



## ORIGINAL ARTICLE

## Letrozole versus Clomiphene Citrate with metformin for Induction of Ovulation in Obese patients with Polycystic Ovarian Disease

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## ABSTRACT

**Background:** the polycystic ovary syndrome (PCOS) is important cause of an ovulatory infertility and a notable proportion of women of reproductive age are affected. Different factors could result in different manifestations and many of these are related to predispositions. **Objectives:** The study was carried out to study the improvement of ovulation induction in obese patients with Polycystic ovarian syndrome (PCOS). **Subjects and methods:** This is prospective clinical trial that was conducted in the infertility unit of Zagazig university Hospital on 120 patient suffering from PCOS were included in this study during the period from October 2018 to May 2019. This trial was designed to compare the improving induction of ovulation in obese females with Polycystic ovarian syndrome undergoing induction of ovulation by Clomid and Metformin (n=60) or Letrozole (n=60). **Results:** There was no significant statistical difference between Clomid and Metformin group and letrozole group in term of pregnancy rate, There was a significant statistical difference between Clomid and Metformin group and letrozole group in term of Size of dominant Graafian follicle (on day 11) (p=0.03) and the Size of dominant Graafian follicle (on day 13-14) (p=0.01). **Conclusion** Letrozole improves endometrial thickness and cervical mucosa and causes monofollicular ovulation but action of clomiphene citrate combined with metformin improved the ovulation and increased total number of follicles. Therefore, Letrozole can be used for the ovulation induction improvement in obese women having PCO

**Keywords:** Letrozole; Polycystic Ovarian Disease; Ovulation; Clomid

## INTRODUCTION

PCOS is a hormonal disorders in women in the reproductive age, which affecting about 5 10 percent. PCOS cause irregular menstrual bleeding and the difficulty of getting pregnancy. The syndrome occurs according to abnormality of hormones levels. The “polycystic ovarian syndrome” means the appearance of small cysts in the outer edge of the enlarged ovaries of women [1].

Ovulation dysfunction is the most common causes of reproductive failure in infertile women. The prevalence is about 30 to 40% in infertile women. Polycystic ovary syndrome is closely related to ovulation

dysfunction and affected about 7% of women in the reproductive age, It is a common endocrine disorders in women [2].

Clomiphene citrate (CC) has been widely used for the treatment of infertility as it has predominant anti-estrogenic action resulting in long-lasting estrogen receptor depletion [3]. It is known that Clomiphene citrate results ovulation rate of 60-80% but the conception rate about 20% [4].

Polycystic ovary syndrome is strongly related with obesity. It is proposed that PCOS-specific inherent insulin resistance with additional obesity and lifestyle-related extrinsic

insulin resistance affected the women with PCOS

Obesity, especially abdominal obesity, increases insulin resistance. Insulin resistance also related with a risk for 2 DM and CVD increase in women with PCOS.

Obesity and insulin resistance affected the reproductive, psychological and metabolic features in women with PCOS. Women with PCOS may also display high rates of obesity and abdominal obesity. However, the obesity prevalence in women with PCOS varied from country to country, although it is difficult to make comparisons between countries [5].

#### AIM OF THE WORK

The aim of this study was to improve ovulation induction in obese patients with Polycystic ovarian syndrome (PCOS).

#### Objectives

- To assess ovulation by serial folliculometry using transvaginal ultrasound in both letrozole and clomiphene citrate groups.
- To assess pregnancy rate by measuring B HCG and transvaginal ultrasound in both letrozole and clomiphene citrate groups.
- To compare the effect of Letrozole versus Clomiphene citrate on the ovulation induction and rate of pregnancy in obese patients with PCOS.

#### PATIENTS AND METHODS

- This Prospective non randomized controlled interventional clinical trial was conducted in the infertility unit of Zagazig university Hospital. The study included 120 patients suffering from PCOS during the period from September 2018 to April 2019. This trial was designed to compare the improving the ovulation induction in obese females with PCOS undergoing induction of ovulation by Clomiphene citrate and Metformin (n=60) or Letrozole (n=60).

