



Manuscript ID ZUMJ-1909-1530 (R1)
DOI 10.21608/zumj.2019.17162.1530

ORIGINAL ARTICLE

Effect Of Letrozole Versus Clomiphene Citrate Plus Estradiol Valerate In Patient With Polycystic Ovarian Syndrome with Inadequate Response To Clomiphene Citrate

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Submit Date 2019-10-08

Revise Date 2019-10-18

Accept Date 2019-10-24

ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) is an endocrine disorder in infertile women. With about Infertility rate of 40% in PCOS women. Determination the infertility causes and choosing the appropriate treatment is a diagnostic and therapeutic priority. **Aim and Objectives :** The aim of this work was to compare the effect of Clomiphene citrate plus Estradiol Valerate versus Letrozole on endometrial thickness and pregnancy rate in infertile PCOS women underwent ovulation induction. **Patients and methods:** this is randomized clinical trial has been carried out in infertility clinic of cytogenetic and endoscopy unit, Gynecology and Obstetrics Department, Faculty of Medicine, Zagazig university, Egypt during the period from March 2019 to September 2019, carried on 70 infertile women with PCO and were divided to 2 two groups , 35 patients patient received clomiphene citrate plus estradiol valerate and 35 patient received letrozole. **Results :** the results showed that there was a statistical significant difference between the studied groups (P value ≤ 0.001) regarding endometrial thickness, which was higher in Letrozole group B (9.7 ± 1.1) than clomiphene plus estradiol group A (8.8 ± 1.2). Rate of pregnancy was higher in the Letrozole group B (45.2%) compared to clomiphene plus estradiol group A (22.9%). **Conclusion:** Letrozole increase the endometrial thickness and rate of pregnancy more than the Estradiol Valerate and Clomiphene citrate in the infertile PCOS women who had abnormal endometrial thickness with Clomiphene citrate, so it is recommended for infertile PCOS women .

Keywords: Letrozole, Clomiphene citrate, PCOS, Endometrial thickness.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is an endocrine disorder in infertile women which causes infertility for about 40% of PCOS women ^[1].

Clomiphene citrate is an treatment modality for induction of ovulation. Clomiphene is

similar to estrogenic compounds which reduce estrogen effect by blocking estrogen receptors ^[2]

It has ovulation rate of 50%-75% were great discrepancy with pregnancy rate, between 25-43% ^[3].

The thickness of endometrial is the most important factor for treatment the infertility. If the thickness endometrial > 6–8 mm, the rate of pregnancy will be very low. [4].

The reduction of endometrial thickness an treatment modality contain Clomiphene citrate which widely recommended in many studies.[5]

Kamath and George showed that adding ethinyl estradiol to Clomiphene citrate give a good results for endometrial response in infertile PCOS women [6].

The addition of ethinyl estradiol to Clomiphene have a significant effect on thickness of endometrial more than Clomiphene alone, but do not any effect on the rate of pregnancy and abortion[7].

Unlike clomiphene, letrozole induces agonistic effects of estrogen on endometrium more than antagonistic effect. It induces ovulation due to the inhibition androgens conversion to estrogen that creates an estrogen-deficient environment [8,9]. Since this drug does not block estrogen receptors and normal central feedback mechanisms remain intact, so, growing dominant follicle increase levels of estrogen and negative feedback decreases FSH and monofollicular growth occur.

The half-life of Letrozole is about 45 hours which is less than Clomiphene, so the Letrozol give a good situation for ovulation compared with Clomiphene. Letrozole do not produce more than one follicle; which reduce the risk of multiple pregnancy and Ovarian Hyperstimulation Syndrome [10].

AIM OF THE STUDY

The aim of this work was to compare the effect of Clomiphene citrate plus Estradiol Valerate versus Letrozole on endometrial thickness and pregnancy rate in infertile PCOS women underwent ovulation induction

PATIENTS AND METHODS

The present randomized clinical trial has been carried out in infertility clinic of cytogenetic and endoscopy unit, Gynecology and Obstetrics Department, Faculty of Medicine, Zagazig university during the period from March 2019 to September 2019. All patient in the study (70) were previously received clomiphene citrate alone as management of

infertile anovulatory PCOs women, but giving improper endometrial thickness < 7mm.

