Comparison of Letrozole and Clomiphene Citrate in Women with Polycystic Ovaries

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Abstract: Background: Polycystic ovary syndrome represents a health challenge, as it is associated with infertility and impaired ovulation. Ovulation induction represents a treatment line. However, the ideal drug or regimen still debated. **Aim of the work:** to observe the role of using clomiphene citrate [clomid] versus using letrozole [Femara] in improving the clinical features (e.g., menstrual irregularities and the sonographic pictures in females with polycystic ovary syndrome. **Patients and methods:** One hundred Forty women fulfilling the clinical criteria for diagnosis of polycystic ovary syndrome were enrolled. Patients were allocated into one of two groups: group A [clomiphene citrate] and group B [letrozole]; each group is 70 females. All underwent full history taking, clinical examination, transvaginal ultrasound and laboratory investigations after treatment. **Results:** both groups were comparable as regard to demographic data, type and duration of infertility, hormonal profile, except significant increase of Mid cycle E2 in clomiphene citrate group. However, endometrial thickness and cumulative ovulation rate, cumulative pregnancy rate were significantly increased in letrozole group. **Conclusion:** results of the present work are in favor of letrozole for treatment of anovulation and subfertility in females with PCOS.
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1. Introduction

In the adult female, the ovaries are flat, nodular and oval structures that measure between 3 and 5 cm in their greatest dimension and weigh between 2 and 4 grams. They are suspended by peritoneal folds and ligaments on either side of the uterus and attached to the back of the broad ligament of the uterus, behind and below the uterine tubes **[Chen et al., 2003].**

The ovary is the "Master" gland of the female reproductive system. In this role, it has dual endocrine and exocrine functions that are involved in ovarian follicle growth, ovulation and regression. Menses is the external sign of reproductive cyclicity in humans **[Baerwald et al., 2012].**

The traditional model of the human menstrual cycle has two phases, follicular and luteal, based on menses. The follicular phase is defined as the stage of the menstrual cycle that begins on the first day of menstrual bleeding. During the mid-follicular phase, a single "dominant" follicle is selected from the recruited cohort for preferential growth and ovulation. The selected follicle secretes increasing amounts of estradiol [as it grows to pre-ovulatory size]. The luteal phase is defined as the stage of the menstrual cycle immediately following pre-ovulatory follicle collapse at ovulation which comprises the formation of the corpus luteum and secretion of progesterone. The luteal phase ends the day prior to the first day of next menses **[Filicori et al., 2002].**

Polycystic ovary syndrome [PCOS] is the most common endocrine disorder in adult women. It affects around 6-8% of females **[March et al., 2010].** There is growing controversy regarding the most appropriate diagnostic criteria for PCOS in adults. Three sets of criteria have been proposed: the so-called National Institute of Health [NIH] criteria [oligo-anovulation and biochemical or clinical hyperandrogenism [HA]] **[Hickey et al., 2011].**

In 2009, the Androgen Excess society [AES] launched a new definition that considered PCOS primarily as a disorder of clinical and/or biochemical androgen excess, plus either chronic oligo-anovulation and/or polycystic ovaries **[Azziz et al., 2009].**

Insulin resistance in women with polycystic ovary syndrome may eventually lead to the development of hyperglycemia and type-2 diabetes mellitus **[Silvia et al., 2011].** Insulin resistance [hyperinsulinemia] causes the reduced production of sex hormone binding globulin [SHBG] in the liver, the over-production of ovarian and peripheral androgen, and an increase in luteinizing hormone levels that manifest as anovulation in PCOS females **[Basirat et al., 2012].** Also, polycystic ovary syndrome is associated with several other metabolic complications including central obesity, hypertension, and dyslipidemia **[Setji and Brown, 2007].**

Letrozole, the most widely used aromatase inhibitor, has mainly been used for the treatment of post-menopausal females with advanced breast cancer. It is given orally in a dose of 2.5–5mg/day and is almost free of side effects **[Casper et al., 2006].** Letrozole has been shown to be effective in early trials, and induction of ovulation and pregnancy in females with anovulatory PCOS and inadequate

clomiphene response and improving ovarian response to FSH in poor responders **[Aswathi et al., 2010].**