Written informed consent was obtained from all subjects and the study was carried according to the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studied involving humans.

**Patients were divided to 2 groups:**

**Group A :** included 60 women received Clomiphene citrate 50mg tab 1x2 orally twice daily with metformin 500mg 1 x 2 per day started from 3<sup>rd</sup> to the 7<sup>th</sup> day of menstrual cycle for three successive cycle

**Group B :** includes 60 women received Letrozole 2.5mg tab twice daily orally started 3<sup>rd</sup> to 7<sup>th</sup> day of menstrual cycle for three successive cycle.

#### Inclusion Criteria:

- Age ranged between 20-35 years old.
- Primary infertility.
- Diagnosis of PCO according to Rotterdam criteria (2004): (two of three criteria).
  - a) Oligomenorrhea and / or anovulation.
  - b) Clinical Hirsutism and or/ hyper-androgenism (increase in the serum free testosterone level ).
  - c) Ultrasound diagnosis of Polycystic ovaries by (presence of more than 12 follicles with 2-9mm diameter or ovarian volume > 10cm<sup>3</sup>).
- Bilateral patent tubes determined by laparoscopy or HSG.
- Normal semen analysis for husbands due to WHO criteria [6].
- Obese patients BMI > 30Kg/m<sup>2</sup>

#### Exclusion Criteria:

- Age less 20 years over 35 years old.
- Uterine pathology for fibroid or ovarian cyst.
- Hypo or Hyperthyroidism (endocrinological disorder) and Hyperprolactinemia,
- Weak liver or kidney functions.
- hypersensitivity to drugs of study.
- Endometriosis.
- Women with bilateral tubal blockage determined by laparoscopy or HSG.
- Past gynecological disorder.

#### Methods:

All Participating subjected to:

- past History including : Menstrual history (Oligomenorrhea or Amenorrhea).
- Regularity of the cycle.
- Medical , surgical history, history of drug intake and family history.
- History of past operations and endocrine disease.
  - Physical examination

- General examination including breast, acne, thyroid, BMI and hair distribution
- Abdominal **examination** For abdominal operations and previous scar pelvic.
- **Pelvic** examination for cystic ovaries enlargement .
- Ultrasound for PCOS diagnosis.
- **Laboratory Investigation:**
- In amenorrhoeic patient progestin was given to induce withdrawal bleeding ( medroxy progesterone acetate 5mg 1x3x7)
- Serum LH and FSH and testosterone levels were determined using an enzyme immunoassay in the early follicular phase after 2 or 3 days from the menstrual cycle induction.
- Progesterone level in (21day).
- Pelvic Ultrasound, Hormonal profile
- **Follow up:**
- transvaginal ultrasound (MINDRAY DC-3) for Folliculometry from the day 9 of the menstruation every day.
- when one follicle at least  $\geq 18$ mm, hCG must be given
- endometrial thickness measurement after administration of hCG.
- Advise Patients to start the intercourse from day of hCG injection.
- Serum B-HSG measured after two weeks for pregnancy diagnosing, transvaginal ultrasound after 4 -weeks and trans-abdominal ultrasound after 5 weeks for confirmation.

### Outcome Measures:

#### 1. Ovulation rate

Follicular monitoring was done using transvaginal ultrasonography (TVS) in alternative days from ninth day of menstrual until the detection of mature follicle ( $\geq 18$  mm).

- A single dose of 10,000 IU hCG was injected, when at least one follicle reached  $\geq 18$  mm). TVS was done after 48 hours after the injection of hCG to estimate follicle rupture. TVS was repeated for the unruptured follicle after 72 hours from the HCG injection to know if the follicle has ruptured or not. ascertained by observe follicle rupture using

ultra-sonogram (USG) for Ovulation confirmation.