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria:

Patients with age between 18–35years, with complete infertility and were diagnosed as having PCOs women defined as per the ESHRE/ ASRM, Rotterdam criteria 2003 demonstrating two of the three critertia: oligo or anovulation, Clinical and / or biochemical signs of hyperandrogenism, Polycystic ovaries on Ultrasonography (12 or more follicles). After exclusion other causes of androgen excess. [11]

Normal infertility workup include normal hormonal profile (prolactin and TSH), and anovulatory cycles were confirmed by mid-luteal progesterone \leq 3 ng/ml.

Bilateral tubal patency was diagnosed by hysterosalpingography, sonohysterography and/or laparo-scopy.

Normal semen analysis due to **Esteves et al.** [12]

Parameters	Lower Reference Limit
Volume (ml)	1.5
PH	\geq 7.2
Sperm Concentration (10 ⁶ /mL)	15
Total Sperm Number (10 ⁶ /mL)	39
Total Motility	40
Progressive Motility	32
Strict Morphology (Normal forms,%)	4
Body mass index (BMI >18 and <30 Kg/ m2).	

Exclusion Criteria:

Patients with male factor infertility, hyperprolactinemia and thyroid disorder, Patients with any tubal pathology or uterine pathology, Contraindication of ovulation induction, (Multiple ovarian cysts or allergy to inducing agent "clomid"), Known or suspected pelvic infection (PID).

Sample size:

Total sample size (70) infertile women with PCOs.

Assuming that mean \pm SD of the thickness of endometrial in clomiphene citrate plus estradiol valerate versus letrozole was (7 \pm 1.76) versus (8.3 \pm 2.08) respectively.

The sample size was calculated to be 70 patients (35 in each group), using OPEN-EPI program with CI 95% and Power 80%.

Operational design:

Explanation of the procedure to all women participating in the study. A written consent was taken from all patients before starting the study with counseling about risk and benefit of CC plus estradiol & letrozole.

Protocol Approval by Ethical Committee

Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents were declared for Ethical and Research approval by Zagazig University Institutional Review Board (IRB).

Study design:

The study was designed as a randomized clinical trial study using a computer-generated randomization list and sequentially numbered opaque sealed envelopes, each containing the allocation information written on a card. Envelopes were opened sequentially by a study nurse to allocate patients to the assigned group. These patients were divided into 2 groups:

Group(A): (35) patient received clomiphene citrate plus estradiol valerate.

Group(B): (35) patient received letrozole.

Methods

Patients were subjected to:

Complete history taking : including (Personal ,Obstetric, Present , Past , Family ,Surgical history, history of allergy to any medication and previous history of induction of ovulation in previous 6 months and drugs used were endometrial thickness < 7mm, follicular growth and ovulation.and ovulation).

Examination: (General, abdominal, local clinical and bimanual pelvic examination).

Investigations:

Basal hormonal studies on Day2 of cycle included serum FSH,LH,E2, androgen level, prolactin level and thyroid stimulating hormone was measured on day 2 of spontaneous menstrual cycle.

Basal transvaginal U/S on day3 of the cycle to examine each ovary for detecting criteria of PCOS and count number of antral follicles in both ovaries and to exclude of any basal ovarian cyst which suspected when diameter of follicle >1.5 cm) and to measure basal endometrial thickness.

Patients divided into 2 groups:

Group A (clomiphene citrate & estradiol group): included 35 anovulatory PCO patients who received clomiphene citrate (Clomid; Aventis pharma S.AE, Global Napi pharmaceuticals, Cairo, Egypt) 100-mg daily from the third day of the cycle to the seventh day with estradiol valerate 4-mg (two white tablets of cycloprogynova) from the fourteen day of cycle to the eighteen day.

Group B (Letrozole group): included 35 anovulatory PCO patients who received letrozole (Femara; Novartis pharma AG, Basle, Switzerland) 5-mg daily from the third day of the cycle to the seventh day.

Follow up:

the treatment starts according to group allocation with follow up and start ultrasound scans on day 8 of cycle and repeated daily or every other day to monitor growth of follicle and thickness of endometrial.

Technique of US: Midisson X4, Korea with a frequency of 9 MHz.

Each patient is advised to empty bladder before examination.