Clomiphene citrate has been used as a first-line ovulation induction agent for over 40 years. It is a selective estrogen receptor modulator that stimulates endogenous FSH production and secretion by interrupting estrogen feedback to the hypothalamus and pituitary **[Wang et al., 2017].**

PCOS patients can be sensitive to ovulation induction medications because of a large number of antral follicles. This places some women with PCOS at risk of over-response with multiple follicular development and ovarian hyper-stimulation: however, other women have a poor response without development of a dominant follicle, despite using higher doses of clomiphene citrate **[Annys et al., 2010].**

Aim of the work

This study objective is to observe the role of using clomiphene citrate [clomid] versus using letrozole [Femara] in improving the clinical features as menstrual irregularities and the sonographic pictures in females with polycystic ovary syndrome within three months.

2. Patients and methods

This study is a clinical trial carried out at Sidnawy Hospital. Each female was followed up for three months after treatment regimen was completed. The study was done during the period from January 2013 through August 2016.

One hundred Fourty women fulfilling the clinical criteria for diagnosis of polycystic ovary syndrome were enrolled. Patients were allocated into one of two groups: group A [clomphine citrate] and group B [letrozole]; each group is 70 females.

Women in group A received clomiphene citrate [Clomid; Aventis Pharma, Egypt] at 50 mg twice daily for 5 days [from the fifth to ninth] each month.

Females in group B received letrozole [Femera, Novartis Pharma, Egypt] at 2.5 mg once daily for 5 days [from fifth to ninth] each month.

Methods:

The study protocol was approved by the local research and ethics committee of Obstetrics and gynecology department of Al-Azhar Faculty of Medicine [Faculty of Girls].

The study protocol was explained for all participated females, and then an informed consent was given by each female. Confidentiality was ascertained and data were used for scientific research only; and the right of withdrawal was guaranteed.

Inclusions criteria

1) Age 18-40 years.

2) Consent for participation.

3) All PCO patients were diagnosed according to Rotterdam-ESHRE criteria: Two of the following three criteria should be present: oligo- or an-ovulation, hyperanrogenism [clinical and/or biochemical], and/or polycystic ovary diagnosed by ultra-sonography.

4) Unable to achieve pregnancy in a period of last 12 months or more despite regular unprotected intercourse.

5) Had patent fallopian tubes proved by hysterosalpingography.

6) Evaluation of husband, revealed no male factor infertility.

7). No history of heart, liver, or kidney disease, and un suspected pregnancy.

Exclusion criteria:

1] Absence of inclusion criteria.

2] Chronic or acute inflammatory diseases.

3] Neoplasm

4] Diabetes mellitus, major surgery 3 months before inclusion, or other hormonal dysfunction.

5] History of recent administration of hormonal therapy.

6] Male factor infertility.

7] Patients aged more than 40 years.

All included females in this study were subjected to:

1- History taking:

Personal history.

Detailed menstrual history, oligomenorrhea OR amenorrhea, Hirsutism, acne, infertility and galactorrhea.

Past history of autoimmune disease, diabetes mellitus, hypertension & thyroid abnormalities.

Family history of PCOS.

Oligomenorrhea: defined as less than 8 spontaneous menses per year for 3 years or more] **[Taponen et al., 2003].**

2- General examination:

Blood pressure [Bp].

Pulse.

Temperature.

Pallor.

Jaundice.

Chest and heart examination.

Acne defined by a history of persistent acne [presence of acne on most days for 3 years or more], recent acne treatment and presence of more than 10 inflammatory acne lesions.

