

# Outcome of Metformin-Letrozole Therapy In Patients With Metformin-Clomiphene Resistant Polycystic Ovarian Syndrome

Nasreen Fatima,<sup>1\*</sup> Shawita,<sup>1</sup> Anum Ellahi<sup>1</sup>

## ABSTRACT

**Objective** To evaluate the therapeutic effects of combined metformin-letrozole in the treatment of sub-fertility in women with metformin clomiphene citrate resistant polycystic ovarian syndrome (PCOS).

**Study design** Cross sectional study.

**Place & Duration of study** Department of Obstetrics & Gynaecology, Jinnah Postgraduate Medical Centre (JPMC) Karachi, from May 2018 to November 2018.

**Methodology** PCOS patients attending Gynaecology outpatient department who were found resistant to the treatment with clomiphene citrate and metformin were enrolled after taking consent. Letrozole 2.5mg tablet was advised to be used daily, orally from day 2 of menstruation cycle for five days with metformin 500mg thrice daily after two months wash out period for clomiphene citrate. Trans-vaginal ultrasound was done at 12<sup>th</sup> day of cycle for measurement of number, size of follicles and endometrial thickness. Data was collected and analyzed using SPSS version 20.

**Results** A total of 147 women with PCOS were enrolled. Mean age of the patients was 34.74±2.81 year. Out of the total, 105 (71.4%) women showed response to the treatment. Moreover, 70 (47.6%) women achieved pregnancy. Finally, 94 (63.9%) women showed good response in terms of endometrial thickness.

**Conclusion** The combined treatment of letrozole with metformin found helpful in restoring menstrual cycle with better rates of ovulation, improvement in the clinical sign of hyperandrogenism and higher rates of full term pregnancies.

**Key words** Polycystic ovarian syndrome, Metformin, Letrozole, Infertility.

## INTRODUCTION:

The polycystic ovarian syndrome is considered to be one of the main reasons of sub-fertility in women with a prevalence of 5-13% in reproductive age.<sup>1</sup> PCOS is associated with the insulin resistance in

majority of patients resulting in hyperinsulinemia that contributes to hyperandrogenism.<sup>2</sup> Metformin is insulin sensitizing drug used in PCOS, which is helpful in restoring ovulation. Moreover it is useful in reducing weight, circulating androgen levels, risk of miscarriage and risk of gestational diabetes mellitus (GDM).<sup>3,4</sup> PCOS is the most common cause for an ovulatory sub-fertility in women.<sup>5</sup>

<sup>1</sup> Department of Gynaecology and Obstetrics Ward-9 JPMC Karachi

## Correspondence:

Dr. Nasreen Fatima<sup>1\*</sup>  
Department of Gynaecology and Obstetrics  
Ward-9 JPMC Karachi  
E mail: drnasreenf@gmail.com

Dasari and Pranahita reported ovulatory and pregnancy rate of about 24% with combination of metformin- clomiphene citrate.<sup>6</sup> Still clomiphene citrate resistance is seen in approximately 15-40% women with PCOS.<sup>7</sup> Letrozole is an aromatase inhibitor with less anti-estrogenic properties and has been shown to be effective in inducing ovulation and

pregnancy in women with anovulatory PCOS and inadequate clomiphene citrate response while improving ovarian response to FSH in poor responders.<sup>8</sup> Moreover it has fewer side effects than clomiphene citrate and gonadotrophins such as multiple pregnancies and OHSS.<sup>9</sup> In a study conducted by Sorabvand et al it was found that in PCOS patients resistant to the treatment with clomiphene citrate, combine treatment with letrozole and metformin lead to the higher rates of full term pregnancies.<sup>10</sup> Considering beneficial effect of metformin-letrozole combination, this study aimed to establish the therapeutic efficacy of this combination in women who had metformin-clomiphene citrate resistant PCOS.

#### **METHODOLOGY:**

In this cross sectional study all consecutive cases of PCOS who were treated at the Department of Obstetrics & Gynaecology, Jinnah Postgraduate Medical Centre Karachi, from May 2018 to November 2018 were enrolled. Detailed history and physical examination including height and weight were taken. Women with history of ovarian drilling, recent administration of hormonal therapy and chronic diseases were excluded.

A two months washout period before starting treatment with letrozole was ensured to eliminate post-treatment effect of clomiphene citrate. In all patients, letrozole 2.5 mg/ per day given orally, started on 2nd day of menstrual cycle and continued for 5 days. Metformin 500mg thrice daily was started concomitantly. Number and size of ovarian follicle as well as endometrial thickness measured by transvaginal ultrasound at day-12 of menstrual cycle. Same treatment protocol followed for three month period.