Endometrial thickness was measured as maximal thickness between the highly reflective interfaces of endometrial myometrial junction.

Follicular monitoring carried out for both groups with transvaginal ultrasound with same technique , started from the eighth day of cycle till attaining a mature follicle with a mean diameter of 18-22 mm, number and size of Dominant follicles, endometrial thickness and pattern were reported on day of hCG administration,

Then, single injection of hCG 10,000 IU was given for triggering ovulation

Timed intercourse was advised from the day of hCG and for 4 days.

Clinical pregnancy detected by serum pregnancy test and transvaginal U/S which detected IUGS and fetal pulsation..

Follow up of both groups was done for 1 cycle.

Primary result was the thickness of endometrial on day of hCG and rate of pregnancy.

Secondary outcome was the ovulation rate.

Statistical analysis

Data were assessed, entered and analyzed using SPSS version 20. $P < 0.05$ was considered to be the level of statistical significance.

RESULTS

This study was conducted on 70 patients suffering from PCOS with endometrial thickness < 7 mm were previously received clomiphene citrate alone attending the infertility clinic at zagazig university hospital divided into two groups; 1st one was

Group (A) which consisted of (35) women and used clomiphene citrate plus estradiol valerate for induction of ovulation. 2nd group was Group (B) which consisted of the same number (35) women and used letrozole for induction of ovulation.

Table (1), showed that there was no statistical significant difference between both groups as regard age, BMI, duration and infertility type.

Table (2), showed that there was no statistical significant difference between studied groups as regard basal hormonal profile (TSH, prolactin, FSH, LH and E2). **Table (3)**, showed that there was high statistical significant difference between both studied groups as regard thickness of endometrial in the day of HCG injection. But regarding basal endometrial thickness and number of stimulation days injection, there was no statistical significant difference. **Table (4)**, showed that there was statistical significant difference between the two studied groups as regard rate of ovulation, where it was high in letrozole group more than clomiphene plus estradiol group.

Table (5), showed that there was a statistical significant difference between the two studied groups as regard rate of pregnancy, which was higher (45.2%) in letrozole group more than clomiphene plus estradiol group.

Figure (1): Bar chart for comparing thickness of endometrial in the day of HCG injection between the studied groups.

Figure (2): Bar chart for comparing pregnancy rate between the two studied groups.

Table (1) : Comparing age and clinical characteristics among women treated with clomiphene citrate plus estradiol valerate (A) and letrozole (B).

Variable	Group (A)		Group (B)		t- test	p-value
	(n =35)		(n =35)			
	mean \pm SD		mean \pm SD			
	(Range)		(Range)			
Age (years)	26.7 \pm 4.4		25.3 \pm 3.9			0.1
	(22-31)		(21-29)			
Body Mass Index (BMI)	25.5 \pm 2.5		24.5 \pm 3.0		1.6	
(Kg/ m ²)	(20-29.5)		(19-29.3)			0.09
Duration of infertility (years)	2.2 \pm 1.3		1.9 \pm 1.4			0.3
	(1-6)		(1-7.5)			
	Group (A)		Group (B)		χ^2	p-value
Variable	No(35)	%	No (35)	%		
Type of infertility						
Primary	19	54.3%	22	62.9%	0.5	0.6
Secondary	16	45.7%	13	37.1%		

Table (2): Comparing TSH, Prolactin , FSH, LH and E2 level between women of the two studied groups:-

Variable	Group (A) (n =35)	Group (B) (n =35)	t-test	p-value
	mean \pm SD (Range)	mean \pm SD (Range)		
TSH (μ /l)	2.1 \pm 0.85 (0.5-3.7)	1.94 \pm 0.83 (0.5-3.8)	0.79	0.42
Prolactin (ng/ml)	14.34 \pm 5.8 (4.1-25.7)	13.7 \pm 5.47 (5.6-26.6)	0.47	0.63
FSH (u/l)	6.53 \pm 1.9 (8.43-4.63)	6.49 \pm 3.2 (3.29-9.69)	0.06	0.94
LH (u/l)	14.9 \pm 6.1 (8.8-21)	14.8 \pm 6.9 (7.9-21.7)	0.06	0.94
E2 (pmol)	369.2 \pm 120.9 (248.1-489.9)	381.9 \pm 110.8 (270.2-492.7)	0.45	0.64

