Original Article

Comparative Effectiveness of Ovulation Induction Therapy in Women with Polycystic Ovarian Syndrome

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Abstract

Objectives: To evaluate the efficacy of letrozole plus metformin in comparison to clomiphene citrate (CC) alone and clomiphene citrate plus metformin in ovulation induction treatment, in Pakistani's infertile women with polycystic ovarian syndrome (PCOS).

Study Design: Prospective randomized controlled study.

Setting: Women & Children Teaching Hospital Bannu and private practice setting from 1.1.2015 to 30.9.2016

Methodology: After taking permission from the ethical committee of Bannu medical college, the study was perused. 147 infertile PCOS women were enrolled and equally divided into three groups. Group A (CC 50mg-150mg/day), Group B (CC 100mg/day + metformin 1500mg/day) and Group C (Letrozole 2.5mg/day + metformin 1500mg/day). The study was continued till pregnancy or CC resistance. All pregnant women were pursued till delivery. The significance of the study was to measure reproductive efficacies of the treatment, live birth rate (LBR), ovulation induction rate and biochemical pregnancy rate.

Results: A significant difference was observed in the percentage of women having mature follicles, ovulation induction rate and live birth rate. The ovulation induction rate, pregnancy rate and live birth rate of group C in comparison to group A was significant at $p < 0.05$ with odd ratio 4.57 (1.45-14.38), 3.59 (1.21-10.60) and 3.75 (1.24-11.40) respectively.

Conclusion: Letrozole along with metformin is more effective as compared to CC in inducing ovulation, achieving higher pregnancy and live birth rate in infertile PCOS women.

Keywords: Polycystic ovary syndrome, clomiphene citrate, letrozole, ovulation induction, live birth rate.

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Introduction

Polycystic ovary syndrome (PCOS) is a common cause of infertility and is diagnosed on the basis of chronic anovulation and hyperandrogenism with associated oligomenorrhea and polycystic ovaries on ultrasonography.[1] It affects 5-10% of women of reproductive age and occurs amongst all races and nationalities. It affects up to 14% of women in western Society and 37.3% in Kashmiri women of Indian subcontinent. In Pakistani women of reproductive age group PCOS was found in 20.7 % of women.[2] PCOS is

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hard to diagnose, as it is strongly associated with obesity and metabolic abnormalities such as insulin resistance and dyslipidemia.[3]

Clomiphene citrate (CC) a careful estrogen-receptor modulator is silently used as first-line therapy for ovulation induction in PCOS patients. However, CC is also responsible for negative consequences on the cervical mucus and endometrium and is associated with inconsistency between ovulation and conception rates. The overall poor efficacy, relatively high multiple pregnancy rates and an adverse side-effect frequently result in the use of more costly treatment options for infertility.[4] In addition, previous studies have also shown a significantly higher abortion rate in patients undergoing CC treatment. Many previous studies have reported that adding metformin to CC in the CC-resistant PCOS can effectively increase ovulation induction up to 68-78%.[5-7]

Letrozole, a recently designed selective aromatase inhibitor, is a safe preference to CC and is seeking attention for a long period to induce ovulation with a reported ovulation rate of 70-85% and a pregnancy rate of 20-27% per cycle.[8-9] Thus, CC, letrozole, and metformin are the most frequently used pharmacological agents and a large amount of data is available. However, there exists marked heterogeneity in outcomes. Comparative efficacy of these two agents and also response following combination of the two with metformin are central issues to be reported. There are no sufficient data of Pakistani's infertile PCOS women on letrozole plus metformin efficacy. The current study was undertaken to evaluate the efficacy of letrozole plus metformin in comparison to CC plus metformin as the key line ovulation induction treatment in Pakistani's PCOS women.

