

## Original Article

# Letrozole Versus Combined Letrozole-Metformin: Effect on Ovulation and Conception Rate in Women with Polycystic Ovarian Syndrome

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## Abstract

**Objective:** To compare the efficacy of letrozole with combined letrozole-metformin in terms of ovulation rate and conception rate in overweight and obese subfertile women with polycystic ovarian syndrome.

**Methodology:** A prospective randomized clinical trial study was conducted in the outpatient department of POF Hospital between February 2019 to January and included 150 overweight and obese subfertile women with polycystic ovarian syndrome. The participants were randomly divided into groups A and B, 75 in each group. Women in group A were given letrozole 2.5 mg twice daily from day 2-6 of menstrual cycle. In addition to letrozole, the patients in group B were also given a tablet metformin 500mg three times daily with meals throughout the cycle, starting from the first day. The women were followed up regularly and treatment continued until the patient conceived or for 3 cycles. The sociodemographic details, ovulation rate, conception rate and side effects were noted on a proforma and analyzed by SPSS version 20.

**Results:** The cumulative ovulation rate was 84% with letrozole and 93.3% with letrozole metformin ( $p=0.071$ ). The cumulative conception rate was 34.6% with letrozole and 47% with letrozole-metformin ( $p=0.135$ ). The metformin was well tolerated without a significant increase in side effects.

**Conclusion:** As compared with letrozole alone, letrozole-metformin combination was associated with a higher ovulation and conception rate but the difference was not significant statistically.

**Key words:** letrozole, metformin, PCOS, ovulation rate, conception rate.

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## Introduction

Subfertility is a distressing issue for approximately 15% of couples.<sup>1</sup> In 30% cases of subfertility, the cause is ovulation disorder, and polycystic ovarian syndrome (PCOS) is responsible for 70-80% of these cases.<sup>2</sup> A local multicenter hospital-based study calculated that 80% of patients with PCOS were obese and 33% were infertile.<sup>3</sup> The high insulin and androgen levels in blood, intrinsic insulin resistance, the disturbed balance of Follicular Stimulating Hormone (FSH) and Luteinizing Hormone (LH) and other derangements in metabolism effect ovulation and fertility in polycystic ovarian syndrome.<sup>4, 5</sup>

Treatment modalities for subfertility caused by PCOS include changes in style of living, medicines to induce

ovulation, drilling of ovaries laparoscopically and assisted reproduction techniques. As ovulatory dysfunction is the main reason of subfertility in PCOS, so induction of ovulation by using drugs is the first choice of treatment. Clomiphene citrate, letrozole and metformin are the most commonly used drugs for this purpose.<sup>6-9</sup>

Letrozole, was initially used for treatment of breast cancer in 1986. It was used for the treatment of anovulation in 2000 in a pilot study, and then a study by Legro et al in 2014 described it a better choice than clomiphene.<sup>10</sup> The use of this drug has increased as first choice for ovulatory disorders.<sup>11</sup> Androgens are converted into estrogen by the enzyme aromatase.

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Letrozole inhibits this process, so gives a negative feedback to HPO axis of low estrogen levels and increases Follicular stimulating hormone which acts on ovaries to promote follicular growth.<sup>12,13</sup> Its half-life is 45 hours as compared to half-life of clomiphene citrate, which is 2 weeks, so it favours development of one ovum and reduces threat of multiple pregnancy.<sup>14</sup> It has no deleterious thinning effect on endometrial lining of uterus.<sup>15</sup>

Metformin, a commonly prescribed drug to treat diabetes mellitus, has been widely used along with clomiphene citrate to treat subfertility due to PCOS. It reduces the insulin resistance which is high in patients with PCOS and decreases glucose production by liver. It reduces the high blood sugar levels but does not cause hypoglycemia. Patients who take metformin along with clomiphene citrate has higher ovulation and conception rate than who only take clomiphene citrate because it ameliorates the metabolic disturbances caused by polycystic ovarian disease and promotes natural ovulation.<sup>16,17</sup> It does not increase the risk of ovarian hyperstimulation syndrome, twin and triplet pregnancy. It also reduces the risk of fetal loss when given during pregnancy.<sup>18</sup> Loose motions, nausea, emesis, cramps and bloated feeling in stomach are the most frequently reported adverse effects with this drug.