- On day 7 after hCG injection, the level of serum progesterone must be measured. The level of 3 ng/ml of progesterone regarded ovulatory. [7].
- The Ovulation rate was evaluated by the mature follicle numbers which diameter ranged between 18-22 mm for cycle.
- Endometrial thickness of 8 mm regarded a good response for endometrium. [8].
- On growing pregnancy: pregnancy when diagnosed by ultrasound.

**Chemical pregnancy :** pregnancy when diagnosed by serum hCG test positive.

#### Statistical analysis

Data were collected, tabulated and analyzed by SPSS 20, software for Windows. The level of significance was  $< 0.05$ .

### RESULTS

**Table (1)**, showed that there was no significant statistical difference between Clomid and Metformin group and letrozole group in term of Age ( $p=0.75$ ), BMI ( $p=0.21$ ), and Duration of infertility ( $p=0.27$ ). **Table (2)**, showed that Clomid and Metformin induction was associated with a significant increase on Number of Dominant follicles  $>18$  mm ( $p<0.001$ ) more than the letrozole induction. **Table (3)**, showed that there was a significant statistical difference between Clomid and Metformin group and letrozole group in term of Endometrial thickness on day of H.C.G ( $p<0.01$ ). Clomid and Metformin induction was associated with a significant lower Endometrial thickness on day of H.C.G then the letrozole induction. **Table (4)**, showed that there was a significant statistical difference between Clomid and Metformin group and letrozole group in term of Size of dominant Graafian follicle (on day 11) ( $p=0.03$ ) and the Size of dominant Graafian follicle (on day 13-14) ( $p=0.01$ ). In Clomid and Metformin induction, Size of dominant Graafian follicle was significantly increased from day 11 to day 13-14 ( $p<0.001$ ). In letrozole induction Size of dominant Graafian follicle was significantly increased from day 11 to day 13-14 ( $p<0.001$ ). **Table (5)**, showed that there was no significant statistical difference between Clomid and Metformin group and letrozole

group in term of pregnancy rate ( $p=0.25$ ). **Table (6)**, showed that there was no significant statistical difference between the pregnant and non-pregnant female in term of age ( $p=0.08$ ), BMI ( $p=0.31$ ), and Duration of infertility ( $p=0.42$ ). Among both study

groups, a highly significant difference was present between pregnant and non-pregnant females as regard Number of Dominant follicles  $>18$  mm, Size of dominant Graafian follicle (on day 11) and (on day 13-14), and thickness of Endometrial on day of H.C.G.

**Table (1): Comparison of the baseline data of the two groups**

Variables	Group (A) N=60	Group (B) N=60	t	P value
Age (Years) Mean $\pm$ SD	26 $\pm$ 4	27 $\pm$ 4	0.32	0.75
B.M.I (kg/m <sup>2</sup> ) Mean $\pm$ SD	31.2 $\pm$ 1.4	31.3 $\pm$ 0.8	0.33	0.21
Duration of infertility (Year) Mean $\pm$ SD	2.2 $\pm$ 2.0	1.8 $\pm$ 0.6	0.38	0.27

**Table 2: Comparison of the number of dominant follicles  $>18$  mm data between the two groups**

Number of Dominant follicles $>18$ mm	Group (A) N=60		Group (B) N=60		Total N	X <sup>2</sup>	P value
	N	%	N	%			
1 follicle	35	59.3%	24	40.7%	59	18.74	<0.001
2 follicles	20	69%	9	31%	29		
3 follicles	9	100%	0	0	9		

**Table 3: Comparison of the Eendometrial thicknesss on day of H.C.G between the two groups**

Variable	Group (A) N=60	Group (B) N=60	T	P value
Endometrial thickness on day of H.C.G (Mean $\pm$ SD)	7.9 $\pm$ 1.6	10.8 $\pm$ 1.5	10.29	<0.001

**Table 4: Comparison of Size of dominant Graafian follicle on day 11 and on day 13-14 between the two groups**

Variables	Group (A) N=60	Group (B) N=60	t	P value*
Size of dominant Graafian follicle (on day 11), Mean± SD	13.4 ±2.3	12.6 ±2.4	<b>2.09</b>	<b>0.03</b>
Size of dominant Graafian follicle (on day 13-14), Mean± SD	17.7 ±2.2	15.8 ±2.7	<b>2.09</b>	<b>0.01</b>
<b>P value**</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>		

\*P value of independent t-test comparing the letrozole group and Clomid/Metformin group.