Table (3): Comparing basal endometrial thickness, stimulation day and endometrial thickness on HCG between the two studied groups:-

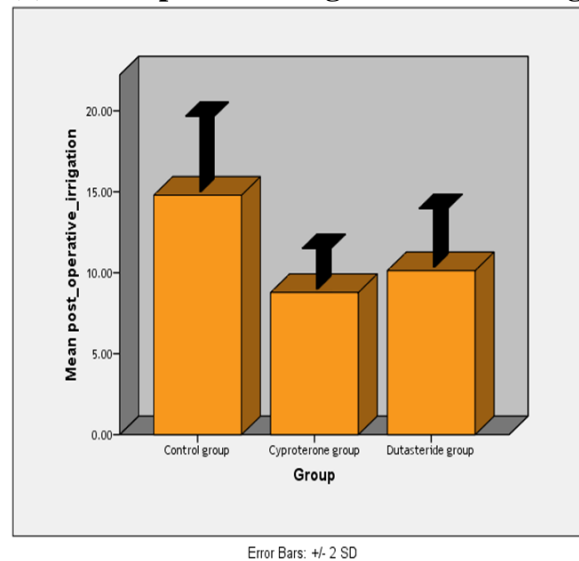
Variable	Group (A) (n =35)	Group (B) (n =35)	p-value
	mean \pm SD (Range)	mean \pm SD (Range)	
Basal endometrial thickness	4.0 \pm 0.5 (3.5 -4.5)	4.1 \pm 0.6 (3.5-4.7)	0.3
Endometrial thickness on day of HCG inj	8.8 \pm 1.2 (7-13)	9.7 \pm 1.1 (7-12)	3.3 0.001**
Number of Stimulation days	14.1 \pm 1.7	14.8 \pm 1.7	0.07

Table (4): comparing ovulation rate between the two studied groups:-

ovulation rate	Group (A)		Group (B)		χ^2	p-value
	No.(35)	%	No.(35)	%		
Positive (No=57)	25.0	71.4%	32.0	91.4%	4.6	0.03*
Negative (No=13)	10.0	28.6%	3.0	8.6%		

Table (5): comparing pregnancy rate between the two studied groups:

pregnancy rate	Group (A)		Group (B)		χ^2	p-value
	No.(35)	%	No.(35)	%		
Positive (No=18)	8.0	22.9%	16.0	45.2%	4.1	0.04*
Negative (No=46)	27.0	77.1%	19.0	54.3%		

Figure (1): Post-operative irrigation fluid among groups:

DISCUSSION

Poly cystic ovaries are the endocrine disorder which affect 10–15% of women. The prevalence of polycystic ovaries detected by ultrasound about 20–30% (age ranged from 18 and 25 years), polycystic ovaries were determined by ultrasound in 33%, and PCOS was in 26%.^[13]

This study show that Age distributed as 26.7±4.4yr in clomiphene-estradiol group and 25.3±3.9yr in Letrozole group and that mean BMI distributed as 25.5±2.5 Kg/m² in clomiphene-estradiol group and 24.5±3.0Kg/m² in Letrozole group B and that mean duration of infertility (years) distributed as 2.2±1.3yr in clomiphene-estradiol group and 1.9±1.4yr in letrozle group with (P=0.3) with no significant difference among groups.

This agreement with study conducted by **Harira**^[14] who studied the administration of letrozole versus clomiphene-estradiol in treatment of infertile women which not responding to clomiphene alone. And reported that Mean patient age was 24.6 ± 3.8 yr in clomiphene-estradiol group and 23.2 ± 4.1 yr in letrozole group and that Mean patient BMI was 24.52 ± 4.02 Kg/m² in clomiphene-estradiol group and 25.06 ± 3.6 Kg/m² in letrozole group and that mean duration of infertility (years) distributed as 3.051 ± 1.32yr in clomiphene-estradiol group and 3.71 ± 1.21yr in letrozle group with (P=0.13) . There were no statistical

significant differences between studied groups regarding age, BMI and infertility duration.

This study show that Type of infertility distributed as percentage of Primary infertility was 54.3% and percentage of secondary infertility was 45.7% in clomiphene-estradiol group and percentage of Primary infertility was 62.9% and percentage of secondary infertility was 37.1% in letrozole group without statistical significant difference between studied groups.

