Mass Index (kg/m^2)	25.01±3.32	23.89±2.23	0.259
FSH (IU/mL) on day 2 of cycle	6.18±1.69	6.35±1.59	0.568
LH(IU/mL) on day 2 of cycle	8.19±2.11	8.95±2.41	0.213
TSH (IU/mL)	2.46±1.04	2.58±1.10	0.655
Prolactin (ng/mL)	19.29±8.65	17.26±4.9	0.212

When compared to the CC group (70.0%), the letrozole group (90.0%) had statistically substantially more follicles that were less than ≥18 millimetres, with a p value = 0.0471 (Table-2).

Table 2: Ovulation rate, in percentages of both groups

Ovulation	Clomiphene		Letrozole		Total	P value
	Number	Percentage	Number	Percentage		
No	6	30.0%	2	10.0%	8	0.0471
Yes	14	70.0%	18	90.0%	32	
Total	20	100.0%	20	100.0%	40	

In the letrozole group, mono follicular growth was substantially higher (CC 25.0%, Let 60%, p value =0.001) [Table 3].

Table 3: Follicular growth in the letrozole and clomiphene citrate group

	Response	Clomiphene citrate		Letrozole		Total	p-value
No. of follicles		Number	Percentage	Number	Percentage		
	No dominant follicle	1	5.0%	2	10.0%	3	0.001
	Mono-follicular	5	25.0%	12	60.0%	17	
	Multi-follicular	14	70.0%	6	30.0%	20	
	Total	20	100.00%	20	100.00%	40	

In terms of pretreatment endometrial thickness, there was no statistically significant difference between the two groups. The mean endometrial thickness was 9.8±1.05 mm in the letrozole group and 9.69±1.22 mm in the CC group, although there was no statistically significant difference (p value = 0.650). (Table 4).

Table 4: Endometrial thickness (mm) in the Letrozole and group CC groups

	Clomiphene citrate		Letrozole		
	Mean	SD	Mean	SD	p value
Endometrial thickness (mm)	9.69	1.22mm	9.8	1.05	0.650

In the letrozole group, there were more pregnancies than in the clomiphene group (L-35.0% versus CC-25.0%) (Table 5).

Table 5: Rate of conception or pregnancy as a percentage

	Clomiphene		Letrozole			
Pregnancy	**Number**	**Percentage**	**Number**	**Percentage**	**Total**	**P value**
No	15	75.0%	13	65.0%	28	0.230
Yes	5	25.0%	7	35.0%	12	
Total	20	100.0%	20	100.0%	40	

Discussion

It is not always possible to induce ovulation or super ovulation using the first-line ovulation inducing agent CC. 15% to 20% of patients develop clomiphene resistance. Due to chronic oestrogen receptor depletion in the endometrium and perhaps in the cervix, the use of CC may be linked to poor cervical mucous and endometrial thinning in 15–50% of individuals. For a long time, CC was the first option for PCOS patients seeking to induce ovulation, but up to 58% of these people are resistant to it and do not ovulate. The PR for each cycle is still quite low. Numerous studies have looked into the aromatase inhibitor letrozole as a potential replacement for clomiphene, although there is mixed evidence regarding its effectiveness.

In this study, the letrozole group 18 (90.0%) had statistically substantially more follicles ≥18 mm than the CC group 14 (70.0%), with a p value =0.0471. It is backed up by earlier research done by Soni et al. in 2020, in which the letrozole group ovulation rate was statistically considerably higher than the CC group (Let-82%, CC-62%, p value=0.045).[17] Letrozole boosted the ovulation rate, according to a meta analysis conducted by Hu S et al in 2018 (RR = 1.18; 95% CI 1.03-1.36, P = 0.01).[18] According to a 2014 study by Legro et al, cycles using letrozole had considerably greater ovulation rates than cycles using clomiphene citrate (61.7% with letrozole and 48.3% with CC, p<0.05).[19] Ovulation occurred in 68.2% of letrozole cycles and 74.3% of CC cycles in a 2015 study by Elsemary et al. without a statistically significant difference. [20]

The mono-follicular response in this study was 12(60.0%) in the Letrozole group and 5(25.0%) in the CC group, respectively. It is corroborated by earlier research conducted by Soni et al in 2020, in which letrozole group monofollicular growth was statistically significantly higher (CC 18%, Let 66%, p value = 0.0001).[17] Shavina et al study from 2020 found that monofollicular formation occurred in 68.4% of ovulatory cycles in the letrozole group versus 44.8% in the CC group (P=0.000).[21] Multi-follicular growth was statistically substantially higher in group CC compared to letrozole in a 2017 study by Wafa Y. S. et al (CC 48.0% and Letrozole 26.0%, p value= 0.023).[16] Contrarily, Kumar Roy et al study from 2005 to 2010 found that the average number of dominant follicles was similar in the letrozole and CC groups (p=0.126), coming in at 1.86± 0.26 and 1.92± 0.17, respectively.[22]

The average endometrial thickness in this study was 9.69±1.22 mm in the CC group and 9.8±1.05 mm in the letrozole group, although the difference was not statistically significant (p value= 0.650). According to a 2015 study by Elsemary et al, there was no statistically significant difference between the two groups endometrial thickness measured using transvaginal ultrasound at the time human chorionic gonadotropin was administered (7.8±2.22 mm in the letrozole group and 8.1±1.2 mm in the CC group, respectively).[20] The mean endometrial thicknesses in the 2020 study by Shavina et al. were 9.86± 2.32 mm and 9.39± 2.06 mm, respectively, with letrozole and CC, not statistically significant (P=0.751).[21] The

endometrial thickness at the time of hCG injection was statistically substantially higher in the letrozole group in a study by Chakravorty R et al. from 2016 (9.82± 0.7 vs. 8.13± 0.56; p<0.001).[23]

The pregnancy rate in our study was 7 (35.0%) for the Letrozole group and 5 (25.0%) for the CC group; however, the difference was not statistically significant (p value = 0.230). Letrozole and clomiphene citrate usage both resulted in equal pregnancy rates. In the letrozole group, there were 1 twin and 1 triplet pregnancy, compared to 2 twin pregnancies in the CC group.

According to Yland et al. in 2022, letrozole had a 43% pregnancy chance compared to clomiphene's 37%.[24] In the Bansal et al. trial from 2020, pregnancy was attained in 42.2% of letrozole-treated women and 20.0% of CC-treated women (P=0.04).[21] According to Wafa Y.S. et al., letrozole had a pregnancy rate of 48.0% when used to induce ovulation in PCOS women compared to 28.0% when clomiphene citrate was used.[16]

Conclusion

Letrozole appears to be a good option in terms of ovulation and conception rates with noticeably improved mono follicular growth, according to the findings of this double-blinded prospective cohort study. Between the two groups, there was no difference in endometrial thickness. Letrozole may be suggested as the first-line medication for ovulation induction in cases with anovulatory infertility since it is a safer and superior option than CC in the protocol for ovulation induction.

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