

## The Negligible Effect of Metformin Addition to Letrozole in Treating Overweight Women with PCOS

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### ABSTRACT

**Aim:** To compare the effects of letrozole alone and letrozole plus metformin on ovulation induction, endometrial thickness, number of ovarian follicles and, the pregnancy rate in overweight, infertile women with the polycystic ovarian syndrome.

**Study design:** Prospective, randomized clinical trial.

**Material and methods:** This study was conducted on 120 patients with polycystic ovarian syndrome, recruited from the infertility clinic of Tanta University Hospital, January 2017 to December 2019. Sixty women were assigned at random to each group. In a group, 1 patient received only daily 5 mg letrozole between days 3 and 7 of the menstrual cycle, and in group 2, continuous metformin was used at the dose of 500mg/TDS/day for three months; afterward, daily 5 mg letrozole between 3 and 7 days of the menstrual cycle was added to the metformin therapy. The patients were treated until pregnancy occurred, or three cycles were reached without pregnancy.

**Results:** There was an insignificant increase in the cumulative pregnancy rate between the metformin-letrozole and the letrozole group. In the metformin-letrozole group, 28.33% of the patents got pregnant, compared with 25% of the patients in the letrozole group. There was no significant difference between the letrozole and the metformin-letrozole group regarding ovulation rate, number of the follicle, endometrial thickness, and progesterone level.

**Conclusion:** The addition of metformin to letrozole does not improve the outcome of overweight PCOS women.

### Keywords:

Letrozole, Metformin, PCOS, Overweight.

### Introduction

Polycystic Ovary Disorder (PCOS) is a huge medical issue. PCOS is probably the most reason that influences the ladies of childbearing age, [1] and regularly prompts barrenness [2]. The research proposes that 5% to 10% of females 18 to 44 years old are influenced by PCOS, making it the most well-known endocrine irregularity among ladies of regenerative age in the U.S [3]. Different administrations proposed for fruitless ladies with PCOS. Be that as it may, the ideal administration choice has not tended to fulfill [4].

Aromatase, a compound containing cytochrome P450 hemoprotein, catalyzes the change of androstenedione and testosterone to estrogen. The ovarian aromatase is delivered in wealth in ladies during the regenerative stage since ovaries are a significant site for the creation of estrogen [5] The third-age aromatase inhibitors like letrozole are profoundly powerful, with a 97-99% decrease in estrogen levels [6].

Letrozole is a particular aromatase inhibitor. It hinders estrogen creation by quelling the protein aromatase [7]. Letrozole diminishes estrogen creation without influencing estrogen receptors, decreases the negative criticism on the nerve center and pituitary, and animates FSH discharge [8]. Letrozole is additionally cleared from the flow all the more quickly because of a shorter half-life, 48 hours when contrasted with clomiphene citrate, which may take as long as two months because of its

drawn-out half-life, two weeks [9]. The present bits of proof recommend that letrozole can put as first-line treatment for the administration of barrenness due to PCOS and unexplained fruitlessness [10].

Metformin is a biguanide that brings down blood glucose levels in hyperglycemic people with type-2 diabetes mellitus yet has no impact on glucose levels in ordinary subjects [11]. Metformin is right now the primary line oral treatment for the administration of type 2 diabetes [12]. Other helpful impacts of metformin were uncovered, such as the hindrance of tumors, postponing maturing, and immunomodulation [13]. The focal point of the component of the activity of metformin is the metabolic modification of the cell vitality [14]. Metformin applies its overwhelming impact in diminishing glucose by the reuptake of insulin-invigorated glucose in skeletal muscles, reduced generation of hepatic glucose, and decreased intestinal glucose assimilation [14,15].

Numerous uncontrolled and some controlled studies showed that metformin diminished insulin obstruction in ladies with PCOS and improved the probability of ovulation and pregnancy without, or some of the time with, clomiphene citrate [16,17]. However, the specific job of metformin in the administration of ladies with PCOS has been very dubious [18]. Several investigations have indicated a good job of metformin in PCOS patients by expanding pregnancy rate and improving the metabolic circumstance [19-21].

