

Comparison of Ovulation Induction with Letrozole with Metformin Versus Letrozole Alone in Females Presenting with Polycystic Ovarian Syndrome

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Abstract

Objective: To compare the frequency of Ovulation Induction after administration of Letrozole with metformin versus Letrozole alone in females presenting with Polycystic Ovarian Syndrome

Methods: This Randomized Controlled Trial was done in unit 5 of Lady Aitchison Hospital Lahore for 6 months. Total 200 females fulfilling the inclusion criteria were recruited from OPD. Lottery method was used for randomization of study subjects. Females in group A were given Letrozole 2.5mg once a day for five days (from third to seventh day) of the cycle for three consecutive months and metformin 1500mg (500mg 3 times a day) daily for three months, while females in group B were given Letrozole 2.5mg once a day for five days (from third to seventh day) for three consecutive months. Then they were followed up in OPD for 3 cycles. In all 3 cycles TVS was done on day 12 to assess the number of follicles and to measure the size of largest follicle, and on day 21 of cycle progesterone level will be assessed for confirmation of ovulation induction. The data was entered and analyzed through SPSS version 20. Mean and standard deviation was calculated for age and BMI. Frequency and percentage was calculated for Ovulation induction. Both groups were compared by using chi-square test taking p-value<0.05 as significant. Data was stratified for BMI (Normal, overweight and Obese). After stratification chi-square test was applied keeping a p value ≤0.05 as significant.

Results: In Group-A mean age of women was 28.18±6.58 years. In Group-B mean age of women was 27.08±5.15 years. In Group-A ovulation induction rate was much higher as compared to that of Group-B women. i.e. (89% vs. 60%). p-value=0.000. Ovulation induction rate was significantly higher with Letrozole+ Metformin in women who were having normal BMI, overweight & obese as compared to that of Letrozole alone.

Conclusion: Letrozole with metformin is more effective for the ovulation Induction females presenting with polycystic ovarian Syndrome as compared to letrozole alone.()

Key Words: Polycystic Ovarian Syndrome, Management, Ovulation Induction, Letrozole, Metformin

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Introduction

PCO is commonest hormonal disorder of females in reproductive age group and it has very high prevalence.¹ PCOS is the leading cause of anovulatory subfertility and it accounts for 70% of

subfertility cases related to ovulatory disorder. 5-10% women of reproductive age group are affected by PCOS.⁴

The cause of this multifactorial condition is not completely known and its phenotype expression varies. Clomiphene citrate (CC) is frequently used drug for ovulation induction. But one fourth of women do not give adequate response to this drug. These resistant cases are typically treated with administration of gonadotrophins but there are more chances of multifetal gestations and hyperstimulation of ovaries.⁵

Recently it has been found that Letrozole makes endometrium more receptive for implantation in addition to increasing ovulation rate therefore chances of

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success-ful pregnancy have increased in women presenting with this disorder.⁶ Additional benefits of Letrozole are decreased number of multifetal gestations and less androgenic side effects and decreased cases of ovarian hyperstimulation so less frequent monitoring is required as compared to gonadotrophins.⁷

PCOS is heterogenous disorder involving genetic, hormonal and environmental factors. No definitive treatment is available for this condition. Weight reduction and lifestyle modification is mainstay of the treatment.⁸ First case of PCOS was recognised in 1721 in Italy.

Studies in different countries show prevalence of PCOS using Rotterdam criteria as follows, 6.3% in Srilanka, 2% in south China, 5 % in Thailand, 8% in UK and 4% in USA (there is no difference among black and white women).²

Literature has reported that letrozole is effective in ovulation induction but there are conflicting results reported in literature. Moreover, there are no study conducted which compares letrozole in combination with metformin and letrozole alone and local magnitudes are also missing. Through this study we wanted to get local magnitudes and results which can be applicable and on the basis of which we can implement the use of letrozole with metformin for management of PCO instead of letrozole alone. Objective of this study is to compare the frequency of Ovulation Induction after administration of Letrozole with metformin versus Letrozole alone in females presenting with Polycystic Ovarian Syndrome. Hypothesis of the study was that there is some difference in frequency of Ovulation Induction with Letrozole with metformin versus letrozole alone in females presenting with Polycystic Ovarian Syndrome.

