Faridpur Med. Coll. J. 2018;13(2):78-81

Original Article

Letrozole or Clomiphene Citrate for Induction of Ovulation in Patients with Polycystic Ovarian Syndrome: A Prospective Randomized Trial

D Zeba[1], R Biswas[2], K Fatema[3], MA Khair[4], F Zesmin[5], J Sharifa[6]

Abstract:

Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder responsible for subfertility in young women. The aim of the study was to compare the efficacy of Letrozole over Clomiphene citrate (CC) for ovulation induction in patients with PCOS. It was a prospective randomized trial in a private practice setting. The study period was 3 years, which includes 240 sub fertile patients with PCOS. Patients were divided into two groups. Group-A: 120 patients got Letrozole (2.5 mg) tab, 2 tabs once daily from D_2-D_6 for 3 cycles. Group-B: 120 patients took tab. Clomiphene citrate (50mg), 2 tabs once daily from D_2-D_6 for 3 cycles. Trans-vaginal ultrasound was done on D_{12}-D_{13} to document number of follicles, measurement of dominant follicle and endometrial thickness. Ovulation and pregnancy rate was measured. Results showed that Letrozole have significantly better effect on endometrial thickness (Let 9.2 mm vs CC 8.1 mm) and pregnancy rate (Let 44% vs CC 24%). In CC, multiple follicles were found (CC 44% vs Let 30%). Ovulation occurred in 65% with Letrozole group and 64% in CC group without a significant statistical difference. The study concluded that Letrozole have better effect for induction of ovulation in PCOS patient in comparison to CC.

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

Introduction:

Polycystic Ovarian Syndrome (PCOS) is one of the most common causes of subfertility in young women. The precedence of PCOS in subfertility is about 30-40%[1]. PCOS is a common endocrine disorder which is closely related to ovarian dysfunction. It is about 7%[2].

In 2003, a consensus panel established a definition (the Rotterdam criteria) for PCOS which includes at least 2 of the following criteria: oligo-anovulation, hyperandrogenism (laboratory confirmed or clinical symptoms), or polycystic ovaries on ultrasound [12 or more follicles measuring 2-9mm in diameter or increased ovarian volume more than 10cm^3]. Ovulation induction is the way to treat infertility in PCOS which can be done by medication or surgery[2].

Clomiphene citrate (CC) is the most commonly used first line treatment for induction of ovulation. It is a non-steroidal selective estrogen receptor modulator that has predominant anti-estrogenic action resulting in long lasting estrogen receptor depletion[4]. CC has a negative effect on the cervical mucus and endometrium, leading to discrepancy between ovulation and conception rate[5]. It is known that CC results in ovulation rate 60-80% but a conception rate of only 20%[6]. CC has side effects like multi-follicular development, hyperstimulation syndrome and cyst formation. For these reasons, an effective and alternative ovulation inducer was a desire[7].

Letrozole is a potent, non-steroidal, aromatase inhibitor acts by decreasing the conversation of androstenedione and testosterone to estrogen in the ovary[8]. This decrease in circulating estrogen increases gonadotropin secretion. Multiple developing follicles appear from day 7, but as Letrozole does not deplete estrogen receptors, normal negative feedback occurs centrally. So, dominant follicle grows and estrogen level increases. This results in follicle stimulating hormone suppression and atresia of smaller follicles[9]. As a result,

1. Dr. Dilruba Zeba, MBBS, DGO, MCPS, FCPS (Gynae &Obst), Associate Professor, Department of Gynae and Obst, Faridpur Medical College, Faridpur.

2. Dr. Rajib Biswas, MBBS, MBGPH, Project Research Physician, ICDDR, B.

3. Dr. Kaneez Fatema, MBBS, MS (Gynae & Obst), Associate Professor, Department of Gynae and Obst, Faridpur Medical College, Faridpur.

4. Dr. Md. Abul Khair, MBBS, MS (Urology), Assistant Professor, Department of Urology, Faridpur Medical College, Faridpur.

5. Dr. Fahmida Zesmin, FCPS (Gynae & Obst), Assistant Professor, Department of Gynae and Obst, Faridpur Medical College, Faridpur.

6. Dr. Jesmin Sharifa, FCPS (Gynae & Obst), Resident Surgeon, Department of Gynae and Obst, Faridpur Medical College, Faridpur.