Methodology

This prospective randomized controlled study was conducted in women and children teaching hospital, Bannu-KPK Pakistan, and private practice setting in time period from January 2015 to September 2016. Women attending gynecology OPD, with the chief complaints of infertility and oligo-menorrhea, were evaluated for PCOS. The diagnosis was done on the basis of Rotterdam criteria.[1] Physical examination and routine investigations of all the selected patients were performed. Exclusion criteria included: infertility of non-PCOS origin, sensitivity to metformin, letrozole or CC, diabetes, liver, heart or kidney diseases etc. Inclusion criteria included: PCOS patients with first-time diagnosis and evaluation of infertility.

A sequence of blind envelopes numbered from 1 to 120 had been arranged. Each patient was invited to drag out an envelope and hand over to the nurse who carefully placed the envelope in the desired group that is in either CC group (Group A: envelop numbers 1-40) or the CC-metformin group (Group B: envelopes number 41-80) or Letrozole-metformin group (Group C: envelopes number 81-120). Those women, who were enrolled in group A, CC group were given 50 mg of chlomiphene citrate as an initial dose on days 3–7 of menstrual cycle, increasing to a maximum of 150 mg/day. Follicular monitoring was done with trans vaginal sonography. If ovulation occurred, the patients were advised for timely intercourse and the same dose of CC was repeated. In case of failure in ovulation, CC dose was increased up to 100mg/day in the next cycle. If again an ovulation occurred than CC dose was increased up to 150mg/day. Women who failed to ovulate with 150 mg CC for 6 months were termed as CC-resistant. Those patients who were assigned to group B, (CC-metformin group) and group C, (letrozole-metformin group) were given metformin 1500 mg/day (500mg three times a day), for one complete month. In addition to metformin, the patients in group B were also given 100mg CC for 5 days starting from day 3 to day 7 of their menstrual cycle, and those in the group C were given 2.5 mg letrozole for 5 days (day 3 to day 7 of their menstrual cycle). Patients were asked to report spontaneous menses. Follicular tracking was done on day 12 of the menstrual cycle. If at least one follicle ≥18 mm was formed, hCG (10000 IU) was given intramuscularly. Women were advised to have timely intercourse 24–36hr after hCG injection. Serum b-hCG was measured 16 days after hCG injection to diagnose pregnancy. All patients were enrolled for 6 months. The study was continued until pregnancy or CC-resistant. All pregnant women were given follow up until delivery.

Ultrasound screening was done on 14th day of the cycle in order to monitor the size and no of developing follicles and endometrial thickness. Outcome measures were a number of follicles ≥18mm, endometrial thickness and ovulation rate.

Other outcomes of the study were the live birth rate (LBR), ovulation induction rate and biochemical pregnancy rate. Secondary outcomes were early pregnancy loss, the percentage of women succeeded to have mature follicles of greater than equal to 18mm and adverse side effects of the prescribed drugs. Quantitative

variables were articulated as a mean ± standard deviation and qualitative variables were expressed as frequencies in percent and were analyzed by Chi-square tests. Statistical analysis was done using SPSS version 18. $P < 0.05$ was considered statistically significant.

Results

One hundred and forty-seven patients were initially enrolled in the clinical study, however, only 90 women succeed to complete the clinical trial and were finally statistically analyzed. Table I indicates that there was no significant difference in baseline and biochemical parameters among the three study groups.

Table II indicates that in regards to outcome measures, a significant difference was observed in the percentage of women having mature follicles, ovulation induction rate and live birth rate. A number of women having mature follicles were significantly higher in group C, 26 (86.7%) as compared to group A, 15 (50%), P=0.04. The ovulation induction rate was significantly different at P=0.03 among the three study groups. In group A, 14 (46.7%), in group B, 18 (60%) and in group C, 24 (80%) women succeed to have induced ovulation. Biochemical pregnancy was significantly reported at P=0.03 among the study groups. In group C, 17 (56.7%) women get pregnant as compared to group B, 09 (30%) and group A 08 (26.6%) respectively. Live birth rate was significant at p=0.03, highest in group C, 16/30 (43.3%) followed by group B, 8/30 (26.7%) and group A, 7/30 (23.3%) respectively.