\*\*P value of paired t-test comparing the size of dominant Graafian follicle on day 11 and on day 13-14

**Table 5: Comparison of pregnancy rate between two groups**

Pregnancy Test	Group (A) N=60	Group (B) N=60	X <sup>2</sup>	P value
Negative	49(52.1%)	45(47.9%)	0.78	0.25
Positive	11(42.3%)	15(57.7%)		

**Table 6: Comparison of different parameters according to pregnancy**

Variable	Negative (n=94)	Positive (n=26)	T	P
Age (years), Mean ± SD	27 ± 3.1	25 ± 4	1.73	0.08
BMI (kg/m <sup>2</sup> ), Mean ± SD	31.3 ± 1.2	31 ± 0.7	1.39	0.31
Duration of infertility, Mean ± SD	2 ± 1.7	1.8 ± 0.5	0.79	0.42
Number of Dominant follicles >18 mm, Mean ± SD	1 ± 1	2 ± 1	4.51	<b>&lt; 0.001</b>
Size of dominant Graafian follicle (on day 11), Mean ± SD	12.4 ± 2.3	15.3 ± 0.8	6.54	<b>&lt; 0.001</b>
Size of dominant Graafian follicle (on day 13-14), Mean ± SD	16.3 ± 2.2	19.8 ± 1.1	7.81	<b>&lt; 0.001</b>
AFC 2nd day, Mean ± SD	16 ± 3	16 ± 2	1.47	0.14
Endometrial thickness on day of H.C.G, Mean ± SD	8.6 ± 1.7	11.7 ± 1.2	8.55	<b>&lt; 0.001</b>

## DISCUSSION

Clomiphene citrate has been widely used for the treatment of infertility as it has predominant anti-estrogenic action resulting in long-lasting estrogen receptor depletion [3]. It is known that Clomiphene citrate

results ovulation rate of 60-80% but the conception rate about 20% [4].

Letrozole is an aromatase inhibitor effective in the induction of the ovulation for women with PCOS [9].

Regarding the metformin, early data also suggested that metformin was effective

in the induction of the ovulation for women with Polycystic Ovarian Syndrome. As a result, metformin was used "off-label" for a number of these indications [10]. In this study we aimed to improve the ovulation induction in obese patients with PCOS. This trial was designed to compare the improving the ovulation induction in obese females with PCOS underwent induction of ovulation by Clomid with Metformin (n=60) or Letrozole (n=60) in Zagazig University Hospitals, Egypt. Similar study by **Rezk et al.**, [11]. was conducted in Menoufia University, Egypt and published last year (2018). In our study, there was no significant statistical difference between Clomid with Metformin group and the letrozole group in term of Age (p=0.75), BMI (p=0.21), and Duration of infertility (p=0.27). In **Rezk et al.** [11] study, there was no significant statistical difference between the studied groups regarding duration of infertility, age, basal FSH and LH levels and body mass index (p>0.05). In addition, **Dehbashi et al.** [12]. reported that the studied groups were similar as regarding the demographic characteristics which including duration of infertility, age, and body mass index.

In our study, there was no significant statistical difference between Clomiphene with Metformin group and letrozole group in term of pregnancy rate (p=0.25). On the other hand reported that Letrozole was associated with higher rates of ovulation and clinical pregnancy compared to combined Clomiphene and Metformin therapy in patients with PCOS over three months with unexpected higher rate of multiple pregnancies with two patients, these results were in agreement with the study of **Dehbashi et al.** [12].