Very few studies have been done to find whether addition of metformin to letrozole will improve the results in subfertile patients due to PCOS as compared to letrozole alone. The results are controversial. The objective of our study was to find out whether addition of metformin to letrozole will improve the ovulation and conception rate in over weight and obese subfertile women with PCOS. The rationale of study was to find a better treatment option for subfertile PCOS women with high BMI to reduce their suffering by improving conception rate.

## Methodology

It was a prospective randomized clinical trial conducted at Pakistan Ordnance Factory hospital Wah Cantt after approval by the ethical committee of hospital. A total of 150 women were included over a period of 3 years from 1-Feb-2019 to 31-Jan-2022. The PCOS was diagnosed according to Rotterdam's criteria set in 2003 that included (1) infrequent or no ovulation, which presents as oligomenorrhea (2) clinical or biochemical evidence of high serum testosterone (3) ultrasound appearance of polycystic ovaries.<sup>19</sup> The woman was labelled as having PCOS if she had 2 of the above 3 features. The

inclusion criteria were subfertile women diagnosed to have PCOS with BMI  $\geq$  25. They had patent fallopian tubes on hysterosalpingography, laparoscopy, or saline sonohysterography. Their male partners had normal semen analysis report according to WHO criteria. Women with other causes of anovulation like hyperprolactinemia, hypothyroidism, hyperthyroidism and who had taken oral contraceptive pills, antiandrogens or any other hormonal drug within last 3 months were excluded from the study. Women with metabolic, hepatic and renal disorders were also excluded from study. Sample size was calculated by using WHO sample size calculator. With expected incidence (ovulation) of 70% in letrozole group<sup>6</sup> and 89% in letrozole-metformin group<sup>23</sup>, enrollment ratio 1:1, 5% margin of error (alpha) and 80% power, the minimum sample size calculated was 140.

The patients were randomized using a computer generated sequence of random numbers to either group A (letrozole) or group B (letrozole-metformin) after written informed consent. There were 75 patients in each group. The treatment was started after spontaneous menstruation or withdrawal bleed induced with oral progesterone. The 2.5 mg letrozole tablet was given twice daily from 2<sup>nd</sup> day of cycle for 5 days in both groups. The patients in group B were also given tablet metformin 500mg three times daily with meals throughout the cycle starting from the first day. The women were regularly followed up on alternate days from 10<sup>th</sup> day of cycle. When a mature follicle of 18-25 mm was visible on transvaginal ultrasound, HCG injection 5000 IU was given intramuscularly for follicular rupture. Transvaginal ultrasound was done by a consultant in OPD to avoid bias. The women were advised to have regular intercourse on alternate days. The ovulation induction was considered failed if no follicle of 18-25mm was visible on ultrasound till day 18 of the cycle. The treatment was continued till the pregnancy test was positive or for three menstrual cycles. The pregnancy was confirmed by urine pregnancy test 5-7 days after the patient missed her periods.

The primary outcome measure was ovulation rate and secondary outcome measure was conception rate with treatment. Side effects of treatment were also noted in both groups. The data was collected on a predesigned proforma by the 3 researchers of this study.

All data was analysed using SPSS version 22. To compare means of sociodemographic characteristics,

an independent sample t -test was used. Qualitative variables such as conception rate, ovulation rate, and side effects were measured as frequencies and percentages and chi-square test was used to calculate p value. A p value of <0.05 was considered statistically significant.

## Results

A total of 150 patients were included in the study, 75 in each group. The mean age of study population was 29.26±2.42 years and the mean BMI was 28.9±2.36. The mean duration of subfertility was 2.26±0.81 years and the majority had 109(73%) primary subfertility. There was no statistically significant difference in baseline characteristics of two groups as shown in Table I.

