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Original Research Article

A study of comparison of effectiveness of letrozole (5mg) versus Clomiphene citrate (100 mg) for ovulation induction among infertile women

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ABSTRACT

Introduction: Clomiphene citrate has been traditionally used as the drug of the choice for treatment of women with anovulatory infertility. In the last decade, an aromatase inhibitor, letrozole has emerged as an alternative ovulation induction agent among anovulatory women with polycystic ovarian syndrome. Letrozole has a definitive role in anovulatory women who have not responded to the clomiphene citrate therapy is confirmed by literatures.

Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility and among causes; PCOS (polycystic ovarian syndrome) is the leading cause.

Clomiphene citrate is considered as the drug of choice for the first line treatment of anovulatory dysfunction for a variety of reasons. Clomiphene citrate has some side effects like multi-follicular development and cyst formation and resistance of clomiphene are areas of concern and desire for an effective alternative persists. An aromatase inhibitor, letrozole, was introduced into infertility practice in the year 2000 and is regarded as a second line option, particularly in women with clomiphene resistance^{1,2} and it has found acceptance in various clinical situations and the indications for use have expanded.^{3,4}

Aim & Objective: To compare the efficacy of letrozole and clomiphene citrate (CC) for ovulation induction in infertile women.

Materials and Methods: The study included 100 women presented with anovulatory infertility. The infertile women were divided into 2 groups of 50: Group A received 100 mg Clomiphene Citrate from day 3 to day 5 and continue up to 5 consecutive days of menstrual cycle, Estradiol Valerate 4 mg on the 12th day of menstruation until 16th day of menstruation; Group B treated by 5 mg Letrozole from day 3 to day 5 of the menstruation and continue up to 5 consecutive days as Group A, Estradiol Valerate 4 mg on the 12th day of menstruation until 16th day of menstruation given to Group B, with visits to determine ovulation and pregnancy, followed by tracking of pregnancies. Participants were of 20 to 39 years age, had normal uterine cavity and had a male partner with a sperm concentration of at least 14 million per millilitre; and during the study the women and their partners agreed to have regular intercourse with the intent of conception. The live birth during the treatment period was the primary outcome.

Results: Women who received letrozole had more cumulative live births than those women who had received clomiphene citrate (36 out of 50 [72%] vs. 28 out of 50 [56%]), without significant differences in overall congenital anomalies, there were no congenital anomalies. With letrozole as compared to clomiphene the cumulative ovulation rate was higher. Higher incidence of hot flushes was associated with a clomiphene, and letrozole was associated with fatigue and dizziness. Rates of other adverse effects were almost similar among these 2 groups. A significant difference in the follicular and endometrial development was evident among these 2 groups.

Conclusion: Compare to clomiphene, an aromatase inhibitor, letrozole was associated with higher live-birth and ovulation rates among infertile women. The results of the study demonstrated letrozole is superior to clomiphene citrate in the maintenance of endometrial thickness.

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1. Introduction

Millions of women of reproductive age are affected by infertility worldwide. In India approximately 8% of currently married women suffered from infertility. Most of them (5.8%) are secondary infertile.

For infertility, PCOS (Polycystic ovarian syndrome) is the most common female endocrine disease and a frequent cause.⁵ Characteristics of PCOS are anovulation, clinical or biochemical hyperandrogenism and presence of polycystic ovaries.⁶ In the fertile age, it affects 5% to 10%,^{7,8} while as per recent studies reporting even higher rates.⁹ Ovulation induction is the cornerstone for treatment of women with PCOS suffering from infertility, because about 80% of women with PCOS have anovulation or oligo-ovulation.¹⁰

Clomiphene citrate (CC) belongs to a selective estrogen receptor modulator drug classification, has traditionally been used as the drug of first-choice for ovulation induction or superovulation in women with PCOS.¹¹ CC has an anti-estrogenic effect, which results in estrogen receptor (ER) depletion, and has long half-life; therefore it accumulates in the body causing long lasting ER depletion.¹² It has been a relatively effective medicine, in general. CC lasts for a long time in the body and may due to it have an adverse effect on cervical mucus and uterine lining, such as endometrial proliferation leading to thinning of endometrium. The endometrial thickness is one of the most important factors affecting pregnancy. The pregnancy rate can be very low, if endometrial thickness is less than 6-8 mm.¹³ Clomiphene citrate is one of the treatment modalities which reduce endometrial thickness,¹⁴ so we should adjust endometrial thickness and proliferation during induction of ovulation to avoid this. In such groups of patients, such as women with PCOS, do not respond well to clomiphene citrate.

