Letrozole Versus Clomiphene Citrate for Superovulation in Intrauterine Insemination Cycles - Retrospective Comparative Study Conducted in the Department of Reproductive Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur

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ABSTRACT

BACKGROUND

Superovulation with intrauterine insemination (IUI) increases the probability of pregnancy by increasing number of oocytes and sperm density. The main oral agents used for superovulation are clomiphene citrate and letrozole. Clomiphene citrate a selective estrogen receptor modulator with predominant antiestrogenic action has adverse effects on endometrium and cervical mucous. Letrozole an aromatase inhibitor acts by reducing estrogen production by blocking androgen conversion to estrogen in ovary and peripheral tissues without affecting endometrium and cervical mucous. We wanted to compare the efficacy of letrozole v/s clomiphene citrate as first line ovulation induction drug in infertile patients undergoing IUI.

METHODS

Based on the inclusion and exclusion criteria, we included 160 patients in our study. They were divided into two groups of 80 each based on the drug given for ovulation induction. The drug was given for 5 days from D3 to D7 of menstrual cycle. IUI was done 38 - 40 hours after trigger and after confirmation of ovulation by sonography.

RESULTS

The mean age, body mass index (BMI), duration of infertility, type and cause of infertility in both groups were similar. Ovulation rate was 85 % in letrozole group and 71.25 % in clomiphene citrate group, which was statistically significant (P=0.035). There was no statistically significant difference between endometrial thickness and total days till ovulation between two groups. Monofolliculogenesis and clinical pregnancy rate were statistically significantly higher in letrozole group.

CONCLUSIONS

Our study shows that letrozole has better pregnancy rate in comparison to clomiphene citrate (C.C.) in IUI cycles with less risk of anovulation, thin endometrium and multi follicular growth.

KEY WORDS

Clomiphene Citrate (C.C.), Letrozole (LTZ), Ovulation Induction (OI), Intrauterine Insemination (IUI)

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BACKGROUND

Superovulation with IUI is usually taken as first line treatment in non tubal infertilities like mild PCOS, mild endometriosis, mild male factor and unexplained infertility, where patient fails to conceive after reasonable trial of conservative treatment i.e. superovulation followed by timed intercourse. Superovulation with IUI augments the probability of pregnancy by increasing the number of oocytes and density of motile sperms available to these oocytes.^{1,2}

The two main oral agents for superovulation are clomiphene citrate (C. C.) and letrozole (LTZ). Clomiphene citrate has been the most widely used first line drug for superovulation in infertile patients, both for timed intercourse as well as IUI since its introduction in 1960's.^{3,4} The different indications for its use are polycystic ovarian syndrome (PCOS), unexplained infertility, IUI and mild stimulation protocols in in-vitro fertilization (IVF). It is a non-steroidal selective estrogen receptor modulator with predominant antiestrogenic action. Clomiphene citrate has a long half-life around 2 weeks resulting in long lasting estrogen receptor depletion and antiestrogenic adverse effects on endometrium,⁵ and cervical mucus.⁶ Anovulation even with high doses is seen in 20 - 25 % cases known as clomiphene citrate resistance. Discrepancy in ovulation and pregnancy rate (60 - 85 % V / s 1020 %) is another problem seen with clomiphene citrate known as clomiphene citrate failure. Miscarriage rate is also higher with clomiphene citrate. So the need for an alternative to clomiphene citrate for ovulation induction was realized since 1990's.

Robert Casper and mohmed F. M. mitwally of Toronto general hospital are credited for proposing the concept of aromatase inhibitor i.e letrozole as an alternative to clomiphene citrate for ovulation induction in women with clomiphene citrate failure or resistance. Letrozole (Femara) was an orally active drug used for the treatment of metastatic breast cancer in receptor positive or post menopausal females. Letrozole acts by reducing estrogen production by blocking androgen to estrogen conversion in ovary and peripheral tissues. So it has no antiestrogenic effects on endometrium and cervical mucus.⁷ Additionally the response is more physiological as it doesn't block estrogen receptors at the level of hypothalamus and pituitary and thus keeps the feedback loop patent. So the induction mostly ends up with monofollicular growth (60 - 80 %). Letrozole has a short half-life i.e. around 48 hours, so effect of drug easily vanes off. Increased levels of intraovarian androgens augment the follicular sensitivity to FSH and stimulates insulin like growth factor (IGF - 1) as well, which helps in follicular growth.⁸ After similar studies letrozole was shown to be very effective both in ovulation rate and live birth rate. But its use was banned in most of the countries including India after Dr. Marinko Biljan of Montreal presented an oral abstract in 2005 ASRM annual meeting, reporting congenital anomalies in 150 babies born from infertile women treated with letrozole.⁹ Later on larger studies with better designs have been published regarding safety of letrozole as ovulation induction drug.¹⁰ Some of them even reported higher incidence of congenital malformation with clomiphene citrate.¹¹ In India letrozole was approved for ovulation induction from 2006 to October 2011 by Drug controller general of India (DCGI). The ban was lifted by Union health ministry on recommendation of Drug technical