Table II compares the ovulation rate between the two groups. A total of 405 ovarian cycles were studied: 205 cycles in the letrozole group and 200 cycles in combined letrozole-metformin group. The mean ovulation rate per cycle was higher in letrozole-metformin group (81.5%) than the letrozole group (75.6%). Similarly, cumulative ovulation rate was also higher in letrozole-metformin group (93.3% versus 84%), but the difference was not significant (p=0.07)

After 3 cycles of treatment, the cumulative conception rate was higher in patients who received both letrozole and metformin (n=35, 47%) as compared to patients who only received letrozole 26(34.6%), although the difference was not statistically significant (p=0.14) (Table III). There was no statistically significant difference (p=0.48) in the mean conception rate/cycle (12.7% in the letrozole group versus 17.5% in letrozole-metformin group).

Although the addition of metformin increased the frequency of nausea, vomiting (13% versus 5.3%), abdominal cramps and diarrhea (12% versus 4%) but the difference remained insignificant statistically. (Table IV).

**Table IV Comparison of adverse effects between letrozole and letrozole-metformin groups. (n=75)**

Adverse effect	Group A (letrozole)	Group B (letrozole-metformin)	P-value
Nausea & vomiting	4 (5%)	10(13%)	0.09
Diarrhea & abdominal cramps	3(4%)	9(12%)	0.07
Hot flushes & night sweats	9(12%)	10(13%)	0.78

## Discussion

The increasing stress, changes in lifestyle, nature of work, and genetic factors have made polycystic ovarian

**Table I: Comparison of baseline characteristics of letrozole and letrozole-metformin group (n=75)**

Baseline characteristic	Group A (letrozole)		Group B (letrozole-metformin)		P-value
	Mean ± SD		Mean ± SD		
Age (years)	29.60±1.96		28.93±2.89		0.1
BMI (Kg/m <sup>2</sup> )	28.65±1.98		29.15±2.75		0.2
Duration of subfertility (years)	2.16±0.66		2.37±0.96		0.11
Subfertility Type	Primary	56(75%)	53(71%)		0.58
	Secondary	19(25%)	22(29%)		

**Table II: Comparison of ovulation between letrozole and letrozole-metformin group**

Cycle	Group A (letrozole)		Group B (letrozole-metformin)		P-value
	No.	%	No.	%	
First cycle	53/75	70.6%	56/75	4.6%	0.58
Second Cycle	52/69	75.3%	54/68	79.4%	0.57
Third Cycle	50/61	82%	53/57	93%	0.11
Mean ovulation rate per cycle	155/205	75.6%	163/200	81.5%	0.42
Cumulative ovulation rate (patients ovulated/total patients)	63/75	84%	70/75	93.3%	0.07

**Table III: Comparison of conception between letrozole and letrozole-metformin group.**

Cycle	Group A (letrozole)		Group B (letrozole-metformin)		P-value
	No.	%	No.	%	
First cycle	6/75	8%	7/75	9.3%	0.77
Second Cycle	8/69	11.5%	11/68	16.2%	0.44
Third Cycle	12/61	19.6%	17/57	29.8%	0.22
mean conception rate per cycle	26/205	12.7%	35/200	17.5%	0.48
Cumulative conception rate	26/75	34.6%	35/75	47%	0.14

syndrome, the most common hormonal disorder that affects 8-18% of young women.<sup>5,9</sup>In this study, we compared the ovulation rate and conception rate with letrozole alone and letrozole-metformin combination in subfertile women with PCOS having BMI >25 Kg/m<sup>2</sup>. The mean age of women in our study was 29.6 years and 28.93 years in letrozole and letrozole-metformin group respectively. This is closer to the age of the women in the Rohaim HSG study, which included 100 overweight women with PCOS, with a mean age of 27.7 years and 28.2 years in the letrozole and letrozole-metformin groups, respectively.<sup>20</sup> In a similar study of 120 patients by El-Gharib MN the mean age of patient was 28±3.13years in letrozole group and 29.55±3.47years in letrozole-metformin group which was closer to patient's age in this study.<sup>21</sup>

The mean BMI of patients in our study was 28.65 and 29.15 which was higher than mean BMI of women 27.2 and 27.3 in letrozole and letrozole-metformin group respectively in Rohaim's study.<sup>20</sup> This might be because we included both overweight and obese women while only overweight (BMI 25-29kg/m<sup>2</sup>) women were included in his study.