Letrozole is an aromatase inhibitor, has also been recommended as a first-line drug therapy for improvement of the fertility outcomes in women with PCOS.^{5,15} Aromatase is an enzyme which is responsible for the production of estrogen in the body. Letrozole works by inhibiting aromatase by completely binding to it, which results in a reduction of estrogen biosynthesis in all the tissues.¹⁶ Mechanism of action of the letrozole is depicted in Figure 1. It has a short half-life, thereby it rapidly eliminated from body within 42 hours, with less risk of ovarian hyperstimulation.¹⁷ On the other hand, clomiphene citrate blocks estrogen receptors. As a result, pituitary gland produces more of hormones which are needed to stimulate the ovaries. FSH and LH, these hormones can cause the development of ovulation in women who are anovulatory or increase the number of eggs developing in ovaries of women who already ovulate.¹⁸ Letrozole offers significantly better endometrial response compared to clomiphene citrate.

Letrozole, clomiphene citrate like fertility drugs can be used to induce an ovum to develop and to be released in women who are not ovulating on their own. This is known as ovulation induction. For increasing the chances of pregnancy in women who are already ovulating, these drugs can be used; which is known as superovulation. As per study done by Wang et al., the network meta-analysis showed that letrozole is the only treatment showing a significant higher rate of live birth, as compared with CC alone.¹⁹ While ovarian stimulation in women with an unexplained infertility aims to achieve multi-follicular growth, in women with an anovulation who are undergoing ovulation induction, mono-follicular growth is thought to be sufficient.²⁰ In order to study the effectiveness and safety of different ovulation induction protocols with less side effects and higher pregnancy rates in women with PCOS treated with clomiphene citrate and letrozole to assess the impact of mono- versus multi- follicular growth, we compared the live pregnancy rates among women with who had ovulation induction with CC and letrozole in a Scientific Research Institute, Surendranagar, Gujarat, India.

Here are some recommendations of different societies for letrozole as a 1st line treatment option in ovulation induction: As per American College of Obstetrics and Gynaecologists²¹ (2016) society, letrozole should be considered as 1st line therapy for OI in patients with PCOS and BMI >30 because of increased live birth rate(LBR) compared to clomiphene citrate; as per Australian National Health and Medical Research Council (NHMRC) guidelines²² (2015), letrozole, under caution, could be offered as pharmacological treatment for OI indicated for infertile anovulatory women with PCOS with no other infertility factors.

2. Materials and Methods

2.1. Study oversight

We previously reported the trial rationale and a detailed protocol summary of study participants, as well as study methods and the full baseline characteristics of the study participants. Letrozole, an aromatase inhibitor, was under an Investigational New Drug application (number 101,671) to the Food and Drug Administration (FDA). Enrolment began in October 2019 and was completed in October 2021. All the data entry, data management, and analyses are performed at the Scientific Research Institute, Surendranagar, and Gujarat, India.

2.2. Patients

A total of 100 infertile women of 20 to 39 years age who had no major medical disorders and who were not taking confounding medications (other fertility drugs, sex steroids, insulin sensitizers, as described in study protocol), their male partners, and their neonates also participated in the