Address of correspondence :
Dr. Dilruba Zeba, MBBS, DGO, MCPS, FCPS (Gynae & Obst), Associate Professor, Department of Gynae and Obst, Faridpur Medical College, Faridpur, Bangladesh. Phone: +8801712090825, E-mail: dilruba_zeba@yahoo.com

mono ovulation occurs in most patients in comparison to CC. Letrozole has no anti estrogenic effect and due to its shorter half-life, pregnancy rate is higher[10].

Letrozole was originally used for postmenopausal breast cancer therapy[4]. There are some recent trials showing the higher efficacy of Letrozole may be taken as a possible replacement for CC for the first line treatment of anovulatory infertility especially in PCOS[11]. The aim of this study was to compare the effect of Letrozole versus Clomiphene citrate (CC) for induction of ovulation in polycystic ovarian syndrome (PCOS) patients.

Materials and Methods:

It was a prospective randomized trial in a private practice setting of Faridpur, Bangladesh. Study period was from 01.01.2015 up to 31.12.2017 (3 years). Among the patients who attended for subfertility, PCOS patients were first selected on the basis of Rotterdam criteria[3]. The study included 240 women with PCOS. Patients of age between 30-35 years, primary subfertility, no conception for at least one year, normal serum prolactin and thyroid stimulating hormone (TSH) level, normal husbands' semen analysis according to WHO criteria (2010) were included. Patients of age <20 years and >35 years, uterine fibroid, ovarian cyst, pelvic endometriosis, impaired hepatic or renal function and history of hypersensitivity to study drug were excluded from the study. Patients were divided into two groups with randomized sheet.

Group A: Included 120 patients taking Letrozole (2.5 mg), 2 tabs once daily from day 2 to day 6 of menstrual cycle for 3 cycles. (LETROL, RENATA).

Group B: Included 120 patients taking Clomiphene citrate (50 mg), 2 tabs once daily from day 2 to day 6 of menstrual cycle for 3 cycles. (OVULET, RENATA).

Withdrawal bleeding was achieved by using Tab. Levonorgestrel (10 mg) thrice daily from day 15 to day 25 of menstrual cycle.

All patients were monitored by trans-vaginal ultrasound on day 12 to day 13 for the measurement of dominant follicle at least two from each ovary, number of follicle and endometrial thickness. hCG injection (5000 IU) was given when at least one follicle measured ≥18mm. Patients were advised to have intercourse 24-36 hours after the hCG injection.

The outcome was measured with the number of growing and mature follicle, ovulation rate, endometrial thickness and occurrence of pregnancy.

Data was statistically analyzed using SPSS computer program.

Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean ± SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. The level of significance was taken at P value <0.050 as significant, otherwise non-significant.

Results:

The study included 240 patients. Among them 120 patients got tab Letrozole and 120 patients got Clomiphene citrate for 3 cycles.

Table I: Demographic characteristics among the study groups.

Variable		Letrozole N = 120	Clomiphene Citrate N = 120	P value
Age (years)	Range	20-35	21-34	0.612
	Mean ± SD	29.1 ± 3.2	29.3 ± 2.9	
BMI (kg/m^2)	Range	26.8-30.9	25.9-31.7	0.431
	Mean ± SD	28.1 ± 1.2	28.2 ± 0.7	
Duration of Subfertility (years)	Range	2-7	1-5	0.304
	Mean ± SD	3.0 ± 0.8	3.1 ± 0.7	

There was no statistical significant difference between the two groups regarding demographic characteristics.

Table II: Basal hormone profile on day 3

Variable		Letrozole N = 120	Clomiphene citrate N = 120	P value
FSH (mIU/ml)	Range	8.5-13.1	7.3-12.5	0.484
	Mean ± SD	9.1 ± 1	9.2 ± 1.2	
LH (mIU/m^2)	Range	13.0-22.0	14-24	0.091
	Mean ± SD	16.5 ± 3.8	17.3 ± 3.5	
Prolactin (ng/ml)	Range	14.0-25.0	16.0-26.0	0.823
	Mean ± SD	21.7 ± 3.4	21.6 ± 3.5	
TSH (IU/ml)	Range	1-3.5	1.3-3	0.204
	Mean ± SD	2.5 ± 0.5	2.4 ± 0.7	

Table II shows no significant difference between the two study groups regarding basal hormone profile on day 3.

Table III: Outcome of ovarian stimulation.

Variable	Letrozole N = 120	Clomiphene citrate N = 120	P value
Mono follicular development	83 (69%)	67 (56%)	0.038
Multi follicular development	36 (30%)	53 (44%)	0.025
Endometrial thickness	9.2 ± 0.6	8.1 ± 0.6	<0.001

Monofollicular development was found statistically significantly higher in Letrozole group. On the other hand, multifollicular development was significantly higher in CC group. Endometrial thickness was significantly higher among Letrozole group.

