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# Combined letrozole with clomiphene citrate versus letrozole only in induction of ovulation in polycystic ovary syndrome patients (A Randomized controlled trial)

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## Abstract

**Objective:** to compare adding clomiphene citrate to letrozole in comparison with letrozole only Patients and method : A total of 64 infertile woman with PCOS were assessed in this randomized controlled trial in Department of Obstetrics and Gynecology at Imbaba General hospital and Banha university hospital .

**Results:** The serum pregnancy test was positive in only (6,3%) group A who receive letrozole alone while shows (12.5%) in group B who took combined therapy with no significance in P value(0.39) so group B shows higher pregnancy rates, The six weeks pulsations shows higher percentages in group B (9.4%) in compare to Group A (3.1%) with P value of (0.3) , There is good significance in the number of follicles (with P value 0.006) with appearance of one follicle in group B was higher than group A (68.8% in group B versus 37.5% in group A) ,Also the appearance of 2 mature follicles happen only in group B (6.3%). the follicular size appeared significance with P value (<0.001) as group B ranges (20.21+\_1.47) versus group A (17.17+\_0.94) , Endometrial thickness also show significance with P value (<0.001) with ranges (10.06+\_1.6) in group B which has better ranges than group A (8.13+\_1.79).

**Conclusion:** combined letrozole plus CC and letrozole alone seem to be two effective approaches, with letrozole plus CC showed better ovulation results and hence better pregnancy rate outcome.

**Keywords:** PCOS, clomiphene citrate, letrozole, Insulin resistance.

## Introduction

Over the last decade, abnormal placentation (accreta, iInfertility is a worldwide problem (1). Female and male factors is about forty percent each. The commonest cause for women is ovulatory failure (twenty five percent), then tubal blockage (twenty percent) (2).Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder, affecting about 6–10% women of reproductive age

worldwide. infertility in PCOS mostly due to insulin resistance and hyperandrogenemia at the center stage in the pathogenesis, PCOS is responsible for 80% of an ovulatory infertility in women.(3) the existence of low-grade inflammation (LGI) and the contribution of oxidative stress (OS) to be included in PCOS disorder.(4) The pathogenesis of PCOS can be observed by the biomarkers such as nitric oxide (NO), Malonaldehyde (MDA), and the anti-oxidative biomarkers, primarily the total antioxidant capacity (TAC), glutathione peroxidase (GPx), superoxide dismutase (SOD), and glutathione stimulating hormone (GSH).(5)

The basic method of managing PCOS is depend on modifications of lifestyle which consist of an appropriate and healthy diet with regular exercises, weight loss for obese patients, and behavioral changes as quitting smoking and drinking alcohol.(6)

One of the main component of PCOS treatment in women with obesity is weight loss. (7)

CC has considered the standard drug for ovulation induction in PCOS patients (8) Letrozole has been proposed for the treatment of CC resistant PCOS patients.(9) To compare between clomiphene citrate and letrozole, the half-life of Letrozole is about 45 hours which is less than Clomiphene citrate, so the Letrozol give a good situation for ovulation in compare with Clomiphene citrate.(10)

## **Patients and methods**

A total of 64 infertile woman with PCOS were assessed in this prospective study in Department of Obstetrics and Gynecology at Imbaba General Hospital.

### **1.Inclusion criteria:**

Age 18-35 with PCOs &infertility , infertility diagnosis known as couple can't achieve pregnancy after twelve months of regular timed unprotected intercourse in women aged less than 35 or after six months

in women aged more than 35, PCOS based on the Rotterdam ESHRE/ASRM-Sponsored consensus with having of at least two of the three criteria (Teede et al.,2018).:( Oligo-ovulation and or anovulation which known as presence of secondary amenorrhea or less than eight menstrual periods per year, clinical Hyperandrogenism. And Poly cystic ovarian morphology with follicular number per ovary equal or more than 20 (follicle measure 2-9mm) and /or ovarian volume >10ml on either ovary.) And Normal concentration of sperm of fifteen million/mL with normal motility of more than forty percent.

