Faridpur Med. Coll. J. 2020;15(2):69-73

Original Article

Efficacy and Side Effects of Letrozole Over Clomiphene citrate for Ovulation Induction of the Patients with PCOS: A Randomized Controlled Trial

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Abstract:

Clomiphene citrate (CC) has been the drug of choice for the treatment of anovulatory subfertility in women with polycystic ovarian syndrome (PCOS) for a long time. Despite high ovulation rate of CC, its pregnancy rate is low. Letrozole, an aromatase inhibitor has been considered as an alternative of CC but its effectiveness is yet controversial. Our aim was to compare the efficacy and side effects of Letrozole over CC. This randomized control clinical trial was conducted in Diabetic Association Medical College and Hospital, Faridpur, Bangladesh from January 2018 to December 2019. A total of 160 women diagnosed as PCOS by Rotterdam criteria seeking treatment of subfertility were included in the study. Participants were randomly divided into two groups. Group A got Letrozole and Group B got CC as treatment. Transvaginal ultrasonogram (TVS) was performed on 12 to 13th day of the cycle to see the details of the follicles and the endometrium. The demographic information of the participants and the side effects of the drugs were recorded. Successful pregnancies were followed up for 12 weeks. Ovulation rate was almost similar among the participants of both of the groups. But monofo licular development and pregnancy rate were significantly higher among the Letrozole group ($p = 0.004$ and $p = 0.008$ respectively). Multifo licular development, multiple pregnancy, and abortion rate were significantly higher in the CC group. Patients who took Letrozole had significantly higher endometrial thickness than CC group. Both of the groups reported relatively similar incidence of side effects. Due to the higher pregnancy rate and lower incidence of abortion or multiple pregnancy, Letrozole can be an effective alternative to CC for the treatment of anovulatory subfertility of the PCOS patients.

Key words: Letrozole, Clomiphene citrate, Polycystic ovarian syndrome, Ovulation induction.

Introduction:

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder of the women in reproductive age and it is the most common cause of anovulatory infertility in young adults[1-4]. Nearly 40% of women with subfertility are diagnosed with PCOS[1,5]. Subfertility in women with PCOS results from oligoovulation, diminished oocyte competence, unfavorable endometrial changes, and obesity[4,6]. Treating subfertility in patients with PCOS is done by ovulation induction either by medication or surgery[7]. The most popular choice of medications for ovulation induction is Clomiphene citrate (CC) and Letrozole.

CC is a selective estrogen receptor modulator (SERM) and is the most common medication used for ovulation induction since its introduction in 1960 by the World Health Organization (WHO). It has been the first-line drug for treating sub-fertile women ever since[8]. On the plus side, CC is given orally, relatively safe, and inexpensive. But on the down-side, it causes negative changes in endometrium and cervical mucus. It may impair implantation in spite of successful induction of ovulation. Ultimately it leads to a discrepancy between ovulation and conception rate[8-10]. It has been observed that per cycle, CC results in a 60%-85% ovulation rate but its pregnancy rate is only 10%-20%[11,12].

Letrozole is a non-steroidal aromatase inhibitor introduced for ovulation induction in 2001 by Mitwally and Casper[13]. It acts by decreasing the conversion of androstenedione and testosterone to estrogen in the ovary[14,15]. It has a short half-life and the elimination time of Letrozole is 48 hours. As a result, Letrozole has fewer adverse effects on endometrium and cervix and is usually cleared out of the system before the

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implantation takes place[8,16-18]. Since its introduction, many clinical trials have been done to find out the effectiveness of Letrozole as ovulation induction medication. Although the outcome data vary, it has been found that Letrozole might be as effective as CC specially in women with failure or resistance to CC[8,19]. Besides, Letrozole has a low risk of multiple ovulation and ovarian hyperstimulation syndrome (OHSS) compared to CC[8,9,20].

However, in 2005, Dr. Marinko Biljan reported that they had found congenital anomalies in 150 babies born from women treated with Letrozole[21,22]. But subsequent larger studies did not find any higher risk for congenital anomalies in the infertile group treated with Letrozole compared with CC[22,23].

As the evidence for and against safety had been controversial over the last decade, randomized control trials are necessary for further understanding of the efficacy and safety margins of Letrozole and CC. In this study, we aimed at comparing the efficacy and adverse effects of these two drugs by a randomized control trial among the women seeking treatment of subfertility resulted from PCOS. Better population-based understanding of the effectiveness and adverse effects of these drugs might help the health care provider select the first-line drug for treating such patients.