advisory board (DTAB) in February 2017 after a large population based study regarding safety of letrozole. There are many comparative studies done for letrozole and clomiphene citrate as first line ovulation induction drug for controlled ovarian hyper stimulation but most of them found both the drugs comparable.¹²

Objective

The study was done to compare the efficacy of letrozole V / S clomiphene citrate as first line ovulation induction drug in infertile patients undergoing IUI.

METHODS

This is a retrospective comparative study conducted in Reproductive Medicine department of Mahatma Gandhi medical college and Hospital from January 2019 to November 2019. Study protocol was approved by the institutional ethical committee.

Based on the inclusion and exclusion criteria, the total number of patients available for our study were 160.

Inclusion Criteria

1. Patients with oligoovulation and menstrual irregularities.
2. Male factor with oligospermia.
3. Patients with unexplained infertility.

Exclusion Criteria

1. Age > 35 years
2. Poor ovarian Reserve (FSH > 10 mIU / ml)
3. Infertility > 5 years
4. H / O of Genital Koch's
5. Moderate to severe endometriosis or PCOS
6. H / O Chronic Pelvic inflammatory disease (PID)
7. H / O OCP use in previous cycle

Each patient was evaluated by detailed history, physical examination, routine investigations, baseline FSH levels and antral follicle count (AFC) on transvaginal sonography (TVS). The tubal patency was confirmed by either HSG or VHL. Detailed evaluation of male partner was also done specially in cases of male factor infertility.

Patients were divided into two groups of 80 each based on the odd and even numbers. Patients in group - 1 were given clomiphene citrate (50 - 100 mg) from day 3 to day 7 and patients in group - 2 were given letrozole (2.5 - 5 mg) from day 3 to day 7. The dose was decided according to age, BMI, baseline FSH and AFC. Follicular monitoring details were taken by TVS from day 10 and continued till mature follicle was > 18 mm. A single injection of HCG 10000 IU was given as trigger in the evening between 6 PM and 8 PM and IUI was planned 38 - 40 hours after the trigger. Ovulation was confirmed by transabdominal sonography before IUI. Luteal support was given as vaginal micronized progesterone 200 microgram twice daily to all patients. HCG was done after 15

days of IUI. Clinical pregnancy was confirmed by visualization of cardiac activity on TVS 15 days after positive HCG.

Primary outcome was clinical pregnancy rate in both the groups. Secondary outcome majors were ovulation rate, total days of induction till ovulation, mono V / S multifollicular growth and endometrial thickness.

Statistical Analysis

Chi - square and student's 't' test was carried out for statistical analysis. Results were expressed as mean and standard deviation. P - Value < 0.05 was considered significant.

RESULTS

The study comprised of 160 patients, 80 patients in the clomiphene citrate group and 80 patients in the letrozole group. Table 1 shows demographic characteristics of two groups. There was no statistically significant differences in age, BMI, duration of infertility, type of infertility and cause of infertility between the two groups.