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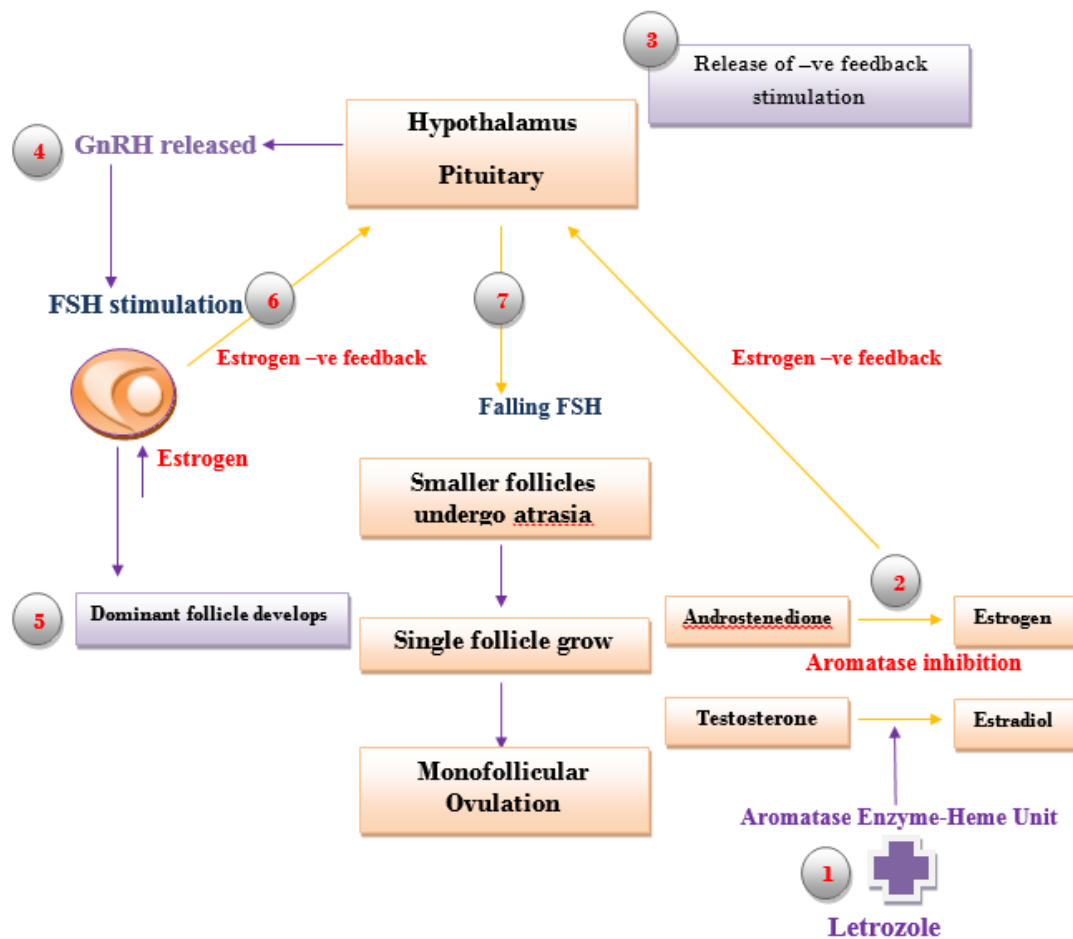


Fig. 1: Mechanism of action of Letrozole

study. Additional eligibility criteria include a normal uterine cavity, or evidence of an intrauterine pregnancy within previous 3 years; a male partner with a sperm concentration of at least 14 million/millilitre, according to World Health Organization cut-off points with the documented motility, in at least one ejaculate during the previous year and a commitment on the part of women and their partners to have a regular intercourse during the study with the intent of pregnancy.

2.3. Design

Randomized double-blind study.

2.4. Setting

Scientific Research Institute, Surendranagar, Gujarat, India and a private practice setting.

2.5. Main outcome measures

Follicular growth, endometrial thickness, pregnancy.

2.6. Exclusion criteria

1. Patients with hyperprolactinemia
2. Thyroid disorder
3. Male factor infertility
4. Suspicious or known tubal factor infertility (endometriosis and pelvic inflammatory disease)

2.7. Study overview

Total 100 women were randomly assigned and divided into 2 groups of 50. 1 group was given clomiphene citrate (100 mg daily) and another group was given; letrozole (5 mg daily), started from day 3 to day 5 of the menstrual cycle and up to 5 consecutive days (Table 1).