This study aims to compare the effect of administration of letrozole versus combined metformin-letrozole in the induction

of ovulation in overweight, infertile women with PCOS.

## Patients and Methods

This prospective randomized study was conducted at the Department of Obstetrics & Gynecology at Tanta University Hospital from January 2017 to December 2019 to treat infertility.

### Subjects

The study included 120 overweight women with BMI 25-30, complaining of polycystic ovary syndrome and attending the infertility outpatient clinic of Tanta University Hospital. All women involved in the study gave written informed consent after proper counselling.

### Inclusion criteria

All patients fulfilled the following inclusion criteria:

- Age 18-30 years.
- Polycystic ovarian syndrome women according to Rotterdam Criteria 2003 [22]
- Standard parameters of the husband's semen

### Exclusion criteria

- Patients with a history of cardiovascular disease, diabetes or liver, and kidney failure were excluded
- Similarly, patients whose partner sperm count was less than 20 million/ ml and sperm motility less than 20% were also not included
- Patients who had undergone surgical treatment of infertility
- Recent history of ovulatory inducing drugs within the last 3 months
- Patients are diabetic mellitus or any systemic disease

The patients were divided randomly into two groups through a series of blind envelopes from 1 to 120. Each patient was invited to pull out an envelope and was placed in either:

- **Group A:** Letrozole group (envelopes number 1-60)
- **Group B:** Metformin-Letrozole group (envelopes number 61-120)

## Methods

Informed written consents were obtained from the patients participating in this study after informing them about the aims of the study, the steps of the study, drugs are given, and the capability to withdraw at any time.

### Patient preparation

History taking including clinical examination, transvaginal ultrasound examination, estimation of serum progesterone on days 21-23 of the cycle.

### Induction of ovulation

**Table 1:** Comparison between the two studied groups according to the characteristics of the study population.

Item	Letrozole Group		Letrozole _Metformin Group		P-value
	Mean	SD	Mean	SD	
Age (years)	28.54	3.13	29.55	3.47	0.21073
Duration of infertility (Y)	3.81	1.5	2.76	1.48	0.55809
BMI (Kg/m2)	28.98	3.83	29.21	2.92	0.99848

\*: Statistically significant at  $p \leq 0.05$

As regards the effect of treatment on ovulation: the letrozole group reported 36 cases (60.00%) ovulation at the first cycle after treatment, increased to 48 patients (78.33%) at the second

All patients of both groups were received 5 mg letrozole (Letrozole, Technopharma, Cairo, Egypt) for five days from 3rd day of their menstrual cycle. The condition of the ovaries was determined by transvaginal sonography every other day from the 10th of the cycle.

Patients of group B received 1500 mg metformin HCl daily, 500 mg three times a day (Cidophage; Chemical Industries Development, Cairo, Egypt).

The hCG hormone (a total of 10,000 IU IM, Choriamon; IBSA, Lugano, Switzerland) was given when one follicle measuring at least 18 was found. Patients advised having intercourse every other day for one week, starting 24-36 h after receiving HCG. The patients continued treatment for three successive cycles using the same protocol.

### Follow up

Follicle monitoring and endometrial thickness measurement were done with the help of transvaginal sonography serially starting from the 6th day of the drug administration when at least one follicle reached maturity (>18mm). Confirmation of the pregnancy was done through a urine test using a pregnancy test kit and transvaginal sonography. After verification of pregnancy, these patients were followed up and treated as antenatal cases. Metformin continued until 28 weeks. The two groups were compared to each other regarding ovulation, evaluated by folliculometry and progesterone levels.

Statistical methods: The data were transferred to IBM cards using an IBM personal computer and analyzed with the Statistical Program for Social Sciences V11.0 (SPSS Inc, Chicago, IL). Descriptive statistics comprised the mean and Standard Deviation (SD). Analytical statistics constituted the student t-test to compare independent quantitative means, and the chi-square test ( $\chi^2$ ) to compare between the different groups concerning qualitative data. The chosen level of significance was  $p < 0.05$  in all studies. The p-value less than 0.05 was considered to be significant, and the confidence interval for the odds ratio was set at 95%.

