

Evaluation of effectiveness of Letrozole in treatment of infertility in women with polycystic ovary syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disease, characterized by hyperandrogenism, oligomenorrhea, and polycystic ovaries. PCOS is one of the most causes that affect the women of childbearing age and often leads to infertility. Various managements were proposed for infertile women with PCOS. However, the optimal management option has not been addressed satisfied. Although multiple treatments including weight reduction, clomiphene citrate, metformin, gonadotropins and ovary cauterization have been reported to treat such condition, the efficacy still has insufficient evidence to support. **Objectives:** Purpose of this study was to evaluate the effectiveness of Letrozole in treatment of infertility in women with polycystic ovary syndrome. **Materials & method:** This study was carried out to assess the effectiveness of letrozole and on pregnancy outcomes including the ovulation induction, pregnancy rate and endometrial thickness in infertile women with polycystic ovarian syndrome (PCOS). Total 106 infertile PCOS patients were recruited and allocated in two groups, Group-L (received letrozole at 2.5 mg twice daily on the 3rd–5th days of menstrual cycle for 5 consecutive days), Group-G 75U/d–1 gonadotropin through intramuscular injection for 5 days starting from the third day of menstrual cycle). All patient in both arm completed treatment and follow-up. Patients in both groups were treated up to 5 treatment cycles. During follow up, transvaginal ultrasonogram (TVS) was performed to see the details of the follicles and the endometrium. Data was processed and analysed with the help of computer program SPSS and Microsoft excel. Quantitative data expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparison was done by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagrams, histogram & charts etc. **Result:** Mean age of the patient was 26.3 ± 5.7 years in group-L and 25.9 ± 6.1 years in group-G. There were no statistical significant differences between the 2 groups regarding age, body weight, height, body mass index (BMI). Present study results showed that patients who received letrozole exert better outcomes in primary endpoint, including ovulation rate (86.7% in group-L & 62.2% in group-G, $P=0.004$), endometrial thickness (9.3 ± 1.1 mm in group-L & 8.5 ± 1.1 mm in group-G, $P=0.003$) and pregnancy rate (64.1% in group-L & 30.1% in group-G, $P=0.005$). Abortion rate (till the end of 12th week) and multiple pregnancy rate were higher in group-G, but result were non-significant in between groups. Live birth rate in the letrozole group was higher 29(54.7%) than group-G 14(26.4%), the difference was statistically significant ($P<.05$). **Conclusion:** Patients who took Letrozole had significantly higher endometrial thickness than other group. Due to the higher pregnancy rate and lower incidence of abortion or multiple pregnancy, letrozole can be an effective for the treatment of anovulatory subfertility of the PCOS patients.

Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disease in women of reproductive age. PCOS is characterized by ovulatory disruption, which can lead to infertility.

Patients with PCOS are also more likely to have poor pregnancy outcomes. For obese women, lifestyle interventions are recommended first, which have general benefits. For women who have difficulty

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changing their lifestyle, drugs for the treatment of obesity or bariatric surgery could be considered. Clomiphene citrate is the first-line medication after weight loss that has been utilized in the past¹. However, it has a certain impact on the endometrium and cervical mucus, and in some condition, it exist clomiphene resistance, as a result of failing to include ovulation².

PCOS often presents in early adolescence. Its etiology is unclear, and its pathogenesis is complicated. PCOS is influenced by environmental factors, particularly nutrition. In 2003, the European Society of Human Reproduction and Embryology joined with the American Society for Reproductive Medicine revised the diagnostic criteria for PCOS as follows³: (1) rare ovulation or anovulation; (2) abnormal clinical manifestations and/or biochemical indicators of hyperandrogenism; and (3) polycystic ovarian morphology (presence of ≥ 12 follicles measuring 0.2–0.9 cm in diameter in one or both ovaries and/or ovarian volume > 10 cm³). PCOS can be diagnosed when at least two of the three criteria are met, and disorders such as thyroid dysfunction, Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, pituitary gland diseases and premature ovarian failure are ruled out.

