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Original Research Article

Efficacy of Clomiphene Citrate and Letrozole in Intrauterine Insemination Cycles

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Abstract

Clomiphene citrate and letrozole are the two major oral contraceptives used for superovulation. the amount of oocytes and sperm density increase during superovulation during intrauterine insemination (IUI), which reinforces the likelihood of pregnancy. Endometrium and cervical mucus are negatively impacted by clomiphene, a selective oestrogen receptor modulator with a predominately anti-estrogenic activity. An aromatase inhibitor, Letrozole, works by preventing the conversion of testosterone to oestrogen in peripheral tissues, including the ovary, without harming the endometrium or cervical mucus. When infertile patients undergo IUI, we assessed the effectiveness of letrozole (85%) vs. Cloniphene (71.1%) because the first line ovulation induction medicine. This study deals with the efficacy of Clomiphene and letrozole in several patients. In IUI cycles, our study concludes that letrozole includes a higher pregnancy rate than clomiphene (C. C.) and lower risks of anovulation, thin endometrium, and multi-follicular development.

Keywords: Clomiphene Citrate, Letrozole, Intrauterine insemination (IUI), Superovulation

Introduction

Since its inception in the 1960s, the most often used first-line medication for superovulation in infertile individuals, both for timed intercourse and IUI is, clomiphene citrate. [1-5] For many years, ovarian hyperstimulation in cases of unexplained infertility has undergone effective clomiphene citrate treatment (CC). By preventing the oestrogen negative feedback effect, clomiphene citrate raises the pituitary's release of FSH, which in turn promotes the growth of follicles. [6,7] CC has drawbacks in therapy, nevertheless, and CC resistance is common (15–40%). Due to the lengthy half-life of clomiphene citrate, which is approximately two weeks, endometrium, cervical mucus, and oestrogen receptors are adversely affected for an extended period of time. [8,9]

In cases of non-tubal infertility, such as mild PCOS, mild endometriosis, mild male factor, and unexplained infertility, superovulation with IUI is typically used line of treatment if the patient is unsuccessful in getting pregnant following a reasonable test of conservative treatment, including superovulation followed by scheduled sexual activity. The probability of pregnancy is increased by

superovulation during IUI by increasing the production of oocytes and the density of motile sperm accessible to these oocytes [8,10].

Because it is thought to boost conception rates while being easy to do and very inexpensive, first-line treatment for couples with unexplained or mild male-factor infertility, worldwide is intrauterine insemination (IUI). Clomiphene citrate (C. C.) and letrozole are the two major oral contraceptives for inducing superovulation (LTZ). [11-16]

Robert Casper and Mohmed F. M. Mitwally of Toronto general hospital are credited for proposing the concept of aromatase inhibitor as a substitute for clomiphene citrate for the induction of ovulation in clomiphene citrate-using women or resistance [17]. Letrozole (Femara) was an orally active drug used for the treatment of metastatic breast cancer in receptor positive or post-menopausal females. Letrozole works by preventing the alteration of androgen to oestrogen in the ovary and surrounding tissues. Consequently, endometrium and cervical mucus do not experience any anti-estrogenic effects [16,17]. Letrozole has a short duration of about 48 hours, which makes the effects of the medicine swiftly wear off. In addition to stimulating insulin-like growth factor (IGF-1), which aids in follicular expansion, increased intraovarian androgen levels also increase the follicular sensitivity to FSH[(21)]. Letrozole was authorised for ovulation induction in India by the Drug Controller General of India from 2006 to October 2011. (DCGI). Following a sizable population-based investigation on the safety of letrozole, the Union Health Ministry lifted the prohibition in February 2017 at the DTAB's suggestion [18].

Letrozole and clomiphene citrate have been the subject of numerous comparison trials as first-line ovulation inducing medications for controlled ovarian hyper stimulation, although most of them found that the two medications were equivalent.

Methods

160 patients, who were admitted in the M.G.M. Medical College, Kishanganj, Bihar, India were enrolled in our studies. The medication used to induce ovulation was used to split them into two groups of 80 each. From Day 3 to Day 7 of the menstrual cycle, the medication was administered for 4 days. IUI was carried out 38–40 hours after the trigger and following sonographic ovulation confirmation. The institutional ethical committee accepted the study protocol.

Inclusion Criteria

1. Patient who experience irregular menstruation and oligoovulation.
2. Male factor combined with oligospermia.
3. Infertility patients who have no known cause.