A similar study conducted by **Syedoshohadaei et al.**^[15] who studied effect of clomiphene- Estradiol Valerate versus Letrozole on the thickness of endometrial, rate of Pregnancy and abortion in Infertile PCOS Women and reported that percentage of Primary infertility was 60% and percentage of secondary infertility was 40% in clomiphene-estradiol group and percentage of Primary infertility was 72% and percentage of secondary infertility was 28 % in letrozole group with no statistical significant difference among studied groups.

This study showed that there was no statistical significant difference between the studied groups as regard basal hormonal profile (TSH and prolactin) (P=0.42), (P=0.63) respectively .These results agreement with study conducted by **Harira**^[14] who reported that there was no statistical significant difference between the studied groups as regard basal hormonal profile (TSH

and prolactin) ($P=0.27$) ($P=0.74$) respectively.

This study showed that there was a high statistical significant difference between the two studied groups as regarding thickness of endometrial in day of HCG injection was $8.8\pm 1.2\text{mm}$ in clomiphene-estradiol group and $9.7\pm 1.1\text{mm}$ in letrozole group with ($P=0.001$). In group of Letrozole the thickness of endometrial was high more than Clomiphene plus Estradiol Valerate in the day of HCG injection. But regarding basal endometrial thickness ($P=0.3$) and stimulation days ($P=0.07$) and number of mature follicles ($P=0.16$), there was no statistically significant difference between the two studied groups.

Similar finding showed by **Harira** [14] who reported that the administration of Estradiol Valerate increased the thickness of endometrial to CC from ($5.44 \pm 1.64\text{mm}$) to ($8.28 \pm 1.7\text{mm}$) and Letrozole alone from ($5.75\pm 1.92\text{mm}$) to ($9.2\pm 1.8\text{mm}$) with statistical significant difference between the studied groups ($P=0.00$). In Letrozole group the thickness of endometrial was higher more than CC plus Estradiol Valerate. But regarding basal endometrial thickness ($P=0.55$) and stimulation days ($P=0.11$) and number of mature follicles ($P=0.39$), there was no statistically significant difference between the studied groups.

Syedoshohadaei et al. [15] reported that the thickness of endometrial in Clomiphene plus Estradiol Valerate group was increased after intervention from ($5.34 \pm 1.98\text{mm}$) to ($7.26\pm 1.76\text{mm}$) and in letrozole group from ($5.68\pm 1.98\text{mm}$) to ($8.17\pm 2.08\text{mm}$) with significant difference between the two groups ($P=0.021$). In Letrozole group the thickness of endometrial was high more than CC plus Estradiol Valerate.

Hendawy et al. [16] studied the effects of Letrozole and Clomiphene citrate on the induction of ovulation and concluded that Letrozole had a good result on thickness of endometrial and rate of pregnancy than Clomiphene citrate.

Also **Mitwally and Casper** [17] reported that Letrozole was related to a greater thickness of endometrial. Administration of aromatase

inhibitor (letrozole) orally for a dose of 2.5mg on 3-7 days of cycle, to twelve PCOS patients and ten patients with ovulatory infertility, all of patients previously received CC with an inadequate outcome (no ovulation and/or endometrial thickness of $\leq 0.5\text{cm}$).

In a study by **Sharief and Nafee** [18] which carried on 75 Iraqi women, they reported number of mature follicles was lower significantly, but the thickness of endometrial and ovulation were higher significantly in Letrozole group than in Clomiphene citrate group ($p<0.05$ each).

The result of this study was in agreement with the study of **Kamath et al.** [6] who reported that letrozole has a good effect on women with either clomiphene failure or resistance.

Also, **Atay et al.** [19] reported that, the number of mature follicles was lower significantly in case of Letrozole; but thickness of endometrial, ovulation and rates of pregnancy were higher significantly.

Study of **Ghomian et al.** [10] revealed that there was no statistical significant differences between Letrozole and Clomiphene citrate regarding the thickness of endometrial, the number of mature follicles and length of follicular phase.

The present study concluded that there was a statistical significant difference between the two studied groups regarding ovulation rate ($P=0.03$), where it was higher in letrozole group than clomiphene plus estradiol group.