Table II: Outcome measures of the three study groups

Variables	Group A	Group B	Group C	P-value
Number of mature follicles				
None	15 (50.0%)	07 (23.3%)	04 (13.3%)	
1 follicle	09 (30.0%)	12 (40.0%)	14 (46.7%)	
2 follicles	05 (16.7%)	09 (30.0%)	07 (23.3%)	
≥ 3 follicles	01 (03.3%)	02 (06.7%)	05 (16.7%)	0.04
Ovulation induction				
Yes	14 (46.7%)	18 (60.0%)	24 (80.0%)	
No	16 (53.3%)	12 (40.0%)	06 (20.0%)	0.03
Biochemical pregnancy				
Yes	08 (26.6%)	09 (30.0%)	17 (56.7%)	
No	22 (73.3%)	21(70.0%)	13 (43.3%)	0.03
Side effects				
None	21 (70%)	15 (50%)	15 (50%)	
Flushing	06 (20%)	09 (30%)	09 (30%)	
GIT discomfort	03 (10%)	06 (20%)	06 (20%)	0.49
Birth condition				
Live births	07 (87.5%)	08 (88.9%)	16 (94.1%)	
Abortions	01 (12.5%)	01 (11.1%)	01 (05.9%)	0.83
LBR	7/30 (23.3%)	8/30 (26.7%)	16/ 30 (53.3%)	0.03

P-value is significant at P < 0.05

Table III shows that ovulation induction, pregnancy rate and live birth rate of group C was significantly higher as compared to group A. Ovulation induction of group C

Table No I: Base line characteristics of the women in the study groups

Variables	Group A	Group B	Group C	*P* value
Age (Yrs)	27.58 ±2.73	26.88 ±3.11	26.78± 2.22	0.77
BMI(Kg/m^2)	27.6±3.22	28.7±2.51	29.1±2.52	0.466
Duration of Infertility	2.5±1.27	3.5±1.43	3.10±1.52	0.297
Type of Infertility (%)				
Primary	21 (70%)	20 (66.6%)	23 (76.7%)	
Secondary	09 (30%)	10 (33.3%)	07 (23.3%)	0.682
Medical comorbidities (%)				
Yes	05 (16.6%)	06 (20%)	04 (13.3%)	
No	25 (83.3%)	24 (80%)	26 (86.6%)	0.79
Prior Pelvic Surgery				
Yes	11 (36.6%)	09 (30%)	12 (40%)	
No	19 (63.3%)	21 (70%)	18 (60%)	0.712
Hirsutism (%)				
Yes	17 (56.6%)	15 (50%)	18 (60%)	
No	13 (43.3%)	15 (50%)	12 (40%)	0.73
PCOS (%)				
Yes	24 (80%)	22 (73.3%)	25 (83.3%)	
No	06 (20%)	08 (26.6%)	05 (16.6%)	0.62
Oligomeenorrhea (%)				
Yes	20 (66.7%)	19 (63.3%)	16 (53.3%)	
No	10 (33.3%)	11 (36.6%)	14 (46.6%)	0.55
Waist Circumference (cm)	89.31± 7.57	83.91± 9.25	86.72± 9.21	0.33
Hip Circumference (cm)	95.31±5.83	96.78± 5.89	99.31± 7.74	0.28
FG Score	17.15±3.42	15.55± 3.28	15.78± 4.34	0.53
FSH(mIU/ml)	4.96 ±1.01	4.55 ± 1.47	5.87 ± 1.29	0.52
LH(mIU/ml)	4.82 ± 1.59	5.92 ± 1.63	5.39 ± 1.36	0.36
Prolactin(ng/ml)	24.77± 7.90	25.89 ± 8.1	26.96 ± 9.27	0.74
TSH(mIU/l)	4.87 ± 3.01	4.39 ± 1.47	5.27 ± 2.07	0.67

Data are presented as mean ± SD, or number (%) as suitable.

was significant at p =0.01 with odd ratio 4.57 (1.45-14.38), pregnancy rate was significant at p= 0.02 with odd ratio 3.59 (1.21-10.60) and live birth rate was significant at p = 0.02 with odd ratio of 3.75 (1.24-11.40) when compared with group A. Comparing group C with group B ovulation induction was not significant however, pregnancy rate and live birth rate was significant at 0.04 with odd ratio of 3.05 (1.05-8.83) and 3.14 (1.06-9.26) respectively.