The majority (73%) of women had primary subfertility in our study which was comparable to Rohaim's study (65%). The mean duration of subfertility was 2.16 year and 2.37years in our study which was less than the study by Mohsin R where the mean duration of subfertility was 3.11years and 3.15 years in letrozole and letrozole-metformin group respectively.<sup>22</sup> The mean duration of subfertility in study by Rohaim HSG was 3.03 years and 2.95 years in letrozole and letrozole-metformin group which was also higher than in our study.<sup>20</sup>

In our study, the cumulative ovulation rate was 9.3% higher in the letrozole-metformin group (84% in letrozole group and 93.3% in letrozole-metformin group) but the difference was not statistically significant (P=0.07). Our results are comparable with study by Rohaim HSG where ovulation occurred in 80 % (n=40/50) and 84%(n=42/50) of women in letrozole and letrozole-metformin group(P=0.834).<sup>20</sup>El-Gharib M in his study of 120 women also noted a 4% higher ovulation rate in letrozole-metformin group (80.5% versus 76.5%) which was insignificant.<sup>21</sup> Contrary to this Aiman Z in a study at Lady Aitchison hospital Lahore observed a 29 % higher ovulation rate in women given letrozole-metformin compared to letrozole alone (89% versus 60 %, P=0.001).<sup>23</sup> In her sub analysis the difference was unrelated to BMI. The reason for lower ovulation rate in

letrozole group in her study than in ours and other studies is not clear.

The cumulative conception rate in our study was 12.5% higher in letrozole-metformin group (34.5% versus 47% in the letrozole and letrozole-metformin group respectively) but the difference was not significant (p=0.135). The results are closer to the study by Rohaim HSG where 6% increase in conception rate was observed after addition of metformin (36% and 42% in letrozole and letrozole-metformin group respectively, p=0.539).<sup>20</sup> Mohsin R in her study of 100 patients, noted a marked improvement in pregnancy rate with the addition of metformin. (56% in letrozole-metformin versus 41% in letrozole group, p=0.03).<sup>22</sup> The reason for this difference might be that she included both normal and obese women in her study and our study included only overweight and obese women who are resistant to treatment. Giang S noted an ovulation rate of 89% but a very high conception rate of 86% in 36 women given letrozole-metformin and nursing support for 5 months. The nursing staff provided advice about diet, exercise, along with psychological support. The high conception rate compared to ours (47%) and other studies discussed above might be because of longer duration of treatment and care provided by nursing staff.<sup>24</sup>

The addition of metformin was tolerated well by majority of patients in our study, with only 13%(n=10) and 12% (n=9) patients having nausea, vomiting, and diarrhea as compared to 5% (n=4) and 4% (n=3) in letrozole alone group respectively. Similar observation was made by Jiang S in his study, in which 11% of participants experienced nausea, vomiting and 5.5% diarrhoea with the combination of letrozole and metformin.<sup>24</sup> Gastric side effects were observed in 5%and 8.3% patients taking letrozole and letrozole-metformin in study by El-Gharib.<sup>21</sup> Khan Z showed that 30% (n=9/30) patients experienced hot flushes and only 6% (n=6/30) gastric side effects with letrozole-metformin.<sup>25</sup> Rohaim HSG noted a statistically significant (P=0.0001) increase in nausea, vomiting and diarrhea with addition of metformin.<sup>20</sup> The reason for very high incidence of side effects in her study as opposed to ours and other studies is not clear.

Our study has shown the benefit of addition of metformin to letrozole for subfertility treatment, but the benefit is not statistically significant. The limitation of our study is that we used a 5mg dose of letrozole instead of starting with a minimum dose and increasing it to maximum according to ovarian response. There is a need for

further multicenter studies with a large sample size to evaluate the efficacy of addition of metformin to letrozole on ovulation and conception rate as well as its effect on risk of miscarriage.

## Conclusion

Combination of letrozole and metformin improves the ovulation and conception rate in overweight and obese women but the effect is not significant statistically.

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