PCOS is a very heterogeneous syndrome in terms of laboratory manifestations and clinical presentation. Non-ovulatory infertility accounts for approximately 30% of infertility, with PCOS accounting for 90% of these cases⁴. Patients with PCOS are prone to ovulatory disturbance, which leads to infertility. They are also more likely to have poor pregnancy outcomes. In PCOS, many factors affect ovarian function. In addition, being overweight, having hyperandrogenemia, and having an elevated serum concentration of luteinizing hormone (LH) can adversely affect fertility⁵. In recent years, an increasing number of scholars have emphasized individualized management and treatment of this disease because of its uncertainty and heterogeneity.

In recent years, Aromatase inhibitors (AIs), such as letrozole or anastrozole, have been introduced for treatment of PCOS women with CC-resistant anovulation. It has been postulated that blocking estrogen production by inhibiting aromatization in

the ovary would release the hypothalamic-pituitary axis from estrogenic negative feedback. As a result, FSH secretion increases, stimulating the development of ovarian follicles, while reducing the gonadotropin-induced ovulation complication⁶. Human menopausal gonadotropin (HMG), which contains follicle stimulating hormone (FSH) and luteinizing hormone (LH), can secrete gonadotropin to promote follicle maturation, so as to stimulate ovulation and to accelerate the development of corpus luteum^{7, 8}. Preliminary studies have reported that the regimen using letrozole had a satisfactory effect on ovulation, medication cycle and clinical pregnancy rate, which provides a promising option for the treatment of patients with PCOS resistant to clomiphene citrate⁹.

Gonadotropins have been used as second-line therapy for ovulation induction. Because many patients with PCOS have elevated serum LH/FSH ratios, FSH preparations are considered the best physiological approach. Gonadotropin therapy is prone to multiple follicular development; thus, the main complications are ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. Because patients with PCOS are relatively younger and have higher numbers of antral follicles than other infertile women, treatment with gonadotropins increases the risk of adverse events, such as OHSS and multiple pregnancy¹.

Letrozole is a third-generation aromatase inhibitor that blocks the conversion of androgens to estrogens in the ovarian follicles, peripheral tissues, and the brain. The reduced estrogens create a positive feedback loop with the estrogens of the hypothalamus-pituitary-ovary axis, which causes the endogenous release of GnRH, promotes FSH secretion and leads to follicular growth. Fat tissue predominates in obese women. Thus, letrozole may offer unique benefits for these individuals. Letrozole is related to a lower rate of multifollicular recruitment and ovulation and a lesser anti-estrogenic effect on the endometrium than clomiphene, and it has its own unique safety profile¹⁰. It has been reported that letrozole can inhibit estrogen levels by at least 97% to 99%¹¹. The other studies also reported that letrozole is effective in clomiphene-resistant patients and also resulted in ovulation of 62% cases, and pregnancy of 14.7%^{12, 13}. Additionally no adverse events have been

reported on fetus. However, current data are still insufficient to support the idea that letrozole can be utilized effectively to treat such condition. Therefore, in this study, we investigated the efficacy of letrozole for infertility women with PCOS.

Materials & Methods:

In this cross sectional study a total of 106 cases of infertility women with PCOS were analyzed. The PCOS was diagnosed by modified Rotterdam criteria. All included cases had no major medical disorders, and their male partners were also required to participate in this study. Moreover, all subjects had ovulatory dysfunction, polycystic ovaries, or increased ovarian volume. Furthermore, all patient cases had normal uterine cavity and at least 1 patent fallopian tube. Women aged 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. In addition, cases were also excluded if they previously received the study medication within past 3 months.

Treatment schedule: A total of 106 women who gave consent to participate in the study were allocated into two groups. Group L (Letrozole group, n =53) was given Letrozole (Letrol; Renata Limited, Bangladesh) 2.5 mg/ twice daily. Group G (Gonadotropin group, n = 53) was given 75U/d-1 gonadotropin through intramuscular injection. All patients in both groups starting on cycle day 3 for consecutive 5 days for up to 5 menstrual cycles. Transvaginal ultrasound (TVS) was performed on day 10 to day 13 of the cycle. During scanning, the number and size of follicles, and the endometrial thickness were recorded. If there was a nonresponse or a poor ovulatory response occurred the dose was increased in subsequent cycles in the either group. Starting from the 10th day of menstruation, the growth conditions of follicles and endometrium in the patients were monitored by transvaginal B ultrasound. When the average diameter of follicles was ≥ 18 mm, the endometrial thickness, number of mature follicles and diameter of the largest follicle

were recorded and 5000 to 10,000 U of human chorionic gonadotropin (HCG) was injected to induce ovulation. On the same day, the venous blood of patients was drawn to examine the LH, E2 and T levels, who were then guided to have sexual intercourse within 24 hour. B ultrasound examination was performed again 48 hour after HCG injection to observe follicle rupture and single follicle ovulation. If fetal heart beat was visible under transvaginal ultrasound on the 30th day after ovulation, the patients were diagnosed as clinical pregnancy.

