LETROZOLE VERSUS CLOMIPHENE CITRATE IN OVULATION INDUCTION IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME

Rajat Kumar Ray[1], Sunita Samal[2]

[1]Director, Ray Hospital and Test Tube Baby Centre, Rourkela, Odisha, India.
[2]Consultant, Department of Obstetrics and Gynaecology, Ray Hospital and Test Tube Baby Centre, Rourkela, Odisha, India.

ABSTRACT

BACKGROUND

Polycystic ovarian Syndrome (PCOS) is a chronic condition with manifestations that begin most commonly in adolescence with menstrual irregularity and hyperandrogenism, with a transition over time into problems including infertility and metabolic complications. It is the most common cause of anovulatory infertility & affects 12-21% of reproductive-aged women.

Clomiphene Citrate (CC) has been used for ovulation induction for decades as a first line treatment. Clomiphene has drawbacks, including its overall poor efficacy, a relatively high multiple-pregnancy rate and an undesirable side-effect profile. To overcome these side effects, Aromatase inhibitors like Letrozole were proposed as new ovulation-inducing drugs.

The aim of the study is to compare the efficacy of letrozole versus clomiphene citrate in ovulation induction in patients with PCOS.

MATERIALS AND METHODS

166 women with PCOS were enrolled in the study. They were randomly divided into group A receiving letrozole (84 patients) & group B receiving CC (82 patients). Patients in the letrozole group were started with 2.5 mg of letrozole daily for 5 days starting on day 2 of the cycle, whereas patients in the CC group were started with 100 mg of CC daily starting day 2 of the cycle for 5 days. The primary outcome measures were presence of ultra sonographically detected pregnancy. Secondary outcomes included ovulation, endometrial thickness on day of HCG.

Settings and Design- Randomised Control Trial.

Statistical Analysis- Data were statistically analysed using by Student's t test. Proportions were analysed using the chi-square test. Results were expressed as mean and standard error of the mean. $P<0.05$ was considered as a statistically significant difference.

RESULTS

There were no statistically significant differences between the two groups in age, duration of infertility, body mass index (BMI). The number of mature follicles was significantly lower in women who received letrozole, but the endometrial thickness, ovulation rates & pregnancy rates were significantly higher in the letrozole group than in the CC group. Pregnancy rates were 21% in letrozole group vs 9% in clomiphene group.

CONCLUSION

Letrozole is more effective than clomiphene citrate as a first-line drug for inducing ovulation in women with PCOS.

KEYWORDS

Clomiphene Citrate, Letrozole, PCOS.

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BACKGROUND

Polycystic Ovarian Syndrome (PCOS) is a chronic condition with manifestations that begin most commonly in adolescence with menstrual irregularity and hyperandrogenism, with a transition over time into problems including infertility and metabolic complications. It is the most common cause of anovulatory infertility & affects 12-21% of reproductive-aged women.

Pharmacological ovulation induction can be used to induce ovulation. However, for women with PCOS, there is a lack of clarity about the effectiveness and safety of ovulation induction agents and other costly infertility treatments such as surgical options or IVF.

The hypothalamic–pituitary axis has been the target of first-line ovulation-induction therapy. Clomiphene citrate, a selective oestrogen-receptor modulator that antagonizes the negative feedback of oestrogen at the hypothalamus with a consequent increase in ovarian stimulation by endogenous gonadotropin, has been used for this indication for decades as a first line treatment. It works centrally to affect ovulation. Clomiphene has drawbacks, including its overall

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Corresponding Author:
Dr. Rajat Kumar Ray,
Director, Ray Hospital and Test Tube Baby Centre,
#N-18, Civil Township,
Rourkela- 769004, Odisha, India.
E-mail: rajatkuray@gmail.com
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poor efficacy, a relatively high multiple-pregnancy rate and an undesirable side-effect profile, including mood changes and hot flushes, and the peripheral anti-estrogenic effects on the endometrium and cervical mucus.[1]

If ovulation cannot be achieved with CC, then the patient is said to have CC resistance. If pregnancy cannot be achieved after six ovulatory cycles with CC, then the patient is described as having CC failure. Clomiphene resistance occurs in 15% to 20% of patients.[2]

