IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 3 Ser.1 (March. 2023), PP 48-53
www.iosrjournals.org

Evaluation of the Outcome of Letrozole or Clomiphene Citrate for Induction of Ovulation in Patients with Polycystic Ovarian Syndrome: A Study in a Tertiary Care Hospital, Dhaka Division, Bangladesh.

Sabiha Sultana[1],Rahima Khatun[2], UmmeHafsaZakiatul Husna[3], Tayeba Sultana[4]
[1]*Sabiha Sultana, Associate Professor, Department of Obs. and Gynae, ShaheedMonsur Ali Medical College and Hospital, Dhaka, Bangladesh.*
[2]*Rahima Khatun, Assistant Professor, Department of Obs. and Gynae, Ad-din Women Medical College and Hospital, Dhaka, Bangladesh.*
[3]*Umme HafsaZakiatulHusna, Associate Professor, Department of Obs. and Gynae, ShaheedMonsur Ali Medical College and Hospital, Dhaka, Bangladesh.*
[4]*Tayeba Sultana, Medical Officer, 300 Bedded Hospital, Narayangong, Bangladesh.*
Corresponding Author:Name: Sabiha Sultana
Email Address:sabihasultana20307474@gmail.com

Abstract:
Polycystic Ovary Syndrome (PCOS) is the commonest endocrinopathy resulting in anovulatory infertility in young women. Recent years have seen a significant rise in women presenting with PCOS and a concomitant spurt in scientific interest to understand the syndrome.
Several studies have reported on ovulation and pregnancy rates in patients with polycystic ovary syndrome (PCOS). However, relevant data on endometrial receptivity are limited. This study was conducted to compare endometrial receptivity during implantation windows among letrozole (LE), clomiphene citrate (CC), and natural cycle, and to assess the predictive value for pregnancy of observed indicators.Themain aim of the study was to evaluation of the outcome of Letrozole or Clomiphene Citrate (CC) for the induction of ovulation in patients with polycystic ovariansyndrome. It was a prospective randomized trial in a private practice setting.
This hospital-based prospective observational study was done on 83fertile patients with PCOS of a tertiary care private hospital in Dhaka division over a period of 2 years from January 2015 to December 2017. Written informed consent was obtained from the outpatients of the hospital. Patients were divided into two groups. Group-A: 42 patients got Letrozole (2.5 mg) tab, 2 tabs once daily from D_2-D_6 for 3 cycles. Group-B: 41 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 67% with Letrozole group and 76% in CC group without a significant statistical difference.
The results of this study suggests that aromatase inhibitors, like letrozole, are safe and superior to CC in terms of ovulation and pregnancy. Letrozole may be a better alternative in patients with PCOS who do not respond or are resistant to CC before embarking on expensive and risky gonadotropins. It may even be considered as the first line treatment for ovulation induction or augmentation in fertility management. Our study shows that letrozole has excellent pregnancy rates compared to clomiphene citrate. Letrozole should be considered at par with clomiphene citrate as first line drug for ovulation induction in infertile PCOS women.

Keywords:*Ovulation induction, polycystic ovary syndrome, letrozole, clomiphene citrate, endometrial receptivity, embryo implantation*

Date of Submission: 20-02-2023 Date of Acceptance: 03-03-2023

I. Introduction

Polycystic Ovarian Syndrome (PCOS) is one of the most common causes of subfertility in young women. Anovulation is responsible for about 20% of female infertility of which polycystic ovary syndrome (PCOS) is a major cause [1]. In euestrogenic anovulation, clomiphene citrate (CC) remains the primary therapy to induce ovulation. Clomiphene citrate is an antiestrogen that results in a 60%–85% ovulation rate and a 10%–20% pregnancy rate (PR) per cycle [2-3].Ovulation induction is the way to treat infertility in PCOS which can be done by medication or surgery.Clomiphene citrate (CC) is the most commonly used first-line treatment for the 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.

Letrozole was originally used for postmenopausal breast cancer therapy[4]. Patients with PCOS who do not respond to CC are the potential candidates for gonadotropins, which are associated with a risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Before administering gonadotropins we wanted to explore the efficacy of a higher dose of letrozole for patients with PCOS. In our previous experience, we had an unsatisfactory response with 5 mg of letrozole in patients with PCOS. CC has a negative effect on the cervical mucus and endometrium, leading to a discrepancy between ovulation and conception rate[5]. However, clomiphene has certain well-defined disadvantages. Treatment with CC is associated with the discrepancy in ovulation and pregnancy rates (60-85%). It is known that CC results in an ovulation rate of 60-80% but a conception rate of only 20%[6]. Endometrial receptivity is critical for embryo implantation, and its impairment has been proven to be an important factor for infertility[7].