Outcome measurements: The primary endpoint was infant outcome. The secondary endpoints comprised of the number of women in conception, number of mature follicles, ovulation rate, endometrial thickness. Successful pregnancies were followed up for 12 weeks.

Statistical analysis: The sample size was calculated based on the previous published study with a pregnancy rate of 46.3%¹⁴. Thus, the desired sample size was 95.38. Due to availability of cases 53 cases were taken for each group. All outcome and characteristic values were analyzed by using SPSS software. Continuous non-normally value was analyzed by Mann-Whitney U test, while normally variables were performed by t test. Categorical value was conducted by Chi-squared test. $P < .05$ was defined as having a statistical significance.

Result:

Table I: Demographic characteristics (n=106)

Demographic characteristics	Group L (n=53) n (%)	Group G (n=53) n (%)	p-value
Age (years)			
18-24	21 (39.6)	20 (37.7)	
25 - 30	27 (50.9)	29 (54.7)	
31 - 35	5 (9.5)	4 (7.5)	
Mean \pm SD	26.3 \pm 5.7	25.9 \pm 6.1	0.727
BMI (kg/m²)	28.5 \pm 2.8	28.3 \pm 2.5	0.698
Duration of infertility (year)	3.2 \pm 0.5	3.1 \pm 0.7	0.399

Table showed demographic characteristics. Study demonstrates that maximum number of patients, 27 (50.9) in group-L and 29 (54.7) in group-G were between 25 – 30 years' age group. Mean age of the patient was 26.3 ± 5.7 years in group-L and 25.9 ± 6.1

years in group-G. There were no statistical significant differences between the 2 groups regarding age, body weight, height, body mass index (BMI).

Figure- 1: Distribution of patients according to residence (n=106)

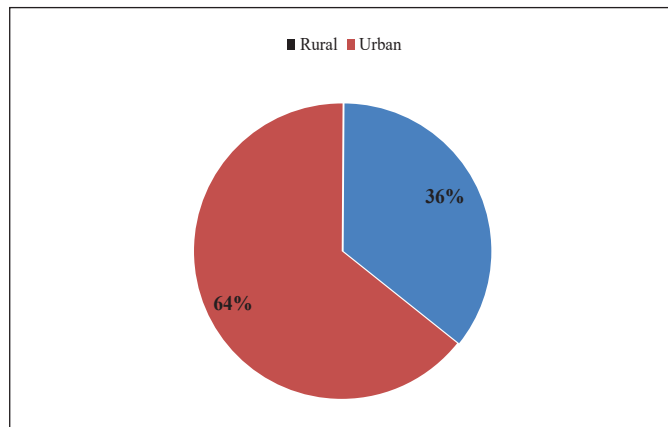


Figure shows the residency of study subjects. Figure shows (36%) patients came from rural, (64%) from urban areas.

Table II: Clinical characteristics (n=106)

Clinical characteristics	Group L (n=53) n (%)	Group G (n=53) n (%)	p-value
Oligo/anovulation	47 (88.6)	48 (90.5)	0.750
Hyperandrogenism	25 (47.1)	21 (39.6)	0.438
Polycystic ovaries	33 (62.2)	35 (66.0)	0.684
FSH (mIU/ml) on day 3 of menstruation	5.9 ± 2.1	6.1 ± 2.1	0.625
E2 (pg/ml) on day 3 of menstruation	62.7 ± 19.4	65.9 ± 20.3	0.408
LH (mIU/ml) on day 3 of menstruation	9.4 ± 2.8	9.7 ± 2.6	0.568
T (ng/ml)	0.81 ± 0.26	0.85 ± 0.31	0.473

Table showed clinical characteristics. There were no statistical significant differences between the 2 groups regarding clinical features and laboratory findings.