## Results

There were no significant differences between both groups in age or duration of infertility (mean age was  $28.54 \pm 3.13$  years and mean duration of infertility was  $3.81 \pm 1.50$  years in the letrozole group and mean age was  $29.55 \pm 3.47$  years and mean duration of infertility was  $2.76 \pm 1.48$  years in the metformin-letrozole group. As regards BMI, the mean BMI was  $28.98 \pm 3.83$  in the letrozole group and  $29.21 \pm 2.92$  in the metformin-letrozole group, as displayed in Table 1.

cycle, and to 55 patients (91.66%) at the third cycle. On the other hand, the Metformin-letrozole group reported 38 patients (63.33%) ovulation at first cycle after treatment, which

increased to 50 cases (83.33%) in the second cycle and 57 patients (95.00%) at the end of the third cycle. Correspondingly, the letrozole group achieved a cumulative ovulation rate of

76.65 %, while the Metformin-letrozole group achieved 80.55%. In conclusion, both drugs affected ovulation without any significant difference, as shown in Table 2.

**Table 2:** Effect of treatment on ovulation in the studied groups.

Item	Letrozole Group		Letrozole _Metformin Group		P-value
	N	%	N	%	
First Cycle	36	60	38	63.33	0.7668
Second Cycle	48	78.33	50	83.33	0.5313
Third Cycle	55	91.66	57	95	0.4799

\*: Statistically significant at  $p \leq 0.05$

Concerning the mean number of follicles in the ovaries of both groups after treatment, we found that in the letrozole group, the mean number of follicles was  $1.34 \pm 0.53$  at the first cycle, elevated to be  $1.38 \pm 0.76$  at the second cycle, and to  $1.41 \pm 0.71$  at the third cycle. In the metformin-letrozole group, the

mean number of follicles was  $1.25 \pm 0.49$  in the first cycle, elevated to  $1.32 \pm 0.72$  in the second cycle and  $1.43 \pm 0.65$  at the third cycle. There was no statistical difference between the two studied groups, as represented in Table 3.

**Table 3:** Effect of treatment on the mean number of follicles.

No. of follicles	Letrozole Group			Letrozole _Metformin Group			P-value
	No.	Mean	SD	No.	Mean	SD	
First Cycle	36	1.34	0.53	37	1.25	0.49	0.3207
Second Cycle	48	1.38	0.76	47	1.32	0.72	0.35621
Third Cycle	52	1.41	0.71	54	1.43	0.65	0.73737

P: p-value for comparing between the two studied groups

In connection with the mean follicular diameter across, there is no factually huge distinction in mean follicular width (MFD) in the two groups. In the letrozole group, it was  $17.04 \pm 1.09$  mm,  $17.39 \pm 1.36$  mm, and  $18.95 \pm 3.04$  mm at the first, second, and third cycles, respectively, while in the metformin-letrozole

group, the corresponding values were  $17.56 \pm 1.05$  mm,  $19.29 \pm 1.27$  mm and  $19.30 \pm 3.03$  mm at first, second and third cycles respectively. There was an insignificant difference between both groups, as displayed in Table 4.

**Table 4:** Impact of treatment on the mean follicular width in studied groups.

Mean follicular diameter	Letrozole Group		Letrozole _Metformin Group		P-value
	Mean	SD	Mean	SD	
First Cycle	17.04	1.09	17.56	1.05	0.5831
Second Cycle	17.39	1.36	18.29	1.27	0.73229
Third Cycle	18.95	3.04	19.3	3.03	0.50952

\*: Statistically significant at  $p \leq 0.05$

Regarding the number of follicles  $>18$ mm in both groups, there was no statistically significant difference between studied groups. In the letrozole group, the average number of follicles measuring  $>18$  mm was  $1.13 \pm 0.48$ ,  $1.05 \pm 0.52$ , and  $1.14 \pm 0.55$

at first, second, and third cycles, respectively. In contrast, in the metformin-letrozole group, the equivalent values were  $1.01 \pm 0.46$ ,  $0.97 \pm 0.51$ , and  $1.22 \pm 0.45$ , as shown in Table 5. There was an insignificant difference between both groups.

