

Research Article**Comparison of Ovulation Induction with Letrozole with metformin versus Letrozole alone in females presenting with Polycystic Ovarian Syndrome**

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ABSTRACT

INTRODUCTION: PCOS is considered one of most prevalent endocrine abnormalities in women who have reached childbearing age. In fact due to involvement of many ovulation factors it leads to infertility constituting 55%–70% of total infertility reports due to chronic ovulation.

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

SUBJECTS & METHODS: This trial was Randomized Controlled designed was done at Lady Aitchison hospital Lahore during 2017, Lahore for 6 month. Total 200 females fulfilling the inclusion criteria were recruited from OPD. Then random ordering of females was done in 2 groups by utilizing lottery method. Females in A-group were given Letrozole 2.5mg once a day for three days (from third day to seventh day) for three cycles 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 three days (from third day to seventh day) for three cycles. 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. SPSS version 20 was used by researchers to analyse the data gathered. Both BMI & age were studied for Mean & S.D. Ovulation induction was studied and Percentage along with frequency was calculated . Chi-square test was conducted taking p value <0.05 as significant value. Data was stratified for BMI (Normal, overweight and Obese). Chi-Square testing was reapplied with 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 significantly 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

INTRODUCTION

Polycystic ovary syndrome, is considered most prevalent endocrine abnormality in females with much high prevalence.¹ It commonly leads to anovulatory infertility & being responsible

for upto 70% of total infertility cases occurring because of anovulation.²

The etiology is somewhat complicated as it is a heterogeneous condition and not understood

with variations in phenotype.¹ Clomiphene citrate is still drug used as first preference for ovarian stimulation. But it is also reported that 20–25% of total women become resistant to this and result in failure to ovulate. For these cases, the gonadotropins are opted though these are related with increased chances of multiple pregnancies & ovarian hyperstimulation.³

It was reported recently that Letrozole has good effects on endometrium, so it enhances rates of pregnancy after prospective ovulation induction for subjects suffering with PCOS.⁴ ^{trozole} These beneficial advantages are lessened rate for occurrence of multiple pregnancies, no anti estrogenic adverse events, and consequently intensive monitoring is not much needed.⁵ Studies has reported that letrozole effective in ovulation induction from 64.9% to 78.7%.⁶ One study reported very low frequency of ovulation induction with letrozole i.e. 60.78%.⁷ While another reported that letrozole is effective for ovulation induction in 88% cases.⁸ In contrast to that ovulation induction with letrozole in combination with metformin was 90.57%.⁹

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.

MATERIAL AND METHODS

This trial was Randomized Controlled designed was done at Lady Aitchison hospital Lahore

during 2017 in 6 month time. Total of 200 cases (100 subjects in every group was calculated using 80% power of the test and 5% significance level & taking ovulation induction percentage expected as 90.57% with Letrozole with metformin and 60.78% with Letrozole alone in cases presenting with PCOs) were enrolled by Non-Probability, consecutive Sampling. Woman age 18-39 years, BMI <35, Infertility due to anovulation, Polycystic Ovarian Syndrome (having at the very least any 2 of following as diagnostic criteria: amenorrhea/Oligomenorrhea, 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 dia meter 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), Hypothyroidism (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.

Hospital ethical committee was contacted for approval and 200 females that passed inclusion specifications were selected from OPD of Obstetrics & Gynecology Department, Services Hospital Lahore. After taking Informed consent, the demographic information (name, age, contact, BMI) was noted. Then subjects were divided on random basis in two categories

by utilizing lottery method. 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 three days (from day 3 to day 7) for three cycles 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 three days (from day 3 to day 7) for three cycles. 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.(as per operational definition). All the data was recorded in especially designed proforma.SPSS version 20 was used by researchers to analyse the data gathered. Both BMI & age were studied for Mean & S.D. Ovulation induction was studied and Percentage along with frequency was calculated. Chi-square test was conducted taking p value <0.05 as significant value. Data was stratified for BMI (Normal, overweight and Obese). Chi-Square testing was reapplied with 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.**(Table-2)**

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.**(Table-3)**

In Group-A ovulation induction rate was significantly higher as compared to that of Group-B women. i.e. (89% vs. 60%). **p-value=0.000(Table-4)**

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 i.e. Group-A (Ovulation induction Rate): Normal BMI Women: 95% vs. Group-B: 65% (p-value=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-5)**