Table III: Outcome of ovarian stimulation (n=106)

Variables	Group L (n=53) n (%)	Group G (n=53) n (%)	p-value
Ovulation rate	46 (86.7)	33 (62.2)	0.004
Endometrial thickness in mm (mean ± SD)	9.3 ± 1.1	8.5 ± 1.1	0.003
Number of women with conception	37 (69.8)	23 (43.3)	0.006
Number of women with pregnancy (Pregnancy rate)	34 (64.1)	16 (30.1)	0.005
Multiple pregnancy rate	1 (1.88)	3 (5.66)	0.309
Abortion rate (till the end of 12th week)	3 (5.66)	7 (13.2)	0.186

Table shows outcome of ovarian stimulation. The results showed that patients who received letrozole exert better outcomes in primary endpoint, including

ovulation rate (86.7% in group-L & 62.2% in group-G, P=0.004), endometrial thickness (9.3 ± 1.1 mm in group-L & 8.5 ± 1.1 mm in group-G, P=0.003) and pregnancy rate (64.1% in group-L & 30.1% in group-G, P=0.005). Abortion rate (till the end of 12th week) and multiple pregnancy rate were higher in group-G, but result were non-significant in between groups.

Figure II: Comparison of Live birth (case, %) rates among the two treatment groups (n=106)

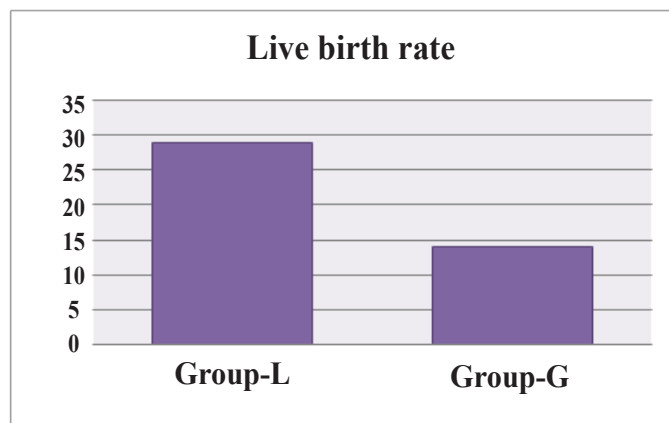


Figure shows the live birth (case, %) rates among the two treatment groups. Live birth rate in the letrozole group was higher 29(54.7%) than group-G 14(26.4%), the difference was statistically significant (P<.05).

Discussion:

The present study was conducted to see the effectiveness of Letrozole in treatment of infertility in women with polycystic ovary syndrome. A total of 106 women diagnosed as PCOS by Rotterdam criteria seeking treatment of subfertility were included in the study. Participants were randomly divided into two groups. Group L got Letrozole and Group G got gonadotropin as treatment. Demographically, there were no significant differences between the participants of both groups. We performed TVS on day 10 to 13 of the cycle and we found significant difference in ovulation rate among the Letrozole and gonadotropin group (p <0.05). We also found that the thickness of the endometrium was significantly higher in Letrozole group (p <0.05). In this study Live birth rate in the letrozole group was higher 29(54.7%) than group-G 14(26.4%), the difference was statistically significant (P<.05).

Previous systematic review and meta-analysis reported that letrozole could significantly enhance the live birth and pregnancy rates in patients with PCOS^{15, 16}. In a study a total of 96 clomiphene resistance polycystic ovary syndrome patients infertility were randomly divided into an LE group, and HMG group (n=48). LE group orally received letrozole, and human menopausal gonadotropin (HMG) was given in HMG group. Result shows that there was no significant difference in the number of ovulation cycles between the 2 groups (53.6% vs 64.7%, $P>.05$). The number of mature follicular cycles in the HMG group was higher than that of the letrozole group ($P<.01$). There were no significant differences in the clinical pregnancy rate (22.9% vs 27.1%, $P>.05$) and abortion rate (6.2% vs 10.4%, $P>.05$). There was no significant difference in the endometrial thickness between the 2 groups on the day of HCG injection [(9.1 ± 0.2) mm vs (10.7 ± 1.6) mm, $P>.05$]; the serum estradiol (E2) was lower in the letrozole group. The incidence of ovarian cysts was lower than that of HMG group ($P<.05$). Letrozole-induced ovulation can obtain ovulation rate and pregnancy rate similar to gonadotropin, but reduce the risk associated with treatment. It can be used as an effective ovulation option for patients with polycystic ovary syndrome who are resistant to clomiphene⁹.