**Table 5:** Effect of treatment on the number of follicles  $>18$ mm.

No. of follicles $>18$ mm	Letrozole Group		Letrozole _Metformin Group		P-value
	Mean	SD	Mean	SD	
First Cycle	1.13	0.48	1.01	0.46	0.5944
Second Cycle	1.05	0.52	0.97	0.51	0.54808
Third Cycle	1.14	0.55	1.22	0.45	0.92108

\*: Statistically significant at  $p \leq 0.05$

Table 6, 6 illustrates that no statistically significant difference was found between letrozole and metformin-letrozole groups regarding the cumulative number of follicles and the aggregate number of mean follicular diameter. On the contrary, there was

a significant increase in the Metformin-letrozole group than letrozole group as regard Cumulative Endometrial thickness as displayed in Table 6.

**Table 6:** Effect of treatment on the cumulative number of follicles, mean follicular diameter, and endometrial thickness between the study groups.

Item	Letrozole Group		Letrozole _Metformin Group		P-value
	Mean	SD	Mean	SD	
Cum. No. of follicles	1.59	0.55	1.55	0.53	0.59632
Cum. Mean follicular diameter	18.03	2.76	18.52	2.95	0.33318
Cum no. of fol. >18 mm	1.32	0.47	1.36	0.38	0.99222

\*: Statistically significant at  $p \leq 0.05$

The endometrium was thicker in the group accepting metformin-letrozole than in that getting letrozole (Table 7) on the day of human chorionic gonadotrophin administration. In the letrozole group, the endometrial thickness was  $7.93 \pm 0.91$ ,  $8.92 \pm 0.94$ , and  $9.33 \pm 0.95$  mm at the first, second, and third

cycles, respectively, while in the metformin-letrozole group, it was  $7.82 \pm 0.79$ ,  $9.02 \pm 0.99$ ,  $9.34 \pm 1.03$  at the first, second and third cycles respectively. The difference between both groups was statistically insignificant.

**Table 7:** Comparison between the two studied groups according to Endometrial Thickness on the day of HCG administration in the three months separately and Cumulative Endometrial thickness.

Item	Letrozole Group		Letrozole _Metformin Group		P-value
	Mean	SD	Mean	SD	
First Cycle	7.93	0.91	7.82	0.79	0.21088
Second Cycle	8.92	0.94	9.02	0.99	0.6351
Third Cycle	9.33	0.95	9.34	1.03	0.74736

\*: Statistically significant at  $p \leq 0.05$

In connection with the progesterone level at the mid-luteal phase, we found an insignificant increase in progesterone levels in the metformin-letrozole group than the letrozole group. In the metformin-letrozole group, progesterone values were 8.73

$\pm 0.96$ ,  $9.09 \pm 0.49$ , and  $9.59 \pm 0.62$  at the first, second, and third cycles, respectively, while in the letrozole group, the equivalent values were  $8.58 \pm 0.90$ ,  $8.97 \pm 0.73$ ,  $9.39 \pm 0.70$  at first, second and third cycles respectively as revealed in Table 8.

**Table 8:** Comparison between the Letrozole and Letrozole metformin groups according to serum progesterone (ng/ml) level.