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: DESCRIPTIVE STATISTICS FOR BODY MASS INDEX OF WOMEN

	Group-A	Group-B
n	100	100
Mean	28.059	27.544
SD	2.8211	2.5492
Minimum	23.0	23.0
Maximum	32.0	31.9

TABLE-3: BODY MASS INDEX STATUS OF WOMEN

BMI	Group-A	Group-B	Total
Normal	20(20%)	20(20%)	40
Overweight	44(44%)	59(59%)	103
Obese	36(36%)	21(21%)	57
Total	100	100	200

TABLE-4: 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-5: 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%)	

DISCUSSION

PCOS is considered one of most prevalent endocrine abnormalities in women who have reached childbearing age (6.8%),¹⁰ and subsequently causes infertility because of ovulation disturbance. 75% of total disturbances are related to PCOS. Ovulation induction is therapy opted for treatment of PCOS. There are many treatment options available for this but none is solely to be considered for therapy. Clomiphene, metformin, letrozole, gonadotropins, ovaries cauterization & wedge resection, gonadotrophin-releasing hormone agonists and reproductive assisted technology.^{11, 12}

Almost 50%–70% of total women affected with PCOS have somewhat insulin resistance. Hyperinsulinemia may lead to hyperandrogenism, which causes signs & symptoms of the PCOS.¹³ A biguanide, Metformin treats insulin resistance in cases with co-occurrence of PCOS reducing production of endrogens in ovaries affecting follicular development & ovulation induction. Also, many reports state that the metformin plus CC in case of CC-resistant PCOS is particularly effective in inducing ovulation for 68.6%– 77.7% of subjects.⁶

Some studies also state that metformin improves metabolic situations in subsequent pregnancies in females suffering from PCOS.⁶

Contrarily Clomiphene citrate is ineffective in some situations for ovulation induction or for super ovulation. Insulin resistance, hyperinsulinemia, & an elevation in production of androgens all linked for patients suffering with PCOS. But when metformin is coadministered the beneficial effects are reported for clomiphene-resistant PCOS cases and is preferred treatment before initiating FSH or laparoscopic ovarian drilling.⁶

Letrozole is in pharmacological class of 3rd generation of aromatase inhibitor. Its administration during follicular stage facilitates ovulation by stimulating the hypothalamic pituitary axis of the E -ve feedback, thus elevating FSH secretion, stimulating development of follicles in ovaries. It elevates FSH effects on follicles sensitivity by androgens accumulation.¹⁴ The advantages of letrozole in CC-resistant PCOS cases are reported with therapy using 2.5 mg doses on daily basis after 3–7 days of menstruation in trials.^{15, 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 inductions with treatment groups. (P-value=0.000)

Davar reported that with the use of Metformin+letrozole as combination showed pregnancy rate per cycle in 8% women.¹⁷ Nahid L in his study reported an induction rate of 88% with the use of letrozole alone.¹⁸ Hatem Abu Hashim from Egypt reported rate of ovulation induction as 64.9% with the use of letrozole alone. Badawy et al. reported ovulatory rate as 62% for cycles of letrozole.¹⁹ In other reports, Mitwally & Casper²⁰ reported ovulatory rate as 75%, Al-Omari et al.¹⁶ reported ovulatory rate as 87.5%, Elnashar et al. Stated ovulation rate as 54.6%.¹⁵

Sohrabvand et al. Stated that CC/letrozole between 6th to 8th weeks of metformin therapy in CC-resistant PCOS cases then reported, the metformin & letrozole when co-administered caused higher full term pregnancies.⁹ Almost 15–40 % of cases suffering from PCOS have CC-resistance which causes antiestrogenic effects on endometrium & cervical mucus or secretion of LH.²¹

In addition to this gonadotropin & laparoscopic ovarian drilling are used as adjunctive therapies to CC for better results in cases with PCOS.²²

Although use of Letrozole for induction of ovulation varies in many studies but overall Letrozole alone is effective in PCOS women. Letrozole is aromatase inhibitor that is orally active, with better results of ovulation induction. After years of research the researchers strongly recommend it for therapy of ovulation induction. Letrozole lessens production of estrogen by inhibiting androgens conversion to estrogens. Additionally, no adverse effects are reported to be affecting endometrium & cervical mucus.²³ 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%. Until now there is no acknowledged study that compared letrozole effects with those of combined metformin.²⁴

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. But no such combination was adopted by studies done previously to see the efficacy of these two combination for ovulation induction in women with PCOS.

CONCLUSION

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

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