### **2.Exclusion criteria :**

Present using hormonal contraception-pregnancy-known other infertility causes-Hyperprolactinemia-Thyroid disease, uncontrolled medical diseases or diseases not recommended with pregnancy as hypertension, diabetes mellitus type 1 or type 2- endometrial cancer or hyperplasia-Allergy to letrozole or CC-any contraindications to letrozole or CC and finally Clinical suspicion of any other reasons similar to PCOS necessitate extra evaluation

### ***Procedure:***

**History:** Age, Menstrual history: age of menarche, menstrual disorders (oligomenorrhea), duration of amenorrhea , History of Infertility: history of previous pregnancy, duration of infertility.

**General examination:** As BMI, blood pressure, acne, no neck masses (thyroid), no galactorrhea, abdominal obesity, excess hair distribution (hirsutism) (clinical signs of hyperandrogenism)

**Local examination:** Normal external female genitalia, no clitromegaly, no vaginal or cervical lesions, bimanual examination.

Ultrasound examination: (transvaginal ultrasound)

To confirm PCOS diagnosis criteria based on Rotterdam ESHRE/ASRM Criteria (follicular number per ovary equal or more

than 20 (follicle measure 2-9mm) and /or ovarian volume >10mm on either ovary) and to exclude any ovarian masses

#### **Basal hormonal assays:**

It will be performed on day two of menstrual cycle in women with oligomenorrhea and at any time in woman with amenorrhea including the measurement of: Luteinizing hormone (LH)-Follicular-stimulating hormone (FSH) - and Estradiol (E2).

#### **In group A (nu=32)**

Letrazole will be started from the third day to the seventh day of the cycle with a dose of 2.5 mg daily

#### **In group B (nu=32)**

Letrazole and clomiphene citrate will be started from the third day to the seventh day of the cycle with a dose of 2.5 mg letrazole daily and 50 mg clomiphene citrate daily

#### **Primary outcome:**

- The Size and the number of developing follicles on cycle day twelve -fourteen by ultrasound.

- Endometrium thickness on cycle day twelve to fourteen by ultrasound
- Ovulation in day twenty one of the cycle by measuring Mid-luteal progesterone level >3ng/dl

#### **Secondary outcome:**

- Pregnancy rate chemical (by serum pregnancy test) and clinical (sac by ultrasound at 6 week gestation).

#### **Statistical Analysis:**

Data were coded and entered using the statistical package SPSS version 22. data will be expressed as frequency and percentage. Chi2 test and Fisher Exact tests used when comparing the incidence of studied parameters. Numerical data will be summarized as mean and standard deviation and compared using independent t test. P value less than or equal 0.05 is considered significant (Chan., 2003).

Chan Y. (2003): Biostatistics 102: Quantitative Data – Parametric & Non-parametric Tests. Singapore Med. J.; 44: 391-396.

**Table (1): age, BMI, Type of infertility and Marriage years of studied groups**

	Group A	Group B	P value
Age	25.03±2.8	24.81±3.64	0.7

  

	Group A	Group B	P value
BMI	28.91±2.33	28.42±2.3	0.4

  

infertility		group A	Group B	P value
1ry	Count	24	31	0.013
	%	75.00%	96.90%	
2ry	Count	8	1	
	%	25.00%	3.10%	

  

	Group A	Group B	P value
marriage yrs.	1.7±0.98	1.28±0.37	0.14

**Table (2): FSH, LH, and E2 D2 of studied groups**

	Group A	Group B	P value
FSH D2	8.03±2.34	8.01±2.07	0.96

	Group A	Group B	P value
<b>LH D2</b>	10.6±3.13	10.39±3.2	0.79
	Group A	Group B	P value
<b>E2 D2</b>	61.53±16.05	72.22±20.96	0.025

**Table (3): Results of studied groups**

		Group A	Group B	P value
0	Count	20	8	0.006
	%	62.50%	25.00%	
1	Count	12	22	
	%	37.50%	68.80%	
2	Count	0	2	
	%	0.00%	6.30%	

	Group A N=12	Group B N=24	P value
Follicle size at day 12-14	17.17±0.94	20.21±1.47	<0.001

	Group A	Group B	P value
Endometrium Thick- ness at day 12-14	8.13±1.79	10.06±1.61	<0.001

	Group A	Group B	P value
Progesterone D21 after induction	19.77±3.28	20.62±4.84	0.4

Serum pregnancy test		Group A	Group B	P value
Negative	Count	30	28	0.39
	%	93.80%	87.50%	
Positive	Count	2	4	
	%	6.30%	12.50%	

Clinical pregnancy		Group A	Group B	P value
Negative	Count	31	29	0.3
	%	96.90%	90.60%	
Positive	Count	1	3	
	%	3.10%	9.40%	

## Discussion

From these considerations and controversies, we had studied combined letrozole- CC and letrozole alone in Infertile Women with PCOS. Throughout the study, no changes in food intake or physical activity were performed. According to our protocol, the patients were given instruction to follow their habitual diet and physical activity to avoid any effect of these co-intervention confounders that might have bias effect on the study results.