Exclusion Criteria

1. Older than 35 years
2. Low ovarian reserve (FSH more than 10 mIU/ml)
3. Long-term infertility
4. H / O of Koch's Genital
5. PCOS or moderate to severe endometriosis
6. inflammatory chronic pelvic disease (PID)
7. Use of H/O OCP in the preceding cycle

Each patient was screened using a thorough medical history, physical examination, regular tests, baseline FSH levels, and transvaginal sonography (TVS) to determine the number of antral follicles (AFC). Either HSG or VHL provided confirmation of the tubal patency. Particularly in situations of male factor infertility, a thorough evaluation of the male spouse was also conducted.

Based on the odd and even numbers, the patients were split into two groups of 80

each. From day 4 to day 8, patients in group 1 underwent the treatment of clomiphene citrate (25–50 mg), while from day 4 to day 8, patients in group 2 received letrozole (3.5–7 mg). Age, BMI, baseline FSH, and AFC were used to determine the dosage. From day 10 until the mature follicle was greater than 18 mm, TVS began collecting follicular monitoring data. The trigger was a single injection of HCG 10000 IU administered in the evening between 7 and 9 PM, and IUI was scheduled 36 to 38 hours afterwards.

Before IUI, transabdominal sonography was used to confirm ovulation. All patients received vaginal micronized progesterone 100 micrograms twice day as luteal support. 15 days after IUI, HCG was performed. Visualizing heart activity on TVS 15 days after positive HCG established a clinical pregnancy.

Clinical pregnancy rate in both groups was the main endpoint. Ovulation rate, the number of days from induction to ovulation, mono V/S multifollicular development, and endometrial thickness were secondary outcome majors.

Statistical Analysis

The statistical analysis used for this study was the chi-square and student's t tests. The mean and standard deviation were used to describe the results. P-values lower than 0.05 were considered significant.

Results

The following study was carried out with 160 patients, for medication of Clomiphene Citrate and Letrozole, each.

The demographics of two groups are shown in Table 1. Age, BMI, length of infertility, type of infertility, and reason of infertility among the two groups did not differ statistically significantly from one another.

Table 1: Demographic Characteristics in Two Groups

Demographic Characteristics	C C Group (N = 80)	LTZ Group (N = 80)	P – Value
Age (Years)	24.30 ± 1.55	25.00 ± 1.50	0.70
BMI (Kg/m²)	24.44 ± **2.11**	24.39 ± 3.18	0.83
Infertility Duration (Years)	2.36 ± 1.11	2.59 ± 1.33	0.71
Type of infertility			
Primary	53 (66.5%)	57 (71.5%)	0.49
Secondary	25 (31.5%)	21 (26.5%)	
Cause of infertility			
Mild PCOS	27 (34%)	29 (36.5%)	0.73
Male Factor	31(40%)	34 (42.75%)	0.62
Unexplained	19 (24%)	14 (17.75%)	0.34

Table 2 demonstrates that the clomiphene citrate group had a statistically substantially greater rate of multiple follicular formation (43.75% V/s 25%, P-0.012). Total days till ovulation and ET did not differ between the clomiphene citrate and letrozole group.

Table 2: Follicular Development, Days till ovulation and ET

Follicular Development and days till ovulation	C C Group (N = 80)	LTZ Group (N = 80)	P – Value
Mono-follicular Development	35(46.25%)	50 (65%)	0.0124
Multi-follicular Development	35(33.75%)	10 (15%)	0.011
Total Days of Ovulation	13.1±2.23	12.8 ± 1.80	0.52
ET (mm)	7.82 ± 1.02	8.02 ± 1.31	0.55

The ovulation rates are 71.25% in the clomiphene citrate group and 85% in the letrozole group in Table 3. (P - 0.035). Clinical pregnancy rates were 10% in the clomiphene citrate group and statistically significant 22.5% in the letrozole group (P - 0.032)

Table 3: Ovulation and Clinical pregnancy rate between two groups

-	C.C Group (N = 80)	LTZ Group (N = 80)	P- Value
Rate of Ovulation	56/22 (71.25%)	67/11 (85%)	0.034
Clinical Pregnancy rate	7/71 (9%)	17/61 (21.5%)	0.031

Discussion

Situations that requires controlled ovarian stimulation, such as mild PCOS, mild endometriosis, mild to moderate male factor, unexplained infertility, and IUI cycles, clomiphene citrate is still regarded as the first-line ovulation induction medication. [19-21] The main drawbacks of clomiphene citrate are endometrial thinning and inadequate cervical mucus, which account for its low success rate. 15% to 20% of PCOS cases exhibit clomiphene resistance. Letrozole is used as an alternate medication to clomiphene citrate in order to prevent these negative effects. It has the advantage of a quicker induction period, improved endometrial thickness and cervical mucus quality, monofollicular development, and a higher pregnancy rate. [22-25] Letrozole not only increases the amount of FSH secreted by the pituitary, but it also increases the sensitivity of follicles to FSH by amplifying the expression of the FSH receptor gene.