Data was entered and analyzed using statistical package for social science (SPSS) soft ware version 20, (IBM corp, Chicago, USA). Quantitative data was described using mean and standard deviation. Qualitative data described as frequency and percentages. Data was stratified on age group, BMI categories and duration of sub-fertility to find out the effect on outcome. Post stratification Chi-square test was used. A P-value of = 0.05 was taken as significant.

#### **RESULTS:**

Among total 147 patients, age was from 20 year - 40 year with mean age  $34.78 \pm 2.81$  year. Mean duration of sub-fertility, BMI, number follicle, size of follicle and endometrial thickness are shown in table I. Of the total, 87 (59.2%) and 60 (40.8%)

women were in age group 18-30 years and 31-40 years respectively. Sixty-five (44.2%) patients had sub-fertility of less than 4 years. Of the total 16 (10.9%), 89 (60.5%) and 42 (28.6%) patients were in BMI group 18-24.9 kg/m<sup>2</sup>, 25-29.9 kg/m<sup>2</sup> and > 30 kg/m<sup>2</sup> respectively.

In this series 105 (71.4%) women responded to the treatment and 70 (47.6%) achieved pregnancy. In 94 (63.9%) study participants good response observed in terms of endometrial thickness. Sixty-three (60%) and 42 (40%) women who were in age group 18-30 years and 31-40 responded to the treatment respectively (P=0.44). Patients who had BMI 18-24.4, 12 (11.4%) showed treatment response (P=0.94). In women with BMI 25-29.9, 47 (67.1%) achieved (P=0.11). In women with sub-fertility for < 4 years, 47 (44.8%) responded to treatment (P=0.49). Patients who had sub-fertility for < 4 years, 27 (38.6%) achieved pregnancy (P=0.12). Fifty-seven (60.6%) and 37 (39.4%) patients who were in age group 18-30 years and 31-40 years respectively achieved good endometrial thickness respectively (P=0.38). Patients who had the sub-fertility for < 4 years, 38 (40.4%) achieved good endometrial thickness thickness (P=0.14).

#### **DISCUSSION:**

PCOS is mentioned as common endocrinopathy in reproductive age women which is associated with metabolic disorders and anovulatory sub-fertility.<sup>11-13</sup> Ghahiri et al evaluated the efficacy of letrozole compared to clomiphene citrate as a first line treatment of PCOS patients. In letrozole group 58% while 47% patients from clomiphene group achieved pregnancy. Thirty-six patients who were in letrozole group and 30 patients from clomiphene group had regular periods during and after the course of treatment.<sup>14</sup> In our study no comparison was made. It was single arm study where combination of drugs was used.

Sohrabv and et al evaluated sub-fertility patients with PCOS dividing into metformin- letrozole and metformin-clomiphene groups. For 6-8 weeks metformin given to both the groups then one group received letrozole (2.5mg) while clomiphene citrate given to the second group that was started from day-3 of the menstrual cycle for five days. No difference observed in mean number of mature follicle > 18mm and ovulation rate. In letrozole group significantly higher endometrial thickness was observed. The rate of pregnancy in letrozole group was 34.5% and clomiphene citrate group 16.67%, whereas full term pregnancy rate was higher in the patients taking letrozole treatment.<sup>8</sup> In our study

**Table I: Baseline Variables n=147**

Variables	Mean	Standard Deviation	MIN - MAX
Age (Year)	34.78	± 2.81	20 – 40
Duration of Sub-Fertility (Year)	4.72	± 0.58	2 – 6
BMI (Kg/m <sup>2</sup> )	29.28	± 2.56	27 – 34
Number of Follicles (n)	8	± 4.30	6 – 15
Size of Follicles (mm)	18	± 2.91	15 – 20
Endometrial Thickness (mm)	12	± 1.78	11 – 13

letrozole was used with metformin and good results were found in terms of size of follicles, endometrial thickness and pregnancy rate. Another prospective study enrolled 106 women with anovulatory PCOS who failed to ovulate with clomiphene citrate alone. Cumulative pregnancy rate was 57.14% with letrozole.<sup>15</sup>

#### CONCLUSIONS:

Combined treatment with letrozole and metformin can restore menstrual cycle with better ovulatory rate and improvement in the clinical signs of hyperandrogenism with higher rates of full term pregnancies.

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