Adding Metformin to Clomiphene in comparison with letrozole also showed no statistical difference between letrozole and Clomiphene plus metformin for ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate per pregnancy and multiple pregnancy rate per pregnancy in women with PCOS in the study of **Abu Hashim et al.** [13]. Our study reported the same non-significant difference between the two treatments in term of pregnancy rate.

This study showed that Clomiphene and Metformin induction was associated with a significant increase on Number of Dominant follicles >18 mm (p<0.001) more than the letrozole induction. We are in agreement with the study from Mansoura University by **Abohashem et al.** [13] that showed the follicles number between 14 mm and 18 mm were higher significantly in Clomiphene and Metformin group.

Comparing of the effect of clomiphene without metformin and letrozole and for ovulation and rate of pregnancy in patients with PCOS revealed that average follicles number which diameter >14 mm after the administration of hCG were the same in studied groups (P=0.96) in the study of **Dehbashi et al.** [12]. These results confirmed that adding metformin to clomiphene is significant for ovulation, but it does not enhance the pregnancy rate [14].

In addition, metformin can improve the function of ovulatory. A meta-analysis studies for PCOS patients demonstrated that there were increase in the rates of pregnancy but not in rates of live birth among those administrated with metformin [15]. Another systematic study and meta-analysis for patients with PCOS underwent IVF or ICSI treatment did not show significant statistical differences for pregnancy and live birth rates between patients received metformin and those received a placebo [16]. Therefore, metformin was not recommended for ovulatory infertility as a first-line treatment, but it is recommended for women with PCOS and bad glucose tolerance or type 2 diabetes which do not responded for lifestyle modifications [17]. Metformin act with several mechanisms; indirectly by decreasing the levels of insulin or directly decreasing the CYP-17 activity and increasing IGFBP-1, which reduce the production of local androgen [18]. A placebo-controlled randomized trial study conducted in Finland included 329 women whom received metformin (1500–2000 mg/day) or placebo for 3 months before treatment of fertility, and more than months during treatment of fertility, and continue for the 12th week of pregnancy in case of pregnancy occur, demonstrated that there was an increase in

pregnancy occurrence with great benefit for obese women [19].

In the present study, there was a significant statistical difference between clomiphene and Metformin group and letrozole group in term of Endometrial thickness on day of H.C.G ( $p < 0.01$ ). Clomiphene and Metformin induction was associated with a significant lower endometrial thickness on day of H.C.G then the letrozole induction. **Dehbashi et al.** [10] showed that the average endometrial thickness at the day of hCG administration for clomiphene and letrozole groups had no significant statistical difference ( $P = 0.16$ ). The same results of no significant statistical difference according to pretreatment endometrial thickness in the two groups were reported by the study of **Abu Hashim et al.** [13].

The present study showed that there was no significant statistical difference between the pregnant and non-pregnant female in term of age ( $p = 0.08$ ), BMI ( $p = 0.31$ ), and Duration of infertility ( $p = 0.42$ ). Among both study groups, a highly significant difference was present between pregnant and non-pregnant females as regard Number of Dominant follicles  $> 18$  mm, Size of dominant Graafian follicle (on day 11) and (on day 13-14), and thickness of Endometrial in day of H.C.G.

The limitation of this study were; it didn't report the letrozole, clomiphene and Metformin side effects and cost effectiveness. The safety of letrozole has confirmed results. Data reported from the study of **Biljan et al.** [20] showed an increase risk of babies congenital anomalies in letrozole treatment group, while in contrast a trial a randomized study contested these results and confirmed its safety [21]. The letrozole cost per cycle is more higher than that in combined metformin– clomiphene, especially for higher doses of letrozole if needed.

**Conclusion:** Letrozole improves endometrial thickness and cervical mucosa and causes monofollicular ovulation but action of clomiphene citrate combined with metformin improved the ovulation and increased total number of follicles. Therefore, Letrozole can

be used for improving the ovulation induction in obese women with PCO .

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