In recent years, ultrasonic parameters, molecular markers in endometrial tissue and uterine secretions, endometrial microstructure, and hysteroscopy have been applied to evaluate endometrial receptivity[8]. The preferred method for assessing endometrial receptivity is transvaginal ultrasound, and multiple ultrasonic indicators have been used to assess endometrial receptivity.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, the dominant follicle grows, and the estrogen level increases. This results in follicle-stimulating hormone suppression and atresia of smaller follicles[9].A literature search did not reveal any report that indicated the efficacy of a high dose of letrozole in CC unresponsive patients with PCOS.

Therefore, the purpose of our study is to compare the efficacy of 7.5 mg of letrozole with that of 150 mg of CC in patients with PCOS who did not respond to 100 mg of CC.Clomiphene citrate (CC) is a long-standing, standard drug for ovulation induction and is still considered as a first-line option in PCOS women.As a result, mono ovulation occurs in most patients in comparison to CC. Letrozole has no anti-estrogenic effect and due to its shorter half-life, the pregnancy rate is higher[10].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 the induction of ovulation in polycystic ovarian syndrome (PCOS) patients.

II. Objectives

General Objective:

To evaluation the outcome of Letrozole or Clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome.

Specific Objectives:

To evaluate the Letrozole citrate for induction of ovulation in patients with polycystic ovarian syndrome.

The main causes of Clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome.

III. Materials And Methods

This prospective randomized trial study was conducted atDepartment of Obs. and Gynae, ShaheedMonsur Ali Medical College and Hospital, Dhaka, Bangladeshover a period of 2 years from January 2015 to December 2017 with a large gynecological practice. Study protocol was approved by the institutional ethics committee.

The study included 83 women with PCOS were recruited from outpatient department. Patients of age between 20-35 years, primary subfertility, and 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.

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.

IV. Results

The study comprised of 83 patients; 42 patients in the letrozole (Let) group and 41 patients in the Clomiphene Citrate (CC) group. Age, duration of infertility, BMI, presenting signs and symptoms were similar in both groups [Table 1].The study included 83 patients. Among them, 42 patients got tab Letrozole and 41 patients got Clomiphene citrate for 3 cycles.

Table 1: Demographic characteristics among the study groups.

Variable		Letrozole N = 42	Clomiphene Citrate N = 41	P value
Age (years)	Range	20-35	20-34	0.525
	Mean ± SD	28.2 ± 2.9	29.3 ± 2.9	
BMI (kg/m2)	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	3-9	1-5	0.304
	Mean ± SD	4.0 ± 0.10	3.1 ± 0.7	
Timed Intercourse		71.50%	66.48%	0.46
IUI		28.50%	33.52%	0.46

There was no statistically significant difference betweenthe two groups regarding demographic characteristics.

Table 2: Basal hormone profile on day 3

Variable		Letrozole N = 42	Clomiphene Citrate N = 41	P value
FSH (mIU/ml)	Range	7.5-12.25	7.2-11.5	0.424
	Mean ± SD	8.2 ± 1	8.2 ± 1.4	
LH (mIU/m^2)	Range	12.0-21.0	12-22	0.081
	Mean ± SD	15.5 ± 3.4	16.2 ± 2.5	
Prolactin (ng/ml)	Range	13.0-22.0	15.0-24.0	0.810
	Mean ± SD	22.5 ± 2.8	22.5 ± 2.5	
TSH (IU/ml)	Range	1.0-1.5	1.0-3.2	0.195
	Mean ± SD	2.2 ± 0.3	2.2 ± 0.6	

Table 2 shows no significant difference between the two study groups regarding basal hormone profile on day 3.

Table 3: Outcome of ovarian stimulation.

Variable	Letrozole N = 42	Clomiphene Citrate N = 41	P value
Mono follicular development	29 (69%)	23 (56%)	0.365
Multi follicular development	13 (31%)	18 (44%)	0.024
Days to ovulation	11.2 ± 3.2	13.13 ± 2.99	0.22
Endometrial thickness	8.2 ± 0.5	8.1 ± 0.6	0.001
Cervical Mucus Score on DHCG	3.0 ± 1.25	4.62 ± 1.26	0.52

Variable Letrozole Clomiphene P value

Monofollicular development was found statistically significantly higher in Letrozole group. On the otherhand, multi-follicular development was significantlyhigher in CC group. Endometrial thickness wassignificantly higher among Letrozole group.

Table 4: Outcome of treatment.

Variable	Letrozole N = 42	Clomiphene Citrate N = 41	P value
Ovulation rate	28 (67%)	31 (76%)	0.001
Pregnancy rate	14 (33%)	10 (24%)	0.001
Multiple pregnancies	None	None	0.00

Variable Letrozole Clomiphene P value

Pregnancy occurred in 14 out of 42 (33%) in the Letrozolegroup and in 10 out of 41 (24%) in the CC group, the difference was highly statistically significant (P = 0.015). The multiple pregnancy rate was zero. [Table 4].There was no significant difference in ovulation rate in the two different study groups. But the pregnancy rate was significantly more in the Letrozole group than CC group.