Methods

This randomized controlled trial was done in Unit 5 of Lady Aitchison Hospital in 6 months time. Total of 200 cases (100 cases in each group was calculated with 80% power of test, 5% level of significance and taking expected percentage of ovulation induction i.e. 90.57% with Letrozole with metformin and 60.78% with Letrozole alone in females presenting with PCOs) were enrolled by Non-Probability, consecutive Sampling. Women age 18-39 years, BMI <35, Infertility due to anovulation, Polycystic Ovarian Syndrome (fulfilling two of the following three crite-

ria atleast: Oligomenorrhea / amenorrhea, Hyper androgenaemia (testosterone \geq 2.5nmol/l) or free androgen index \geq 5 or clinical evidence (acne/hirsutism), Ultrasound evidence of Polycystic Ovarian Syndrome (either \geq 12 follicle measuring 2-9mm in diameter or ovarian volume > 10ml)), Normal husband semen analysis (sperm count 20 million/ml, 60% are motile and 30% have normal morphology), Patency of both fallopian tubes by hysteroscopy and laproscopy, and No recent treatment within six months for induction of ovulation on history were included. Ovulation induction was measured as production of follicles confirmed on Ultrasonographic findings (follicles size >18mm at 12 day of menstruation) and day 21 progesterone level >3ng/dl for three cycles, if these findings were achieved then labelled as ovulation induction. Women with Uterine pathology by ultrasound, Hyperprolactinemia (<500mIU/l), Hyperthyroidism (TSH <0.5Uu/ml)/ Hypothyroidism (TSH >6Uu/ml), FSH >9mIU/mn (during early follicular phase), Previous surgery related to genital tract, Impaired hepatic (serum bilirubin level >2mg/dl)/ impaired renal functions (serum creatinine >1mg/dl), Diabetes Miletus / BSR >140mg/dl were excluded.

After taking permission from institutional review board/head of department, 200 females who are fit in the inclusion criteria were recruited from Outpatient department of Lady Aitchison Hospital Lahore. Informed consent and personal information (name, age, BMI and contact) was obtained. Lottery method was used for randomization. Females of both groups were counseled about dietary modification and encouraged to do brisk walk for 30 min twice a day. Females in group A were given Letrozole 2.5mg once a day for five days (from third to seventh day) of cycle for three months and metformin 1500mg (500mg 3 times a day) daily for three months, while females in group B were given Letrozole 2.5mg once a day for five days (from third to seventh day of cycle) for three consecutive months. Then they were followed up in OPD for 3 cycles. In all 3 cycles TVS was done on day 12 to access the number of follicles and to measure the size of largest follicle, and on day 21 of cycle progesterone level will be assessed for confirmation of ovulation induction. All the data was collected according to predesigned proforma. The data was entered and analyzed through SPSS version 20. Mean and standard deviation was calculated for age and BMI.

Frequency and percentage was calculated for Ovulation induction. Both groups were compared by using chi-square test taking p-value <0.05 as significant. Data was stratified for BMI (Normal, overweight and Obese). After stratification chisquare test was applied keeping a p value ≤0.05 as significant.

Results

In Group-A mean age of women was 28.18±6.58 years. In Group-B mean age of women was 27.08±5.15 years. In Group-A minimum and maximum age of women was 18 and 39 years while in Group-B this was 18 and 37 years respectively. (Table-1)

In Group-A mean BMI of women was 28.05±2.82. In Group-B mean BMI of women was 27.54±2.54 Kg/m². In Group-A minimum and maximum BMI of women was 23 and 32 while in Group-B this was 23 and 31.9 respectively. As per body mass index criteria in Group-A 20(20%) women were having normal BMI, 44(44%) were overweight and 36(36%) were obese. In Group-B 20 (20%) women were having normal weight, 59(59%) were overweight and 21(21%) were obese. In Group-A ovulation induction rate was much higher as compared to that of Group-B women. i.e. (89% vs. 60%). p-value=0.000(**Table-2**)

Ovulation induction rate was much higher with Letrozole+ Metformin in women who were having normal BMI, overweight & obese as compared to that of Letrozole alone i.e. Group-A (Ovulation induction Rate): Normal BMI Women: 95% vs. Group-B: 65% (pvalue = 0.018), Over Weight Women: Group-A:86.4% vs.55.9% (p-value=0.001)& Obese women: Group-A: 88.9% vs. Group-B:66.7% (p-value=0.040). (**Table-3**)

Discussion

PCOS is responsible for 75% cases of ovulatory disorders.⁹ PCOS-related subfertility is treated appropriately by ovulation induction. Many treatment modalities including medical and surgical options have been employed to treat PCOS linked infertility. Medical options include Metformin, Clomiphene citrate, Letrozole and gonadotrophins.¹⁰ Surgical options include ovarian drilling and wedge resection. Resistant cases to both medical and surgical treatments are offered Intrauterine insemination with stimulated cycle and In-vitro fertilization.¹¹