The total number of days from induction to ovulation in our study were 13.1 ±2.23 in the clomiphene citrate group and 12.8±1.80 in the letrozole group. Letrozole had fewer days, but the difference was statistically insignificant. This is comparable to the research done by Mitwally and Casper [16], who discovered that there was no significant difference between letrozole and clomiphene citrate in terms of total days until HCG (14.8±2.7 Vs. 14.2±2.1). In their investigation of PCOS patients, Sujata Kar et al. likewise discovered no difference (C.C.14.2±3.41 and LTZ 13.13± 2.99, P - 0.24) [14].

The mean ET in our study was 7.82 ± 1.02 for the clomiphene citrate group and 8.02 ± 1.31for the letrozole group. Additionally, it was marginally higher in the letrozole group, but not statistically significant (P - 0.55). This study was analogous to that of Jee et al.15 (LTZ 9.3 1.7 Vs C.C. 9.1 1.7, NS) and Abu Hashim et al. (LTZ 8.8 1.2, Vs C.C. 8.2 0.09, P - 0.53), which both showed a non-significant rise in ET on the day of HCG in the LTZ group. Although smaller than our investigation, Sujata kar et al. also discovered a somewhat higher ET in the letrozole group (7.65 2.1 Vs 7.61 1.96, P - 0.91) [14]. Studies by Akbari et al. (LTZ 9.08 1.2 Vs C.C. + HMG 8.1 1.9, P - 0.0001) [1] and Mitwally and Casper (LTZ 8.1 1.4 Vs C.C. 6.2 2.5, P - 0.01) established a link between letrozole and increased endometrial thickness [17]. Davar et al. found a nonsignificant rise in ET in the clomiphene citrate group (LTZ 6.9 2.2 Vs C.C. 7.8 1.8, NS) [26].

In our study, the difference between the ovulation rates for the letrozole and clomiphene citrate groups was 85%, which is statistically significant (P - 0.034). This is comparable to the study of M. Zeinalzadeh et al., which showed that the letrozole group had a greater ovulation rate (86% Vs 72%, P - 0.07) [25]. The ovulation rate was higher with letrozole in PCO patients according to Sujata Kar et al. (73.08% Vs 60.78%, P0.39) but not statistically significant [14]. Clomiphene citrate was reported to have a higher ovulation rate in studies by Bayar et al. (C.C. 74.7% Vs LTZ 65.7%) and Jawad et al. (C.C. 87.33% Vs LTZ 82.66%) [13].

In the trial by Bo Hyon et al., the clinical pregnancy rate was comparable and greater in the clomiphene citrate group (18.3% Vs 12.2%, p - 0.177), however gonadotropins were also utilised in both groups [24]. In the studies by Sammour et al. (LTZ - 16.7% Vs C.C. 5.6%, P - 0.55), Fozan et al. (LTZ 11.5% Vs C.C. 8.9%) [2], and CPR was quite low but comparable. [27]

In our study, clomiphene citrate group multifollicular growth was statistically considerably higher than letrozole group (C. C. 33.75% Vs LTZ 15%, P - 0.11). In the studies by Abu Hashim et al. (2.8 0.04 Vs 1.4 0.02, P - 0.042) [11] and Badaway et al. 21 (3.1 0.36 Vs 1.6 0.41, P - 0.045), the total number of follicles was larger in the clomiphene citrate group than in the LTZ group [4].

While most studies revealed equal pregnancy rates in both groups following IUI, the clinical pregnancy rate in our study was significantly greater in the letrozole group as compared to the clomiphene citrate group (21% Vs 19%, P - 0.031%).

Conclusion

Improved endometrial thickness, cervical mucus, mono follicular development, and a higher ovulation rate are the outcomes of LTZ's pharmacodynamics (does not deplete oestrogen receptor, has a short half-life, and intact hypothalmopitutary axis).

As a result, letrozole group in our study has a greater clinical pregnancy rate. Although more extensive research is required to prove it, letrozole is a superior first-line treatment for super ovulation in IUI cycles when compared to clomiphene citrate.

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