This randomized controlled study included 64 young infertile women with PCOS to compare the hormonal-metabolic profile FSH, LH, E2, and outcomes between women receiving combined letrozole and cc versus letrozole alone in induction of ovulation

There were no significant differences between the two groups in terms of age- BMI- marriage years before starting the treatment.

The serum pregnancy test was positive in only (6,3%) group A who receive letrozole alone while shows (12.5%) in group B who took combined therapy with no significance in P value(0.39) so group B shows higher pregnancy rates which is similar in a study by (11) documented that Letrozole was found to be associated with a higher probability of clinical pregnancy compared to CC. And also similar in (11) as its study showed the clinical pregnancy and ongoing pregnancy rates of the Letrozole group were significantly higher than in the CC group.

The six weeks pulsations shows higher percentages in group B (9.4%) in compare to Group A (3.1%) with P value of (0.3) which is similar in a study done by (13) showed highly significant number of pregnancies as evidenced by positive pregnancy test results and intrauterine gestational sacs in letrozole group versus gonadotropin group with also statistically significant in pregnancy rate per cycle.

The level of progesterone has no significance

(P value =0.4) with ranges (19.77+ 3.28) in group A and ranges (20.62 +-4.84) in group B. also (14) shows the same results.

There is good significance in the number of follicles (with P value 0.006) as the results shows the appearance of one follicle in group B was higher than group A (68.8% in group B versus 37.5% in group A) ,Also the appearance of 2 mature follicles happen only in group B (6.3%) which is similar in (15) which showed that the ovulation rate in the combined letrozole and CC was slightly higher than the CC only with no statistically significance .and also in (16) which proved that Letrozole was reported to be significantly better for induction of ovulation in females who were resistant to the CC. but the results of (12) show different results as the successful ovulation rate was the same between the Letrozole group and CC group .

Study by (17) reported that the total number of follicles during stimulation in long time letrozole was significantly greater than short time letrozole.

Our study showed that the follicular size appeared significance with P value (<0.001) as group B ranges (20.21+ 1.47) versus group A (17.17+ -0.94) which was different as in the study by (15) Which showed that the median number of women with follicle more than 14 mm and the median largest follicle size in the combined letrozole and CC versus CC group were comparable. Also in study by (19) resulted that there were significant differences between the letrozol group compared to the letrozol plus electro acupuncture group on the endometrial thickness and on the number of follicles on days six, eight, ten, and twelve in infertile women with PCOS.

Endometrial thickness also show significance with P value (<0.001) with ranges (10.06+ 1.6) in group B which has better ranges than group A (8.13+ 1.79) which is similar in (15) which measured the mean measurement of endometrial thickness was 6.85 mm in the combined letrozole and CC



group, and 7.40 mm in the CC group, and the same results in (16) which proved higher Endometrial thickness value was noted in letrozole group than to Clomiphene Citrate group.

### **Conclusion and Recommendations**

1. The current RCT showed that combined letrozole plus CC and letrozole alone seem to be two effective approaches to the treatment of patients with PCOS. In view of the effectiveness for a higher pregnancy rate, letrozole plus CC showed better ovulation results and hence better pregnancy rate outcome. Even if, a wider trials to detect statistically significant differences between the 2 different strategies are recommended.