To overcome these side effects, Aromatase inhibitors (AIs) were first proposed as new ovulation-inducing drugs in anovulatory women in 2001.[3] AIs, unlike CC, do not affect oestrogen receptors centrally. The enzyme aromatase catalyses the conversion of androgens to oestrogens, specifically the conversion of testosterone and androstenedione to estradiol (E_2) and estrone, respectively in the ovary. Therefore, AIs inhibit oestrogen biosynthesis, releasing the hypothalamus/pituitary axis from the estrogenic negative feedback and increasing the secretion of FSH by the pituitary. As a result, the ovary receives increased FSH stimulation, allowing for greater follicular growth and development. In addition, androgens that are normally converted to oestrogens accumulate in the ovary and these androgens increase follicular sensitivity to FSH.[4] The most commonly used AIs in ovulation induction are letrozole and anastrozole, with letrozole being the most widely used. There is a more physiologic hormonal stimulation of the endometrium, a lower multiple-pregnancy rate through single-follicle recruitment, a better side-effect profile with fewer vasomotor and mood symptoms, and more rapid clearance.

Objective

We tried to compare the efficacy of letrozole versus clomiphene citrate in ovulation induction in patients with PCOS.

MATERIALS AND METHODS

A total of 166 women with PCOS enrolled in the study from January 2017 to December 2017 at Ray Hospital & Test Tube Baby Centre, Rourkela. They were randomly divided into group A receiving letrozole (84 patients) & group B receiving CC (82 patients).The diagnosis of PCOS was based on the Revised 2003 consensus Rotterdam diagnostic criteria for PCOS.[5] Accordingly, all participating women had polycystic ovaries, defined by (a) multiple small antral follicles of 2-9mm ≥12 in number, or (b) an increased individual ovarian volume of >10 cm^3 or both, (c) ovulatory dysfunction and/or(d) hyperandrogenism. All women had patent fallopian tubes proved by either hysterosalpingography, sonohysterography or laparoscopy. Husband's semen analysis parameters were within normal range. All patients had normal serum prolactin, thyroid-stimulating hormone (TSH) and 17-OH progesterone.

Patients in the letrozole group were started with 2.5 mg of letrozole daily for 5 days starting on day 2 of the cycle, whereas patients in the CC group were started with 100 mg of CC daily starting day 2 of the cycle for 5 days. All patients were monitored by transvaginal ultrasound for the mean follicular diameter and thickness of the endometrium starting from day 7 of the cycle. The serum estradiol (E_2, pg/mL) concentration was measured at the time of human chorionic gonadotropin (hCG) injection and serum progesterone (ng/mL) concentration was measured on days 21 to 23 of the cycle. The hCG injection 5000 IU intramuscular was given when at least one follicle reached a diameter of 17 mm. Patients were advised to have intercourse 24 to 36 hours after the hCG injection. TVS was done after 20 days of HCG injection for diagnosis of pregnancy.

The primary outcome measures were presence of ultrasonographically detected pregnancy. Secondary outcomes included ovulation, endometrial thickness on day of HCG.

Study Type

Randomised control trial.

Statistical Analysis

Data were statistically analysed using by Student's t test. Proportions were analysed using the chi-square test. Results were expressed as mean and standard error of the mean. P<.05 was considered a statistically significant difference. MEDCALC statistical software was used for calculation.

RESULTS

A total of 166 patients participated in the study, out of which 84 received letrozole & 82 received CC. Table 1 summarises the demographic characteristics. There were no statistically significant differences between the two groups in age, duration of infertility, body mass index (BMI). Table 2 summarizes the responses of the women in the two groups to ovarian stimulation. The number of mature follicles was significantly lower in women who received letrozole, but the endometrial thickness and ovulation rates were significantly higher in the letrozole group than in the CC group. The day on which hCG was given did not differ between the groups. 18 patients became pregnant in letrozole group with a pregnancy rate of 21%. Similarly, 7 patients became pregnant in Clomiphene citrate group with a pregnancy rate of 9%. There was a significant difference in pregnancy rates in between both groups. One twin pregnancy occurred in the CC group.