About half of all women with PCOS show some

Table 1: Age Distribution Of Patients

	Group-A	Group-B
n	100	100
Mean	28.18	27.08
SD	6.585	5.154
Minimum	18	18
Maximum	39	37
Group-A= Letrozole + Metformin Group-B= Letrozole		

Table 2: Ovulation Induction In Study Groups

Ovulation Induction	Group-A	Group-B	Total
Yes	89(89%)	60(60%)	149
No	11(11%)	40(40%)	51
Total	100	100	200
Chi-Square Test= 22.13 p-value= 0.000			

Table 3: Ovulation Induction In Study Groups Stratified For Bmi

BMI	Ovulation Induction	Group-A	Group-B	p-value
Normal	Yes	19(95%)	13(65%)	0.018
	No	1(5%)	7(35%)	
Overweight	Yes	38(86.4%)	33(55.9%)	0.001
	No	6(13.6%)	26(44.1%)	
Obese	Yes	32(88.9%)	14(66.7%)	0.040
	No	4(11.1%)	7(33.3%)	

degree of insulin resistance. Hyperinsulinemia ultimately leads to the hyperandrogenism, which is responsible for the clinical manifestation of disease. 77 Metformin increases insulin sensitivity and in turn decreases the production of androgens from ovaries, also improves quality of the egg and induces ovulation. However several studies showed that the combination of metformin plus Clomiphene Citrate in the CC-resistant patients was very effective in inducing ovulation in 68.6%– 77.7% of patients.78-80.¹²

Several case reports have shown the effective role of metformin in PCOS patients by enhancing conception rate and improving the metabolic profile.¹³

Clomiphene citrate does not give equal response in all patients for ovulation induction. It acts by antagonising the effects of estrogen and thus causes raised levels of gonadotrophins from pituitary gland, this in turn will stimulate growth of ovarian follicles and ovulation.¹⁴

Letrozole inhibits actions of enzyme aromatase. It blocks the conversion of androgens to estrogens in ovarian follicles, this will result in fall in circulating

level of estrogen and rise in intraovarian androgens, this decreased level of estrogen in turn causes negative effect on hypothalamic–pituitary thus raising FSH level and it will enhance ovarian follicular development.¹⁵ The effective role of letrozole in patients with clomiphene-resistant PCOS has been documented with the use of 2.5 mg daily doses on third to seventh day of menstrual cycle in various studies.¹⁶

In this study it was observed that women who were given Letrozole + Metformin among them rate of ovulation was 89% as compared to the women who were given Letrozole among them rate of ovulation induction was 60%. A statistically significant association was seen between ovulation induction with treatment groups. (p-value=0.000).¹⁷

Davar reported that with the use of Metformin+ letrozole as combination showed pregnancy rate per cycle in 8% women. Nahid L in his study reported an induction rate of 88% with the use of letrozole alone. Hatem Abu Hashim from Egypt reported rate of ovulation induction as 64.9% with the use of letrozole alone. Badawy et al. who had an ovulatory rate of 62% for letrozole cycles.⁹⁰ In other trials, Mitwally and Casper⁹¹ had ovulatory rate of 75%, Al-Omari et al. had an ovulatory rate of 87.5%, whereas Elnashar et al. reported an ovulation rate of 54.6%.

Sohrabvand et al. added either CC or letrozole initially after 6–8 weeks of treatment with metformin in CC-resistant PCOS women, they found that the combination of metformin plus letrozole leads to more pregnancies. About 15–40 % of women with PCOS have CC resistance which can be ascribed to the anti-estrogenic effect of CC on endometrium and cervical mucus or by hypersecretion of luteinizing hormone.

Although administration of Letrozole for induction of ovulation varies in many studies but overall Letrozole alone is effective in PCOS women. It is widely used for many years and various studies have proved its beneficial role for ovulation induction. In addition to it, it does not have adverse effect on endometrium and cervical mucus.¹⁸

In literature only one study was found who had used combination of these both treatment in PCOS women. Ibrahim Abd Elgafo in his study used metformin plus letrozole and reported an ovulation rate of 48.9%. To our knowledge, no studies have yet compared the effects of letrozole with combined metformin.¹⁹

This study is the first of its kind in our set up and in

local literature which both these drugs have been used in combination. However different studies have used letrozole with CC.²⁰ But no such combination was adopted by studies done previously to see the efficacy of these two combination for successful outcome in women with PCOS.¹⁶

Conclusion

Letrozole with metformin is more effective for the ovulation Induction in females presenting with polycystic ovarian syndrome as compared to letrozole alone.

Conflict of Interest: None

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Authors Contribution

AZ: Concept, Design, analysis

KA: Analysis, Interpretation

MM: Interpretation

AM: Drafting Revising, Analysis

A: Analysis and Interpretation

KT: Design, Interpretation