This is followed by giving Estradiol Valerate 4 mg on the 12th day of menstruation until 16th day of menstruation in both groups. Couples were instructed to have a regular intercourse two to three times a week. Participants who conceived were followed until a viable intrauterine pregnancy was observed (on ultrasonography-fetal heart motion visualized) and prenatal care given to

Table 1: Treatment methods in study group

Letrozole group	Clomiphene citrate group
The patients were orally administered 5.0 mg/day Letrozole starting between the 3 rd to 5 th days of menstrual cycle for five consecutive days.	The patients were orally administered 100 mg/day Clomiphene Citrate starting between the 3 rd to 5 th days of menstrual cycle for five consecutive days.

them. Through the review of maternal and infant medical records, the outcomes were tracked.

2.8. Outcomes

Live birth during the treatment period was the primary outcome; secondary outcomes included ovulation, pregnancy loss, singleton birth, and congenital anomalies. The follicular development, growth and endometrial thickness were also calculated to see difference among the 2 groups.

3. Results

3.1. Characteristics of the patients

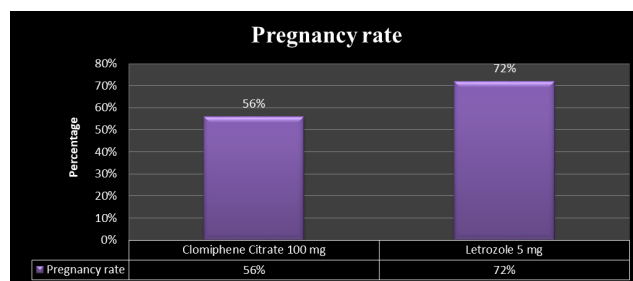
A total of 100 infertile women were randomly assigned to treatment group and they were divided into 2 groups; the 2 groups were well matched at baseline. Study participants are of age 20 to 39 years. Study began in October 2019 and was completed in October 2021.

3.2. Live births and secondary outcomes

Women who received letrozole as compared to those who received clomiphene citrate had more cumulative live births (36 of 50 [72%] vs. 28 of 50 [56%]) (Table 2). The ovulation rate was significantly higher with letrozole than with clomiphene citrate. Among the study participants who ovulated, there was a significantly greater chance of singleton pregnancy with letrozole compared to clomiphene citrate.

The mean number of dominant follicles (≥ 18 mm) was 1.4 ± 0.58 for letrozole and 1.1 ± 0.86 for clomiphene citrate (P -value = < 0.05). The significant difference in the follicular and endometrial development was evident between letrozole and clomiphene citrate treated cycles (Table 3).

The live birth rates after cycles induced with clomiphene citrate and letrozole were 56%, 72% respectively. Multiple pregnancies were recorded in 2 women who had given clomiphene citrate in whom 1 woman had twin pregnancy and another woman had triplet pregnancy; both women are delivered at term and babies are healthy; there were no maternal or neonatal complications present.

**Fig. 2:** Pregnancy outcomes and gestation rates with 2 ovarian stimulation treatment methods

3.3. Adverse effects and pregnancy and neonatal complications

Two adverse events related to ovarian-cyst formation occurred during infertility treatment: one with letrozole (a ruptured corpus luteum cyst) and one with clomiphene (ovarian cyst). Clomiphene citrate was associated with a significantly higher incidence of hot flushes and letrozole was associated with significantly higher incidences of fatigue and dizziness. The number of patients reporting side effects who had given letrozole are 3 and who had given clomiphene citrate are 6.

The most common neonatal complications were jaundice, respiratory distress syndrome, a condition requiring hospitalization for more than 3 days, and intrauterine growth restriction, without significant differences between treatment groups.

Letrozole was associated with a greater increase in endometrial thickness as compared with clomiphene citrate. The comparison of ovulation induction among clomiphene citrate and letrozole is given below:

4. Discussion

Since many years, clomiphene citrate is considered to be the first line therapy in women with infertility for ovulation induction. Clomiphene citrate has antiestrogenic effect as it induces prolonged estrogen receptors depletion with an estrogen target tissues especially endometrium. Several studies showed that clomiphene has a deleterious effect on endometrial development resulting in endometrial thinning, luteal phase effect, decreased uterine flow, and implantation failure. So we added Estradiol Valerate 4 mg on the 12th day of menstruation until 16th day of menstruation per oral to prevent detrimental effects of clomiphene on the endometrium.