Demographic Characteristics	C C Group (N = 80)	LTZ Group (N = 80)	P - Value
Age (Years)	25.31 ± 2.56	26.11 ± 2.60	0.80
BMI (Kg / m ²)	25.45 ± 3.13	25.49 ± 3.19	0.93
Duration of Infertility (Years)	3.46 ± 2.12	3.59 ± 2.33	0.71
Type of Infertility			
Primary	54 (67.5 %)	58 (72.5 %)	0.49
Secondary	26 (32.5 %)	22 (27.5 %)	
Cause of Infertility			
Mild PCOS	28 (35 %)	30 (37.5 %)	0.74
Male Factor	32 (40 %)	35 (43.75 %)	0.63
Unexplained	20 (25 %)	15 (18.75 %)	0.34

Table 1. Demographic Characteristics in Two Groups

Table 2 shows that the rate of multiple follicular development was statistically significantly higher in the clomiphene citrate group (43.75 % V / s 25 %, P - 0.012). There was no difference in total days till ovulation and ET between the clomiphene citrate and letrozole group.

Follicular Development and days till ovulation	Clomiphene Citrate (C. C.) Group (N - 80)	LTZ Group (N - 80)	P - Value
Mono follicular Development	45 56.25 %	60 75 %	0.0125
Multi follicular development	35 43.75 %	20 25 %	0.012
Total days to ovulation	14.1 ± 3.23	13.8 ± 2.80	0.53
ET (mm)	8.82 ± 2.02	9.02 ± 2.32	0.56

Table 2. Follicular Development, ET and Days till Ovulation

Table 3 shows the ovulation rate of 71.25 % in clomiphene citrate group and 85 % in letrozole group. (P - 0.035). The clinical pregnancy rate was 10 % in clomiphene citrate group and 22.5 % in letrozole group which was statistically significant (P - 0.032)

	Clomiphene Citrate group (N - 80)	LTZ Group (N - 80)	P - Value
Ovulation rate	57 / 23 71.25 %	68 / 12 85 %	0.035
Clinical pregnancy rate (CPR)	8 / 72 10 %	18 / 62 22.5 %	0.032

Table 3. Ovulation and Clinical Pregnancy Rate among Two Groups

DISCUSSION

Clomiphene citrate is still considered as first line ovulation induction drug in cases where controlled ovarian stimulation is needed like mild PCOS, mild endometriosis, mild to moderate male factor, unexplained infertility and IUI cycles. Endometrial thinning and poor cervical mucus are the main disadvantages with clomiphene citrate, responsible for low success rate. Clomiphene resistance is seen in 15 - 20 % cases of PCOS. To avoid these adverse effects of clomiphene citrate, letrozole is taken as an alternative drug with advantage of shorter induction time, better endometrial thickness & cervical mucus quality, monofollicular growth and better pregnancy rate. Letrozole not only increases the FSH release by pituitary but it also increases the follicular sensitivity to FSH through amplification of FSH receptor gene expression.

In our study, the total days of induction till ovulation were 14.1 ± 3.23 in clomiphene citrate and 13.8 ± 2.80 in letrozole group, though less in letrozole group but statistically not significant. This is comparable to the study of Mitwally and Casper,¹³ who also found no significant difference in total days till HCG between clomiphene citrate and letrozole (14.8 ± 2.7 Vs 14.2 ± 2.1). Sujata kar et al.¹⁴ in her study of PCOS patients also found no difference (C.C.14.2 ± 3.41 and LTZ 13.13 ± 2.99, P - 0.24).

In our study, the mean ET was 8.82 ± 2.02 in clomiphene citrate group while 9.02 ± 2.32 in letrozole group. It was also slightly higher in letrozole group but statistically not significant (P - 0.56). This was comparable to study of Jee et al.¹⁵ (LTZ 9.3 ± 1.7 Vs C.C. 9.1 ± 1.7, NS) and Abu Hashim et al.¹⁵ (LTZ 8.8 ± 1.2, Vs C.C. 8.2 ± 0.09, P - 0.53) showing a non - significant increase in ET on the day of HCG in the LTZ group. Sujata kar et al.¹⁴ also found slightly higher ET in letrozole group (7.65 ± 2.1 Vs 7.61 ± 1.96, P - 0.91), though less than our study. Studies that found letrozole associated with greater endometrial thickness were those of Akbari et al.¹⁶ (LTZ 9.08 ± 1.2 Vs C.C. + HMG 8.1 ± 1.9, P - 0.0001), Mitwally and Casper¹³ (LTZ 8.1 ± 1.4 Vs C.C. 6.2 ± 2.5, P - <0.01) Davar et al.¹⁷ (LTZ 6.9 ± 2.2 Vs C.C. 7.8 ± 1.8, NS) found nonsignificant increase of ET in clomiphene citrate group.