The present study revealed that there was a statistical significant difference between the two studied groups as regard rate of pregnancy, where it was higher (45.2%) in letrozole group than clomiphene plus estradiol group (22.9%, $P=0.04$).

This agreement with the study of **Syedoshohadaei et al.** [15] who reported that the total pregnancies women were 24 cases (24%). in letrozole group, the number of pregnancies was (32%), while in clomiphene-estradiol group was (16%) and there was a statically significant differences between studied groups as regard the pregnancy rate ($P=0.05$).

Different finding showed by **Harira** ^[14] who reported that there was increase in the rate of pregnancy in Letrozole group but without statistical significant difference between studied groups ($P=0.42$), although the addition of estradiol improved the thickness of endometrial. Which could be explained by results of **Bao et al.** ^[20] who reported that the markers of endometrial receptivity (HOXA10) and integrin alpha (v) beta (3) in rats were suppressed by clomiphene citrate and Letrozole had no effect.

also, **Cortinez et al.** ^[21] concluded that administration of letrozole in infertile ovulatory women was related with in-phase histological dating of endometrium and normal pinopode expression .

Homburg et al. ^[22] concluded that the treatment by CC increase significantly the prevalence of out-of-phase endometrium and reported that this could be due to the large difference between ovulation and rates of pregnancy.

The study of **Baruah et al.** ^[23] revealed that the thickness of endometrial and sub-endometrial blood flow were improved significantly in patient receiving Letrozole of ovulatory induction more than CC despite the difference of follicular response, and also it is less inhibitory on endometrial alpha (v) beta (3) integrin expression which is linked to endometrial receptivity.

This was different from the results of **Nahid and Sirous** ^[24] who studied the effects of Letrozole and CC for induction of ovulation in PCOS infertile women, they reported that the rate of pregnancy in studied groups was almost similar .

The study of **Hendawy et al.** ^[16] showed that the rate of pregnancy in Letrozole group was higher than Clomiphene citrate group. The study of **Kar** ^[25] revealed that Letrozole had excellent rates of pregnancy compared with Clomiphene citrate .

This study showed that there was no statistically significant difference between the studied groups as regard multiple pregnancy 1 case (2.9%) in clomiphene-estradiol group and 1 case (2.9 %) in letrozole group ($P=0.1$).These result agreement study by

Harira, ^[14] showed 2 cases (2.3%) in clomiphene-estradiol group and 0 case(0.00%) in letrozole group. There was no statistical significant difference between the studied groups.

Conclusion: Letrozole increase the endometrial thickness and rate of pregnancy more than the Estradiol Valerate and Clomiphene citrate in the infertile PCOS women who had abnormal endometrial thickness with Clomiphene citrate, so it is recommended for infertile PCOS women .

No conflict of interest

No financial disclosures

REFERENCES

1. **Teede H, Deeks A, Moran L.** Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med* 2010;8:41
2. **EL-Gharib M, Mahfouz AE, Farahat M.** Comparison of letrozole versus tamoxifen effects in clomiphene citrate resistant women with polycystic ovarian syndrome. *J Reprod Infertil* 2015; 16 (1) : 30–35.
3. **Cetinkaya K, Kadanali S.** The effect of administering vaginal estrogen to clomiphene citrate stimulated cycles on endometrial thickness and pregnancy rates in unexplained infertility. *Journal of the Turkish German Gynaecological Association* 2012; 13(3):157–61.
4. **Shaikh S, Abro S, Shaikh A, Abbasi A.** Role of Clomiphene citrate in unexplained infertility at CMC Larkana. *Medical Channel* 2016; 16 (1) : 69–71.
5. **Satirapod C, Wingprawat S, Jultanas R, Rattanasiri S, Jirawatnotai S, Choktanasiri W.** Effect of estradiol valerate on endometrium thickness during clomiphene citrate-stimulated ovulation. *J Obstet Gynaecol Res.* 2013; 40 (1):96–101
6. **Kamath M, George K.** Letrozole or clomiphene citrate as first line for anovulatory infertility: a debate. *Reprod Biol Endocrinol* 2011; 9 (1) : 86.
7. **Morad A, Elhadi Farag M.** Impact of letrozole on ultrasonographic markers of endometrial receptivity in polycystic ovary syndrome women with poor endometrial response to clomiphene citrate despite adequate ovulation. *Middle East Fertility Society Journal* 2015; 20 (3):182–87.
8. **Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK.** A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *Journal of human reproductive sciences* 2012; 5 (1) : 20.
9. **Xi W, Liu S, Mao H, Yang Y, Xue X, Lu X.** Use of Letrozole and Clomiphene citrate combined