V. Discussion

Polycystic ovarian syndrome is the most common endocrine disorder responsible for subfertility among 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]. Ovulation induction is regarded as an important therapeutic method for PCOS women with infertility. Previous studies reported that the ovulation rate of CC in PCOS women was 70%–80%. Nevertheless, the pregnancy rate was relatively low (25%–60%). In addition to the side effects on cervical mucus [15], the main reason is that CC impaired endometrial development, which resulted in endometrial thinning and lower receptivity in PCOS women[16].

Furthermore, approximately 15%–40% of women with PCOS are resistant to CC for ovulation induction[17]. Because LE does not affect the central feedback mechanisms, they remain intact, making it superior to CC in ovulation induction. Hence, LE is recommended as first-line medication for ovulation induction in PCOS women according to the evidence-based medical evidence guidelines released internationally in 2018[18].In our randomized control study,83 female patients were selected who attended for subfertility. They were diagnosed PCOS patients by Rotterdam criteria. They were divided into two groups randomly and were treatedwithLetrozole or Clomiphene citrate.Age, BMI, and duration of subfertility were statistically similar in both groups (Table 1).

Although the basal hormone profile was statistically non-significant in both groups (Table 2). This is responsible for the discrepancy between ovulation and pregnancy rate. 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]. It is postulated that aromatase inhibitors may have superior ovulation induction properties in terms of mono-follicular growth and endometrium development, which is important for embryo implantation[20].Monofollicular development was found statistically significantly higher in Letrozole group. On the other hand, multi-follicular development was significantly higher in CC group. Endometrial thickness was significantly higher among Letrozole group.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 pregnancies was only two in Letrozole group and eight in CC group [11,19]. described mono-follicular development 74% in Letrozole and 55.76% in cc group.

Few studies have no significant difference between the two groups.In our study, ovulation rate was almost same in two groups (Let 67% vs CC 76%) which is similar to many studies[11, 19, 25, 26]. 80 In this study, pregnancy rate per cycle was significantly higher with Letrozole group (44%) vs CC group (24%). The pregnancy rate in Letrozole group is higher than the CC group[27]. This may be explained by Kar, in a study showed that Letrozole has an excellent pregnancy rate compared to CC28.The fact that anti-estrogenic effect of CC results in 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]. 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). 147 Indian women with PCOS were compared between Letrozole (2.5 mg) vs clomiphene (100 mg)[24].

Mean endometrial thickness was 8.72 ± 1.41 mm in Letrozole and 8.78 ± 1.16 in CC group (P = 0.004)[25, 26]. The study of 438 patients with 1063 cycles, reported statistically significantly higher endometrial thickness in CC group (9.2 ± 0.7) vsLetrozole (8.1 ± 0.2, p = 0.021)[24]. In addition, CC causes thinning of endometrium and implantation failure. Letrozole was associated with improved ovulation, pregnancy, and live-birth rates compared with clomiphene citrate. We recommend letrozole over clomiphene citrate as an ovulation induction drug in women with infertility and PCOS, although the quality of the evidence is mixed. Due to these undesirable effects in spite of the 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.Pregnancy occurred in 14 out of 42 (33%) in the Letrozolegroup and in 10 out of 41 (24%) in the CC group, the difference was highly statistically significant (*P* = 0.015). The multiple pregnancy rate was zero. [Table 4]. There was no significant difference in ovulation rate in the two different study groups. But the pregnancy rate was significantly more in the Letrozole group than CC group.

Limitations of the study: Since this is a hospital-based study, the incidence does not reflect the actual incidence of the community. The study sample size was also small, it is not found to be statistically significant and no control was taken.The study was done only in one OPD which did not represent the whole country. Many risk factors and symptoms were subjective; we depended on parents or patients.

VI. Conclusion

The study concluded that Letrozolehasa better effect onthe induction of ovulation in PCOS patients in comparison to CC. Our study showedstatistically significantly higher mono-follicular development and pregnancy rates when used as a first-line ovulation induction drug in infertile PCOS women. This enhanced response to letrozole could be related to ethnic differences in PCOS women. The pharmacodynamics of Letrozole (does not deplete estrogen receptors, short half-life, intact hypothalamoovarian axis) ensures a better rate of successful mono follicular ovulation and ensures improved endometrial thickness and cervical mucus. All these factors lead to a higher pregnancy rate and a greater likelihood of singleton pregnancy.

Funding: No funding sources
Declaration of Conflicting Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Ethical approval: The study was approved by the Institutional Ethics Committee

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Sabiha Sultana, et. al. "Evaluation of the Outcome of Letrozole or Clomiphene Citrate for Induction of Ovulation in Patients with Polycystic Ovarian Syndrome: A Study in a Tertiary Care Hospital, Dhaka Division."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 22(3), 2023, pp. 48-53.