Table IV: Outcome of treatment.

Variable	Letrozole N = 120	Clomiphene citrate N = 120	P value
Ovulation rate	78 (65%)	77 (64%)	0.872
Pregnancy rate	52 (44%)	29 (24%)	0.001

There was no significant difference in ovulation rate in two different study groups. But pregnancy rate was significantly more in Letrozole group than CC group.

Discussion:

Polycystic ovarian syndrome is the most common endocrine disorder responsible for subfertility among the young adult[11]. The prevalence of PCOS is increasing and as high as 15-20%[12]. Safe and effective ovulation induction is important for women with WHO group II anovulation[13].

Clomiphene citrate has been used for ovulation induction since 1960s[14]. It is still considered first line drug for anovulatory PCOS woman[15]. Clomiphene resistance occurs in 15% to 20% of patients[16]. The use of Clomiphene may be associated with poor cervical mucous and endometrial thinning in 15% to 50% of patients due to prolonged estrogen-receptor depletion[17]. This is responsible for discrepancy between ovulation and pregnancy rate[18].

Letrozole which is an aromatase inhibitor, has been explored as a good alternative by many researchers, but the evidence about its efficacy as compared to clomiphene is still conflicting[19].

Letrozole is a third generation aromatase inhibitor that acts by preventing negative feedback inhibition of the hypothalamopituitary axis by estrogen, thus increasing FSH level and also increasing the follicular sensitivity to FSH[18]. It is postulated that aromatase inhibitor may have superior ovulation induction properties in terms of mono-follicular growth and endometrium development, which is important for embryo implantation[20].

In our randomized control study 240 female patients were selected who attended for subfertility. They were diagnosed PCOS patients by Rotterdam criteria. They were divided in two groups randomly and were treated by Letrozole or Clomiphene citrate.

Age, BMI, duration of subfertility was statistically similar in both groups (Table I). Although the basal hormone profile was statistically non-significant in both groups (Table II).

Multi-follicular development was significantly higher in our study in CC group (CC 44%, Let 30%). This is expected and found in number of studies[11,19,21,22]. Letrozole resulted in mono-folliculogenesis in 69% in comparison to 56% in CC, which is comparable to other studies[11,19, 23]. As a result ovarian hyperstimulation syndrome (OHSS) was absent in Letrozole group and three patients were found with OHSS in CC group. Multiple pregnancy was only two in Letrozole group and eight in CC group. Mobusher I et al[19]. and Yehia El et al[11]. described mono-follicular development 74% in Letrozole and 55.76% in cc group. They also found multi-follicular development in 44.24% and 26% respectively.

Endometrial thickness is a predictor for successful implantation following ovulation induction. In this trial, endometrial thickness was significantly higher in Letrozole group (9.2 ± 0.6) in comparison to CC group (8.1 ± 0.6). In a recent study by Banerjee et al[24]. 147 Indian women with PCOS were compared between Letrozole (2.5 mg) vs clomiphene (100 mg). Mean endometrial thickness was 8.72 ± 1.41 mm in Letrozole and 8.78 ± 1.16 in CC group (P = 0.004)[25, 26].

Badawy et al[21]. in their study of 438 patients with 1063 cycles, reported statistically significantly higher endometrial thickness in CC group (9.2 ± 0.7) vs Letrozole (8.1 ± 0.2, p = 0.021). Few studies have no significant difference between the two groups.

In our study, ovulation rate was almost same in two groups (Let 65% vs CC 64%) which is similar to many studies[11, 19, 25, 26].

In this study, pregnancy rate per cycle was significantly higher with Letrozole group (44%) vs CC group (24%). In a study by Hendawy et al[27]. pregnancy rate in Letrozole group is higher than the CC group. This may be explained by Kar, in a study showed that Letrozole has excellent pregnancy rate compared to CC[28].

The fact that the anti-estrogenic effect of CC results in a long lasting estrogenic receptor depletion and its accumulation in the body due to its long half-life (2 weeks), causing adverse effect on the quality and the quantity of cervical mucosa[28]. In addition, CC causes thinning of endometrium and implantation failure. Due to these undesirable effects inspite of same ovulation rate, CC has a lower clinical pregnancy rate.

In this study, we used the two medicine Letrozole (2.5 mg), named LETROL, and CC (50 mg), named OVULATE from Renata pharmaceuticals. There was no conflict of interest.