- with gonadotropinsin clomiphene-resistant infertile women with polycystic ovary syndrome: a prospective study. Drug design, development and therapy 2015. 9 : 6001.
10. **Ghomian N, Khosravi A, Mousavifar N.** A randomized clinical trial on comparing the cycle characteristics of two different initiation days of letrozole treatment in clomiphene citrate resistant pcos patients in iui cycles. *Int J Fertil Steril* 2015; 9 (1) : 17–26.
 11. **Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.** Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility* 2003; 81(1):19-25.
 12. **Esteves SC, Zini A, Aziz N, Alvarez JG, Sabanegh Jr ES, Agarwal A.** Critical appraisal of World Health Organization's new reference values for human semen characteristics and effect on diagnosis and treatment of subfertile men. *Urology* 2012, 79(1), 16-22.
 13. **Bellver J, Rodríguez-Tabernero L, Robles A, Muñoz E, Martínez F, Landeras J.** Polycystic ovary syndrome throughout a woman's life. *Journal of assisted reproduction and genetics* 2018, 35 (1): 25-39
 14. **Harira M.** Use of Letrozole versus clomiphene-estradiol for treating infertile women with unexplained infertility not responding well to clomiphene alone, comparative study. *Middle East Fertility Society Journal* 2018, 23 (4): 384-387.
 15. **Seyedshohadaei F, tangestani L, Zandvakili F, Rashadmanesh N.** Comparison of the effect of clomiphene-estradiol valerate versus letrozole on endometrial thickness, abortion and pregnancy rate in infertile women with polycystic ovarian syndrome. *Journal of Clinical and Diagnostic Research* 2016; 10(8): QC10-QC13.
 16. **Hendawy SF, Samaha HE, Elkholy MF.** Letrozole versus Clomiphene citrate for Induction of Ovulation in patients with polycystic Ovarian syndrome Undergoing Intrauterine Insemination. *Clinical medicine insights Reproductive health.* 2011; 5 : 11.
 17. **Mitwally MF, Casper RF.** Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. *Fertil Steril* 2001; 75:305–309.
 18. **Sharief M, Nafee NR.** Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation *JPMA J. Pakistan Med. Assoc.* 2015, 65 (11), pp. 1149-1152.
 19. **Atay V, Cam C, Muhcu M.** Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *J Int Med Res* 2006; 34:73–76.
 20. **Bao SH, Sheng SL, Peng YF, a De Lin Q.** LinEffects of letrozole and clomiphene citrate on the expression of HOXA10 and integrin alpha v beta 3 in uterine epithelium of rats *Fertil. Steril.* 2009, 91 (1) . pp. 244-248
 21. **Cortinez A, De Carvalho I, Vantman D, Gabler F, Iniguez M.** VegaHormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients *Fertil. Steril.* 2005, 83 (1) : 110-115
 22. **Homburg R, Pap H, Brandes M, Huirne J, Hompes P, Lambalk CB.** Endometrial biopsy during induction of ovulation with clomiphene citrate in polycystic ovary syndrome *Gynecol. Endocrinol.* 2006, 22 (9): 506-510
 23. **Baruah J, Roy KK, Rahman SM, Kumar S, Sharma JB, Karmakar D.** Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. *Archives of gynecology and obstetrics* 2009, 279(3), 311-314.
 24. **Nahid L, Sirous K.** Comparison of the effects of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome *Miner. Ginecol.* 2012, 64 (3) : 253-258
 25. **Kar S.** Clomiphene citrate or Letrozole as first-line ovulation induction drug in infertile PCOS women: a prospective randomized trial *J. Hum. Reprod. Sci.* 2012, 5 (3) : 262

TO CITE THIS ARTICLE

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; (1524-1532): -. doi: 10.21608/zumj.2019.17162.1530