Progesterone (ng/ml)	Letrozole Group		Letrozole _Metformin Group		P-value
	Mean	SD	Mean	SD	
First Cycle	8.58	0.9	8.73	0.96	0.39068
Second Cycle	8.97	0.73	9.09	0.49	0.9548
Third Cycle	9.39	0.7	9.59	0.62	0.71979

\*: Statistically significant at  $p \leq 0.05$

The menses were regular in 65% of patients in the letrozole group and 68.33 % of the metformin-letrozole group. Side effects as gastritis and sickness happened in 5% of patients in letrozole and 8.33% of metformin-letrozole groups. Regarding pregnancy rate (per cycle) in the letrozole and metformin-letrozole groups, there was no critical distinction between the pregnancy rates per cycle in the letrozole and the metformin-letrozole gatherings ( $\chi^2 = 0.045$  and  $P = 0.8323$ ). The cumulative pregnancy rate in the letrozole group was 25.00% versus 28.33% for the metformin-letrozole group. In the letrozole group, three cases got pregnant in the first month; six cases got pregnancy within the second and third months, respectively. The corresponding figure relating to the metformin-letrozole group were three, seven, and eight cases got pregnancy within the first, second, and third months respectively.

## Discussion and Conclusion

The high predominance of PCOS in ladies and its fruitlessness results has prompted various studies focusing on new medications with fewer or no reactions. Letrozole-metformin is a broadly suggested substitute that can animate FSH discharge and ovarian follicular improvement [23]. Overweight (BMI  $\geq$

25 kg/m<sup>2</sup>) is associated with an all-encompassing danger of anovulatory barrenness [24]. This examination was performed to research the impacts of letrozole-metformin versus letrozole alone in the administration of overweight ladies having PCOS.

The consequences of this examination demonstrate that overweight ladies with PCOS experienced an unimportant higher pregnancy rate when they got metformin in addition to letrozole in correlation with in addition to letrozole alone. In our present investigation, we found that the aggregate pregnancy rate in the letrozole bunch was 25.00% versus 28.33% for the metformin-letrozole bunch in the letrozole gathering. This considers the aftereffects of Hurley et al. They reported that the expansion of metformin during ovulation acceptance with letrozole does not influence pregnancy result in fruitless ladies with polycystic ovary disorder [25].

As respects the adequacy of letrozole, our outcomes are similar to that found by Elnashar et al. [26], Badawy et al. [27], and Nupur et al. [28] studies in which pregnancy/cycle, with letrozole, were 13.6%, 12.2%, and 14.2% individually. Mitwally and Casper [29], Al-Omari et al. [30], Atay et al. [31], and Begum et al. [32] in which pregnancy/cycle were 17.5%, 25%, 19%, and

15.1% separately. Sohrabvand et al. detailed that the pregnancy rate in the metformin-letrozole bunch was 34.5% [33]. Multiple randomized preliminaries inspecting clinical pregnancy rates in patients treated with metformin versus fake treatment are underpowered and neglect to distinguish any improvement with metformin [34-39].

Our results disprove those of Rabia Mohsin et al., who found a high pregnancy rate in patients getting letrozole in addition to metformin versus letrozole alone [40]. Liu et al. revealed a pregnancy pace of 57.9% in letrozole in addition to metformin gathering and just 46.8% in patients who got letrozole alone [41]. Another examination directed by Elgafore et al. revealed that letrozole, in addition to metformin blend, can have a triumph pace of 90.57% and fruitful pregnancy in 34.50% females [42].

While Davar et al. announced a pregnancy pace of just 8.3% in PCOS ladies, these creators found a very lower speed of pregnancy acceptance after letrozole and metformin mix [43]. No critical connection between age, BMI, or term of fruitlessness, the pace of ovulation, number of follicles, or endometrial thickness seen in both examined gatherings.

Only one RCT in anovulatory ladies with PCOS and a weight file (BMI) >32 kg/m<sup>2</sup> (got metformin or fake treatment) and ≤ 32 kg/m<sup>2</sup> (acquired CC, metformin, or both) announced live-birth rates. This preliminary found no factually noteworthy distinction, detailing a live-birth pace of 16% (5/32) with metformin and 6% (2/33) with fake treatment in ladies with BMI >32 kg/m<sup>2</sup>. For ladies with a BMI ≤ 32 kg/m<sup>2</sup>, there is no proof of considerable contrasts in results whether treated with metformin CC or both [44].

Lastly, we conclude that the expansion of metformin to letrozole does not improve the overweight PCOS ladies.

## Conflicts of Interest

The authors declare that there is no conflict of interest.

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N/A

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