Currently, CC and LE are used to treat PCOS. CC remains the first-line drug for ovulation induction, however, Cc also has peripheral antiestrogen effects, such as endometrium and cervix, which partly explains the contradiction of high ovulation rate and low pregnancy rate and high abortion rate. There are about 20% to 25% of patients Cc resistance causes ovulation treatment failure¹⁷. For this group of patients, the traditional choice is laparoscopic ovarian surgery and administration of gonadotropins such as HMG, recombinant follicle stimulating hormone and other drugs to promote ovulation^{18, 19}. However, both of these options have problems of high price and high risk, especially gonadotropin-induced ovulation may lead to excessive ovarian stimulation and multiple pregnancy.

It was shown that letrozole ovulation induction was easier to obtain a single mature follicle; the total pregnancy rate reached 23 (25%), and the abortion

rate was 7 (7.2%), there was no statistically significant difference in ovulation rate, pregnancy rate, and abortion rate compared with HMG group, moreover, The incidence of ovarian cysts and the incidence of OHSS in the letrozole group were lower than those in the HMG group, confirming that letrozole ovulation induction therapy can achieve similar therapeutic effects as gonadotropin⁹. Ganesh et al 20 conducted a large randomized, single-blind clinical trial comparing the effects of letrozole, CC with recombinant FSH, and recombinant FSH alone in the treatment of CC-resistant PCOS patients with letrozole 5mg/d, obtaining ovulation rate 79.3% (295/372), the cycle pregnancy rate was 23.39% (87/372), The ovulation rate was better in the letrozole group than others. There was no significant difference in pregnancy rate and abortion rate between the 2 groups.

The management of PCOS-infertility depends on the prevention of follicular atresia which turns against the follicular formation. This requires re-establishing a state of balance in the synthesis of intra-ovarian hormones that take part in the maturation and ovulation process. In the PCOS case, patients will first undergo a regimen of lifestyle modification followed by the administration of certain drugs to induce ovulation²¹. Aromatase inhibitors are used as a second-line treatment. This group has a minimal effect on androgens preventing their conversion into estrogen which inhibits the feedback on the hypo-thalamic-pituitary axis leading to the release of normal GnRH and FSH levels²². Moreover, together with aromatase inhibitors, low doses of gonadotropins have been used to induce ovulation. It has been reported that letrozole can inhibit estrogen levels by at least 97% to 99%¹¹. The other studies also reported that letrozole is effective in clomiphene-resistant patients, and also resulted in ovulation of 62% cases, and pregnancy of 14.7%^{12, 13}.

Conclusions:

Polycystic ovary syndrome (PCOS) is a common endocrine disorders for women of childbearing age, and induced to an ovulatory infertility. Ovulation induction therapy can achieve satisfactory cumulative pregnancy rates and low multiple birth rates, but follicle numbers must be strictly monitored. For women with PCOS, various treatment choices are available for ovulation treatment. Present study

concluded that letrozole is best option. In summary, the regimen using letrozole had a satisfactory effect on ovulation, medication cycle and clinical pregnancy rate, which provides a promising option for the treatment of patients with PCOS.

DECLARATIONS

Author Contributions

Dr. Jasrin Akter Mile designed the study, supervised the project and participated in patients' enrollment. Dr. Mashuma Mumi supervised the project's accuracy; Mahabubul Islam Majumder prepared the draft of the manuscript; Dr. Dilara Rahman, Dr. Tahmina Parvin and Dr. Shanaz Pervin participated in patients' enrollment and gave a substantial contribution. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability statement

Data will be made available on request.

Ethical Approval

The ethical permission received from the ethics review committee of Central Medical College Hospital, Cumilla, Bangladesh. A formal letter was approved or given by the authority Prior to data collection, patients were told about the project and consented and anonymity was maintained through out the study.

Consent for Publication: Not applicable

Code Availability: Not applicable

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