Material and Methods:

This randomized controlled clinical trial was conducted at Diabetic Association Medical College and Hospital, Faridpur, Bangladesh, between January 2018 and December 2019. During this period, PCOS patients were sorted out based on the Rotterdam criteria[24] among the women attended for treatment of subfertility.

Women aged <20 years and >35 years, diagnosed with secondary infertility, having abnormal serum prolactin and thyroid stimulating hormone (TSH) level, abnormal husbands' semen analysis report, or having different medical and surgical conditions such as uterine fibroid, ovarian cyst, pelvic endometriosis, impaired hepatic or renal function, history of hypersensitivity to study drug were excluded from the study.

The study purpose and procedures were explained to all eligible women with PCOS and those who gave written informed consent were enrolled in the study. A total of 160 women who gave consent to participate in the study were allocated into two groups. Randomization was done by a computer-generated randomization plan and each enrolled subject was allocated the next available number of the randomization sequence.

Group A (Letrozole group, *n* =80) was given Letrozole (Letrol; Renata Limited, Bangladesh) 2.5 mg/day from day 2 to day 6 of the menstrual cycle for 3 cycles. Group B (CC group, *n* = 80) was given Clomiphene citrate (Ovulet; Renata Limited, Bangladesh) 100 mg/day from day 2 to day 6 of the menstrual cycle for 3 cycles.

Transvaginal ultrasound (TVS) was performed on day 12 to day 13 of the cycle. During scanning, the number and size of follicles, and the endometrial thickness were recorded. Human chorionic gonadotropin (5,000 IU) (HCG; Popular Pharmaceuticals Ltd., Bangladesh) was given intramuscularly when at least one mature follicle was ≥18 mm in diameter.

Demographic information collected included patient's age, duration, and type of infertility, BMI, medical and surgical histories. Outcome measures were the number of mature follicles, ovulation rate, endometrial thickness, and pregnancy rate. All side effects of the drugs were recorded in a standard questionnaire during the study period. Successful pregnancies were followed up for 12 weeks.

Data were analyzed using GraphPad Prism version 8.4.0 for Mac (GraphPad Software, San Diego, California, USA). Qualitative data were described in the form of number of cases and percentages. Student's t-test and Chi-squared tests were done for analysis of numerical variables and categorical data respectively. *p* value <0.05 was considered statistically significant.

Prior ethical clearance was taken from the institutional review board (IRB) of Diabetic Association Medical College and Hospital.

Results:

A total of 160 PCOS patients with subfertility were included in the study. Participants were randomly divided into two groups: Group A (n= 80) received letrozole (2.5 mg/day) and Group B (n= 80) received CC (100 mg/day).

The demographic characteristics of the study participants are shown in Table I. There were no significant differences between participants of both groups concerning age, BMI, and duration of subfertility.

Table I: Demographic characteristics of the study group

Variable	Group A (Letrozole group, *n* = 80)	Group B (CC group, *n* = 80)	*p* value
Age (years)	29.3 ± 3.1	29.5 ± 2.1	0.633
BMI (kg/m^2)	28.4 ± 1.9	28.1 ± 1.2	0.234
Duration of subfertility (years)	3.3 ± 0.9	3.5 ± 0.8	0.139

Values are expressed as mean ± SD
BMI:Body mass index

On subsequent follow-up by TVS, we found that there was no significant difference in ovulation rate among the Letrozole or CC groups. However, the pregnancy rate was significantly higher in the Letrozole group. Multifollicular development and multiple pregnancy rate were significantly higher in CC group (p = 0.023 and p = <0.001 respectively). On the other hand, monofollicular development and endometrial thickness were significantly higher in the Letrozole group (p = 0.021 and p = <0.001 respectively). Table II shows the outcome of ovarian stimulation in both groups.

Successful pregnancies were followed up till twelve weeks. During this period, abortion rate was significantly higher in CC group (p = <0.001). None of our patients in either of the group had ectopic pregnancy or OHSS. However, 13.7% of patients in Letrozole group and 18.7% of patients in CC group complaint of gastrointestinal symptoms such as nausea, vomiting, abdominal distension, abdominal pain, constipation, flatulence, and stomach discomfort. Among the other side effects, both of the groups had an almost equal incidence of hot flashes, fatigue and generalized malaise, dysmenorrhea or cramps, and breast tenderness or pain. Table III shows the unwanted outcomes in both groups.