In our study, ovulation rate was 71.25 % in clomiphene citrate group while 85 % in letrozole group, which is statistically significant (P - 0.035). This is similar to the study of M. Zeinalzadeh et al.¹⁸ who reported higher ovulation rate in letrozole group (86 % Vs 72 %, P - 0.07). Sujata kar et al.¹⁴ in PCO patients showed better ovulation rate with letrozole (73.08 % Vs 60.78 %, P0.39) but not significant statistically. While studies by Bayar et al.¹⁹ (C.C. 74.7 % Vs LTZ 65.7 %) and Zawad et al.²⁰ (C.C. 87.33 % Vs LTZ 82.66 %) found better ovulation rate with clomiphene citrate.

In our study, multifollicular development was statistically significantly higher in clomiphene citrate group as compared to letrozole (C. C. 40 % Vs LTZ 22.5 %, P - 0.016). Total number of follicles were higher in clomiphene citrate group as compared to LTZ in the study of Abu Hashim et al.¹⁵ (2.8 ± 0.04 Vs 1.4 ± 0.02, P - 0.042), Badaway et al.²¹ (3.1 ± 0.36 Vs 1.6 ± 0.41, P - 0.045)

Akbari et al.¹⁶ (2.2 ± 0.68 Vs 2.02 ± 0.63, p - 0.025), Davar et al.¹⁷ (5.45 ± 4.2 Vs 3.07 ± 2.1, P - 0.01) and Jawad et al.²⁰ (1.44 ± 0.56 Vs 1.13 ± 0.32, P - 0.001). Akbari et al. also used gonadotropins with clomiphene citrate. Total number of

follicles were significantly greater in C. C. group in the study of Badaway et al.²¹ (4.1 ± 0.46 Vs 2.6 ± 0.43) when combined with gonadotropins. While study by fozan et al.²² (C.C. 1.1 ± 0.05 Vs LTZ 1.4 ± 0.7), Hyon Yun et al.²³ (C.C. 1.44 ± 0.88 Vs LTZ 1.53 ± 0.89 , P - 0.432), Barroso et al.²⁴ (C.C. 1.9 ± 0.5 Vs LTZ 2.1 ± 0.9 , NS) found no significant difference between two groups.

Sujata kar et al.¹⁴ in PCOS patients also observed that multifollicular development was significantly higher in clomiphene citrate group (45.16 % Vs 20.51 %, P0.027). The mono follicular development was higher in letrozole group (75 % Vs 56.25 %, P - 0.0125) in our study.

In our study, the clinical pregnancy rate was significantly higher in letrozole group as compared to clomiphene citrate group (22.5 % Vs 10 %, P - 0.0325) while most of the studies showed comparable pregnancy rates in both the groups after IUI. The clinical pregnancy rate per cycle and the cumulative pregnancy rate after four cycles were comparable (15.9 % Vs 14.5 %, P - 0.82 and 64.7 % Vs 57.2 %, P - 0.71) in letrozole and clomiphene citrate group respectively in a study by Abu Hashim et al.¹⁵ but they included only minimal to mild endometriosis cases in their study. Similarly the CPR was comparable between two groups in study by Akbari et al.¹⁶ (LTZ 21.3 % Vs C.C. 13.8 %, P - 0.146), Barroso et al.²⁴ (LTZ 23.8 % Vs C.C. 20 %, NS) All of them used gonadotropins also.

The clinical pregnancy rate was comparable and higher in clomiphene citrate group (18.3 % Vs 12.2 %, p - 0.177) in study by Bo Hyon et al.²³ but they used gonadotropins also in both groups. CPR was quite low but comparable in the study of fozan et al.²² (LTZ 11.5 % Vs C.C. 8.9 %) Sammour et al.²⁴ (LTZ - 16.7 % Vs C.C. 5.6 %, P - 0.55).

CONCLUSIONS

The pharmacodynamics of LTZ (does not deplete estrogen receptor, has short half life and intact hypothalamic-pituitary axis) results in improved endometrial thickness and cervical mucus, mono follicular growth and better ovulation rate. Therefore the clinical pregnancy rate is also better in letrozole group in our study. Letrozole is a better first line drug as compared to clomiphene citrate for super ovulation in IUI cycles though further larger studies are needed to confirm this.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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