### **References**

1. Abdullah A, Ahmed M, Oladokun A. Prevalence of infertility in Sudan: A systematic review and meta-analysis. *Qatar Medical Journal*. 2021 Oct 1;2021(3):47.
2. Madziyire M, Magwali T, Chikwasha V, Mhlanga T. The causes of infertility in women presenting to gynaecology clinics in Harare, Zimbabwe; a cross sectional study. *Fertility Research and Practice*. 2021 Dec;7(1):1-8.
3. Sinha S, Kumari A, Sinha J. A prospective, comparative study of N-acetyl cysteine with metformin on clinical profile in an ovulatory infertile woman 4. with PCOS. *European Journal of Molecular & Clinical Medicine*. 2021 Apr 12;7(10):4003-8.
4. Mancini A, Bruno C, Vergani E, d'Abate C, Giacchi E, Silvestrini A. Oxidative stress and low-grade inflammation in polycystic ovary syndrome: controversies and new insights. *International Journal of Molecular Sciences*. 2021 Jan;22(4):1667.
5. Dubey P, Reddy S, Boyd S, Bracamontes C, Sanchez S, Chattopadhyay M, Dwivedi A. Effect of Nutritional Supplementation on Oxidative Stress and Hormonal and Lipid Profiles in PCOS-Affected Females. *Nutrients*. 2021 Sep;13(9):2938.
6. Kłosińska M. and Kaczyńska A. Polycystic ovarian syndrome-management and treatment. *Journal of Education, Health and Sport*. 2021 Sep 7;11(9):123-30.
7. Chang C, Chang S, Poles J, Popov V. The Impact of Bariatric Surgery Compared to Metformin Therapy on Pregnancy Outcomes in Patients with Polycystic Ovarian Syndrome: a Systematic Review and Meta-analysis. *Journal of Gastrointestinal Surgery*. 2021 Jan 22;1-9. (8) Bansal S, Goyal M, Sharma C, Shekhar S. Letrozole versus clomiphene citrate for ovulation induction in anovulatory women with polycystic ovarian syndrome: A randomized controlled trial. *International Journal of Gynecology & Obstetrics*. 2021 Mar;152(3):345-50.
8. Sakar M. and Oğlak S. Comparison of the efficacy of letrozole stair-step protocol with clomiphene citrate stair-step protocol in the management of clomiphene citrate-resistant polycystic ovary syndrome patients. *Journal of Obstetrics and Gynaecology Research*. 2021 Nov;47(11):3875-82.
9. Alhibshi L, Sarhan A, Abdo A. Effect of letrozole versus clomiphene citrate plus estradiol valerate in patient with polycystic ovarian syndrome with inadequate response to clomiphene citrate. *Zagazig University Medical Journal*. 2021 Nov 1;27(6):1524-32. 11.
10. Tsiami A, Goulis D, Sotiriadis A, Kilibianakis E. Higher ovulation rate with letrozole as compared with clomiphene citrate in infertile women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hormones*. 2021 Sep;20(3):449-61
11. Wang L, Lv S, Li F, Bai E, Yang X. Letrozole versus clomiphene citrate and natu-

- ral cycle: endometrial receptivity during implantation window in women with polycystic ovary syndrome. *Frontiers in Endocrinology*. 2021;1074
12. Dawood A, Abdelghaffar S, Borg H. Letrozole versus Gonadotropins for Ovulation Induction in Clomiphene Citrate Resistance: A Randomized Controlled Study. *Annals Gynecol Obstet*. 2021;5(1):127-32.
  13. Mejia R, Summers K, Kresowik J, Van Voorhis B. A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome. *Fertility and sterility*. 2019 Mar 1;111(3):571-8.
  14. Chera-aree P, Tanpong S, Thanaboonyawat I, Laokirkkiat P. Clomiphene citrate plus letrozole versus clomiphene citrate alone for ovulation induction in infertile women with chronic anovulation: A randomized controlled trial. 2022
  15. Zafar T, Asif F, Naurin R, Majeed T, Mahmood Z. Comparing Effectiveness of Letrozole Versus Clomiphene Citrate to Evaluate the Ovulation Induction in patients with Polycystic Ovarian Syndrome. *Age (years)*.;26(4.81):27-89.
  16. Morad A, Barakat E, Bayomey A, Hassen M. Extended Letrozole Regimen for Treatment of Clomiphene Resistant Polycystic Ovary Syndrome Patients. *Benha Medical Journal*. 2021 Nov 1;38(3):962-71.
  17. Wesliaprilus T, Budihastuti U, Melinawati E, Sulistyowati S, Nurwati I, Hadi C. The Effectiveness of Letrozole Adjuvant Therapy-Electro Acupuncture in Reducing the Number of Follicles and Body Weight and Increasing Endometrial Thickness in Women with Polycystic Ovary Syndrome. *Journal of Maternal and Child Health*. 2021 Mar 16;6(2):219-28. 20.