Table II: Outcome of ovarian stimulation

Variable	Group A (Letrozole group, *n* = 80)	Group B (CC group, *n* = 80)	*p* value
Ovulation rate	50/80 (62.5%)	47/80 (58.8%)	0.627
Monofollicular development	53/80 (66.3%)	35/80 (43.7%)	0.004
Multifollicular development	26/80 (32.5%)	45/80 (56.2%)	0.002
Endometrial thickness (mean ± SD)	9.3 ± 0.4	6.2 ± 0.2	<0.001
Pregnancy rate	37/80 (46.3%)	21/80 (26.3%)	0.008
Multiple pregnancy rate	1/37 (2.7%)	5/21 (23.8%)	0.011

Values are expressed as n/n (%)

Table III: Unwanted outcomes

Variable	Group A (Letrozole group, *n* = 80)	Group B (CC group, *n* = 80)	*p* value
Abortion rate (till the end of 12th week)	1/37 (2.7%)	4/21 (19.0%)	0.033
Ectopic pregnancy	0/37 (0%)	0/21 (0%)	NA
OHSS	0/80 (0%)	0/80 (0%)	NA
Gastrointestinal side effects	11/80 (13.7%)	15/80 (18.7%)	0.391
Hot flashes	3/80 (3.7%)	4/80 (5.0%)	0.699
Fatigue	5/80 (6.2%)	6/80 (7.5%)	0.754
Dysmenorrhea or cramps	10/80 (12.5%)	8/80 (10.0%)	0.616
Breast tenderness or pain	9/80 (11.2%)	12/80 (15.0%)	0.322

Values are expressed as n/n (%)
OHSS:Ovarian hyperstimulation syndrome

Discussion:

Polycystic ovarian syndrome is one of the main endocrine causes of subfertility[4,25]. Clomiphene citrate has been the first line treatment for treating anovulatory subfertility since 1960s[9,26]. Due to several changes in the endometrium caused by CC and CC resistance, low rate of pregnancy occurs in spite of higher rates of ovulation[13,27,28]. Letrozole, a third-generation aromatase inhibitor has been introduced as a good alternative but its efficacy and side effects are still controversial.

In our study, we have randomly divided 160 patients diagnosed with PCOS seeking for treatment of subfertility in 2 groups. One group got CC and another group got Letrozole as treatment for ovulation induction. Demographically, there were no significant differences between the participants of both groups.

We performed TVS on day 12 to 13 of the cycle and we didn't find any significant difference in ovulation rate among the Letrozole and CC group (p = 0.627). In a review in 2013, Kar had also found that there was no statistical difference of ovulation rate per cycle between women taking Letrozole or CC[22].

However, we found that the thickness of the endometrium was significantly higher in Letrozole group than CC group (p = <0.001). In a study by Bayar et al. have found that some of the participants of CC group had endometrial thickness <5 mm but none of the participants in Letrozole group had endometrial thickness <5 mm[29]. Mitwally and Casper have also found significantly higher endometrial thickness in women treated with Letrozole compared with women treated with CC[13].

Although the ovulation rate among both groups had no significant difference, pregnancy rate was significantly higher in Letrozole group (p = 0.008). In several other similar studies done by Ibrahim et al, Legroet al and others have also found that pregnancy rate was significantly higher among the women in Letrozole group[30,31].

We have found that multifollicular development and incidence of multiple pregnancy was significantly higher in the CC group. Badawy et al and others have also found higher multifollicular development in CC group compared to Letrozole group[19,30,32].

As we followed up the pregnancy until twelve weeks, we have found that abortion rate was significantly higher in the CC group. In a study done by Ibrahim et al. followed up pregnancy till eight weeks and similarly, they have found that abortion rate was higher among the women who took CC[30]. However, in a study done by Legro et al found no significant difference in pregnancy loss between these two groups[31].

In our study, women in the CC group had more gastrointestinal symptoms compared to the women in the Letrozole group. At the same time, the incidence of hot flashes, fatigue, breast tenderness, or pain was higher among the women in the CC group, but the incidence of dysmenorrhea or cramps was higher among the Letrozole group. But none of the side effects was statistically significant difference among the two groups. None of the women in either of the groups developed ovarian hyperstimulation syndrome or had an ectopic pregnancy in our study.

A study done by Legro et al among 750 women had found that CC had a higher incidence of hot flushes whereas Letrozole had a higher incidence of fatigue and dizziness. Other adverse effects were almost similar in two groups[31].

Comparing both groups, Letrozole shows promising effectiveness as fertility treatment and a potent alternative to CC for the treatment of anovulatory subfertility. Further study with larger numbers of participants might help clarify the efficacy and safety of Letrozole over CC.

Conclusion:

Letrozole can be an effective alternative to CC for the treatment of anovulatory infertility. Letrozole offers a higher pregnancy rate and a greater likelihood of singleton pregnancy. It can be the choice of drug for the treatment of subfertility in women with polycystic ovary syndrome.

Conflict of interest: None

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