Conclusion:

The pharmacodynamics of Letrozole (does not deplete estrogen receptors, short half-life, intact hypothalamo-ovarian axis) ensures better rate of successful mono-follicular ovulation, ensures improved endometrial thickness and cervical mucous. All these factors lead to a higher pregnancy rate and greater likelihood of singleton pregnancy.

References :

1. Nelson LR, Bulun SE. Estrogen production and action. Journal of the American Academy of Dermatology. 2001;45(3): S 116-24.

2. Nahid L, Sirous K. Comparison of the effects of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome. Minerva Ginecol. 2012;64(3):253-82.

3. Rotterdam ES. ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and sterility. 2004;81(1):19.

4. Casper RF, Mitwally MF. Use of the aromatase inhibitor letrozole for ovulation induction in women with polycystic ovarian syndrome. Clinical obstetrics and gynecology. 2011;54(4):685-95.

5. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertility and sterility. 2004;82(6):1561-3.

6. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertility and sterility. 2002;78(2):280-5.

7. Guzick DS. Ovulation induction management of PCOS. Clinical obstetrics and gynecology. 2007;50(1):255-67.

8. Aletebi F, Alaa N. The effect of letrozole versus clomiphene citrate on ovulation induction in polycystic ovarian syndrome patients: RCT. Journal of Evidence-Based Women's Health Journal Society. 2013;3(2):51-3.

9. Badawy A, Aal IA, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertility and sterility. 2009;92(3): 849-52.

10. Baillargeon JP, Carpentier AC. Brothers of women with polycystic ovary syndrome are characterized by impaired glucose tolerance, reduced insulin sensitivity and related metabolic defects. Diabetologia. 2007;50(12):2424-32.

11. Wafa YAES, Labib MM, Fatah AGKAE. Role of Letrozole Versus Clomiphene Citrate in Induction of Ovulation in Patients with Polycystic Ovarian Syndrome. Journal of Gynecology & Reproductive Medicine. 2017;1(1):2-6.

12. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Human Reproduction Update. 2009;15(4):477-88.

13. Slowey MJ. Polycystic ovary syndrome: new perspective on an old problem. Southern medical journal. 2001;94(2):190-6.

14. Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Human Reproduction. 1990;5(6):670-4.

15. Yagel S, Ben-Chetrit A, Anteby E, Zacut D, Hochner-Celnikier D, Ron M. The effect of ethinyl estradiol on endometrial thickness and uterine volume during ovulation induction by clomiphene citrate. Fertility and sterility. 1992;57(1):33-6.

16. Franks S, Adams J, Mason HD, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. Clinics in obstetrics and gynaecology. 1985;12(3):605-32.

17. Kistner RW. Induction of ovulation with clomiphene citrate (clomid). Obstet Gynecol Survey 1965;20:873-900.

18. Homburg R. Clomiphene citrate-end of an era? A mini-review. Human Reproduction. 2005;20(8):2043-51.

19. Movusher I. Comparison of the efficacy of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome.2014;24(2.33):24-9.

20. Eckmann KR, Kockler DR. Aromatase inhibitors for ovulation and pregnancy in polycystic ovary syndrome. Annals of Pharmacotherapy. 2009;43(7-8):1338-46.

21. Badawy A, Aal IA, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertility and sterility. 2009;92(3):849-52.

22. Bayar Ü, Tanrıverdi HA, Barut A, Ayoğlu F, Özcan O, Kaya E. Letrozole vs. clomiphene citrate in patients with ovulatory infertility. Fertility and sterility. 2006;85(4):1045-8.

23. Zeinalzadeh M, Basirat Z, Esmailpour M. Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome. The Journal of reproductive medicine. 2010;55(1-2):36-40.

24. Ray PB, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Archives of gynecology and obstetrics. 2012;285(3):873-7.

25. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertility and sterility. 2002;78(2):280-5.

26. Kilic-Okman T, Kucuk M, Altaner S. Comparison of the effects of letrozole and clomiphene citrate on ovarian follicles, endometrium, and hormone levels in the rat. Fertility and sterility. 2003;80(6):1330-2.

27. Hendawy SF, Samaha HE, Elkholy MF. Letrozole versus clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome undergoing intrauterine insemination. Clinical Medicine Insights: Reproductive Health. 2011;5:11.

28. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial. Journal of human reproductive sciences. 2012;5(3):262-5.

29. Badawy A, Aal IA, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertility and sterility. 2009;92(3):849-52.