	Group A	Group B	p-value
Age (years)	25.6 ±1.1	26.1 ± 0.9	NS
Duration of Infertility (years)	2.6 ± 0.7	2.4 ± 0.9	NS
BMI(kg/ m2)	26.2 ± 1.67	25.6 ± 1.77	NS

Table 1. Demographic Characteristics

	Group A	Group B	p- value
No. of follicles ≥17 mm on day of HCG	1.2 ± 0.61	2.4 ± 1.13	<0.0001
Endometrial thickness (mm)	8.6 ± 1.8	5.4 ± 1, 2	<0.0001
Ovulation (%)	82	63	0.0062
Pregnancy (%)	21	9	0.0312

Table 2. Response to Ovarian Stimulation

DISCUSSION

Clomiphene citrate initiates ovulation by blocking the negative feedback of endogenous oestrogen at the level of hypothalamus and pituitary, promoting an increase in the pulsatile release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in anovulatory PCO patients. For many years, the first treatment of choice for ovulation induction in PCO patients has involved the use of CC, but up to 55% of such patients are resistant to CC and do not ovulate It has also been demonstrated that CC has an antagonistic effect on the endometrium and may reduce endometrial thickness. Furthermore, CC may block oestrogen receptors in the cervix, producing a negative effect on the quality and quantity of cervical mucus. There is therefore a discrepancy between the ovulation and conception rates associated with CC use. Alternatives to clomiphene citrate such as letrozole have been used for ovulation induction, but it has not been clear whether these alternatives are as effective as CC for inducing ovulation, especially in PCOS.

In our study, we found a smaller number of follicles of >16mm on day of HCG in the letrozole group compared with clomiphene group. Clomiphene citrate results in central oestrogen receptor depletion for a lengthy time because of its greater half-time for clearance (2 weeks). As a result, supraphysiologic levels of oestrogen can occur without central suppression of FSH because the normal oestrogen receptor–mediated feedback mechanisms are blocked. This results in multiple follicle growth. Letrozole acts by decreasing the conversion of androstenedione and testosterone to oestrogen in the ovary. The decrease in circulating oestrogen increases gonadotrophin secretion. Multiple developing follicles appear on day 7 but, because letrozole does not deplete oestrogen receptors, unlike CC, normal negative feedback occurs centrally as the dominant follicle grows and oestrogen levels increase. This results in FSH suppression and atresia of smaller follicles, and mid-cycle mono-ovulation occurs in most patients. Mono-ovulation is the major advantage of using aromatase inhibitors for ovulation induction. A drug that consistently results in a single ovulation is particularly desirable in patients with PCOs, who are often hyper responsive to gonadotrophins.

We had a twin pregnancy in CC group, but no multiple pregnancy in letrozole group. The findings of our study can be explained by multiple follicle growth resulting in higher multiple pregnancy rates with CC than are found in letrozole cycles.

Aromatase inhibitors do not have negative effects on endometrial thickness or cervical mucus.

A double-blind, randomized trial comparing the use of an aromatase inhibitor with CC for ovarian stimulation in 49 women with unexplained infertility found that patients receiving the aromatase inhibitor had increased endometrial thickness compared with those receiving CC.[6]

Another well-designed study comparing CC with letrozole in patients with PCOs, letrozole produced a significantly thicker endometrium on the day of hCG administration and no apparent adverse effects on the endometrium were seen with letrozole treatment.[7] We also found thicker endometrium in letrozole group in our study. The meta-analysis for ovulation rate per patient demonstrated a higher ovulation rate per patient with letrozole.[8] We also observed a higher ovulation rate (82% vs. 63%) in letrozole group.

Cortinez et al[9] found normal morphologic features of endometrium and full expression of pinopodes during the implantation window when letrozole was used. This may contribute to increase in implantation & pregnancy rates. Another study suggests that letrozole is associated with a higher pregnancy rate in PCO patients than CC.[10] Another study found that letrozole was more effective as a fertility treatment than clomiphene in women with the polycystic ovary syndrome. Ovulation, conception, pregnancy, and live birth were significantly more likely after treatment with letrozole.[11] In our study the pregnancy rate in letrozole group was 21% in comparison to 10% in Clomiphene citrate group. Our study correlates with the findings of the above studies.

CONCLUSION

Letrozole is more effective than clomiphene citrate as a first-line drug for inducing ovulation in women with PCOS.

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