This study showed that endometrial thickness was higher in letrozole group than clomiphene group. It is supported by previous studies carried by Hendawy et al.²⁶ in which they compared the effects of letrozole and clomiphene citrate on ovulation induction and the result was the letrozole had a better effect on endometrial thickness and pregnancy

Table 2: Outcomes regarding the ovulations, live birth and pregnancy

Parameters	Letrozole 5 mg	Clomiphene citrate 100 mg
No. of patients	50	50
Women who ovulated- number (%)	42 (84%)	39 (78%)
Live birth- number/total number (%)	36/50 (72%)	28/50 (56%)
Conception- number of women (%)	36 (72%)	28 (56%)

Table 3: Ovulation induction outcomes of letrozole and clomiphene citrate groups

Parameters	Letrozole 5 mg	Clomiphene citrate 100 mg	P value
Number of follicles \geq 18 mm	1.4 \pm 0.58	1.1 \pm 0.86	P<0.05
Size of follicular development by day 14 (mm)	17.6 \pm 2.92	15.8 \pm 3.84	P<0.05
Endometrial development by day 14 (mm)	7.2 \pm 0.77	6.8 \pm 0.92	P<0.05
Pregnancy (among ovulated patients)	36/50	28/50	-

Table 4:

Ovulation induction with Clomiphene citrate(CC) ^{23–25}	Ovulation induction with Letrozole ^{23–25}
Multi-follicular ovulation	Mono-follicular ovulation
Peripheral anti-estrogenic effect	No anti-estrogenic effect
Causes endometrial thinning	Better endometrial thickness
Thick cervical mucus	Better cervical mucus quality
Longer half-life of 5-7 days	Shorter half-life of 45 hours
Higher miscarriage rate	Improved implantation
Higher multiple pregnancy rate	Lower multiple pregnancy rate
High rates of resistance in PCOS	Effective in CC-resistant PCOS
Lower live birth rate	High live birth rate

rate than clomiphene citrate. Mitwally and Casper found that letrozole was associated with greater endometrial thickness¹⁷ when they give aromatase inhibitor (letrozole) to patients with anovulatory infertility, ovulatory infertility; all of them had previously received clomiphene with an inadequate outcome.

As per our study we found that letrozole was more effective drug as a fertility treatment than clomiphene citrate in women with infertility and polycystic ovary syndrome. After treatment with letrozole given to infertile women these factors were significantly more likely as compared with clomiphene citrate group: ovulation, conception, pregnancy, and live birth. The mean pregnancy duration and birth weight, and rates of neonatal complications did not differ significantly between treatment groups. Although multiple pregnancy (twins, triplets) rate was higher with clomiphene citrate.

In our study we used letrozole and clomiphene citrate for ovulation induction has been designated by FDA as pregnancy category X (although clomiphene is approved for ovulation induction). The live-birth rate was higher with letrozole than with clomiphene citrate among women with infertility and polycystic ovary syndrome in our study. In our study, we did not require a lifestyle intervention before enrolment; although such interventions are recommended by experts, but there is currently no evidence from high-

quality clinical trials that they improve pregnancy outcomes in obese women.²⁷

5. Conclusion

An aromatase inhibitor, letrozole, as compared to clomiphene, was associated with higher live-birth and ovulation rates among infertile women. The results of the study demonstrated letrozole to be superior to clomiphene citrate in the maintenance of endometrial thickness.

Clomiphene citrate has some drawbacks; including its overall poor efficacy (56% rate of live birth), a relatively high multiple pregnancy rate, and an undesirable side effect profile which includes mood changes and hot flushes. The important public health goal is to develop the effective, simple, and safe treatments for infertility.

Aromatase inhibitors, letrozole, which blocks estrogen synthesis, directly affect hypothalamic-pituitary-ovarian-uterine function and theoretically might increase pregnancy rates. Potential advantages of letrozole over clomiphene citrate include a more physiological hormonal stimulation of endometrium, a lower multiple pregnancy rate through single-follicle recruitment, a better side effect profile with lesser vasomotor and mood symptoms, and greater rapid clearance, thus reducing chances of periconceptional exposure.

6. Source of Funding

None.


7. Conflict of Interest

The authors declare no conflict of interest.

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