Table III: Comparing Ovulation induction, pregnancy and live birth rates of the study groups.

Comparison	Odd ratio	z-statistic	p-value
Group B verses Group A			
OI	1.71 (0.61-4.77)	1.03	0.30
PR	1.17 (0.38-3.62)	0.28	0.77
LBR	1.19 (0.37-3.85)	0.29	0.76
Group C verses Group A or			
OI	4.57 (1.45-14.38)	2.59	0.01
PR	3.59 (1.21-10.60)	2.31	0.02
LBR	3.75 (1.24-11.40)	2.31	0.02
Group C verses Group B or			
OI	2.66 (0.84-8.46)	1.66	0.09
PR	3.05 (1.05-8.83)	2.05	0.04
LBR	3.14 (1.06-9.26)	2.08	0.04

P-value is significant at P < 0.05.Ovulation Induction (OI), Pregnancy Rate (PR), Live Birth Rate (LBR)

Discussion

CC has been considered as first-line therapy for ovulation induction for the past fifty years in infertile PCOS women. In this study, only 46.7% women succeed to ovulate with CC alone and 60% women with CC plus metformin. The 53.3% women (16/30) who failed to ovulate with 150 mg of CC could be associated with tribal variations in the population of Asian countries, who are famous to have an increased frequency of hyperinsulinemia and visceral obesity.

The outcome of this study designates that in PCOS women, pregnancy and live birth rates were higher when treated with Letrozole + Met as compared to treatment with CC + Met. Advantages of the use of letrozole over CC in combination with metformin in moderately obese patients with polycystic ovarian syndrome was also reported in previous retrospective studies carried by Roque et al and Bjelica et al.[10-11] Letrozole also appear to improve live birth and pregnancy rates in subfertile women with an-ovulatory PCOS, compared to clomiphene citrate.[12] However, Robab Davar et al reports no significant difference in ovulation induction rate and achieving pregnancy in treating PCOS women either with letrozole or combined metformin–CC.[13] Two well-designed studies concluded that treatment with anastrozole was less effective than a 5-day course of CC. The discrepant outcomes with similar drugs may reflect the greater suppression of aromatase with letrozole than with anastrozole.[14-15] The high pregnancy rate and live birth rate across all groups may be due to the reason that all registered women in our study were very young, with small duration of infertility and nonobeses (BMI ≤ 30).

Some researchers reported and showed low manifold gestation rates after ovarian stimulation by aromatase inhibitors.[16] In many subjects, especially in PCOS infertile women, letrozole is the ideal choice, because of a limited number of mature follicles, multiple pregnancies, and risk of hyperstimulation syndrome.[17,18] Badawy *et al* reported that incidence of multiple pregnancies with oral induction ovulation is not significantly higher than normal ovulatory women.[19] We observed higher miscarriage rates in pregnancies after Clomiphene compared with pregnancy after letrozole. Ruiz-Velasco *et al* reported a higher spontaneous abortion rate in their cohort of letrozole-treated patients compared with clomiphene-treated patients, whereas Boostanfar et al observed only one abortion in the tamoxifen group and non-in clomiphene group.[20] But similar to our study, Wu Ch. reported lower miscarriage rate in pregnancy after letrozole as compared with clomiphene.[21]

Conclusion

On the basis of earlier reports and the results of the current study, we suggest that letrozole along with metformin may be a better choice in the treatment of an-ovulation in PCOS women belonging to Pakistani population who are genetically more prone to abdominal obesity and insulin resistance.

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