Hirsutism: evaluated by Ferriman-Gallwey [FG] map scoring system [hirsutism was diagnosed if FG more than 8]. The Ferriman–Gallwey score is a method of evaluating and quantifying hirsutism in women. The method was originally published in 1961 by D. Ferriman and J.D. Gallwey in the Journal of Clinical Endocrinology. The original method used 11 body areas to assess hair growth, but was decreased to

9 body areas in the modified method **[Ferriman and Gallwey, 1961]:**

Upper lip
Chin
Chest
Upper back
Lower back
Upper abdomen
Lower abdomen
Upper arms

Forearms [deleted in the modified method]

Thighs

Legs [deleted in the modified method]

In the modified method, hair growth is rated from 0 [no growth of terminal hair] to 4 [extensive hair growth] in each of the nine locations. A patient's score may therefore range from a minimum score of 0 to a maximum score of 36. A score of 8 or higher is regarded as indicative of androgen excess.

Height
Body weight.
BMI [BMI= weight in kg /height in m2].
Waist/hip ratio
The presence of central obesity.
Thyroid gland examination.

3-Abdominal examination:

- Inspection of Hair distribution.
- Palpation for pelvi-abdominal masses.

4-Pelvic examination:

- P/V for exclusion of adenexal masses.

5- Transvaginal sonography: to confirm the ultrasonic criteria of PCOS by transvaginal probe 10MHZ [Toshiba Neoamio, Japan] used in our study, and PCOS criteria at ovaries are [12 or more follicles measuring 2-9mm and/or an increased ovarian volume of >10cm3].

6-Hormonal profile:

1] TSH [to exclude thyroid abnormalities as a cause of an-ovulation

2] Prolactin [PRL] [to exclude hyperprolactinemia as a cause of anovulation]

3] LH, FSH, LH/FSH ratio

4] Total testosterone.

5] Fasting blood glucose.

Outcome

The primary outcome measured in these treated groups was the number and size of the growing and mature follicles and endometrial thickness [ET] monitored with transvaginal ultrasound [TVU] at day 12 of the menstrual cycle. Good response was considered when at least one mature follicle becomes 18 mm in diameter and the patients was advised to have timed intercourse every other day, starting at least 24 h after the leading follicular diameter reached 17 mm in size **[Hamilton-Fairley et al., 1992].**

The secondary outcome measure was the occurrence of pregnancy. Chemical pregnancy was assessed by measurement of β-hCG in blood after at least 3 days after missed period and clinical pregnancy by detection of fetal heart beat on sonography at 6–7 weeks of gestation **[Yarali et al., 2001].**

The overall outcome included in the statistical analysis is the cumulative outcome, where for example pregnancy occurred after the first cycle of ovulation induction, this cycle considered as the last one for this female and measurements at this cycle was included in statistical analysis.

Failure of ovulation is defined as the inability of the female to produce follicles ≥18 mm in size at any of the 3 cycles.

Statistical analysis of data:

The collected data organized, tabulated and statistically analyzed by statistical package for social sciences [SPSS] version 16 [SPSS Inc., Chicago, USA] running on IBM-compatible computer. Numerical values were expressed as mean values and standard deviation, while categorical variables were expressed as frequency and percent distribution. Independent samples [t] test, Chi square or Fisher Exact test were used for comparison between groups. P value < 0.05 was considered statistically significant.

3. Results

In the present work, both groups of females who received clomiphene citrate [CC] or aromatase inhibitor [letrozole] were comparable as regard to their age, weight, height or BMI; the mean age in CC group was 25.55±2.39 years compared to 25.18±2.20 years in letrozole groups. In addition, weight, height and BMI were 74.90±3.48, 1.64±0.022 and 27.51±1.12 respectively in CC group, while in the letrozole groups, the values were 74.18±2.87, 1.64±0.018 and 27.34±1.18 respectively (Table 1).

Table [1]: Distribution of studied females as regard to age, weight, height and BMI.

	CC		Letrozole		Statistics	
	Mean	SD	Mean	SD	t	p
Age	25.55	2.39	25.18	2.20	0.95	0.34
Weight	74.90	3.48	74.18	2.87	1.32	0.18
Height	1.64	0.022	1.64	0.018	0.66	0.50
BMI	27.51	1.12	27.34	1.18	0.90	0.36

As regard to type of infertility in the studied females, it was of primary type in 108 [77.1%] and secondary in 32[22.9%]; and there was no statistically significant difference between CC and letrozole groups [primary infertility was 75.7% and 78.6% in CC and letrozole groups respectively] Table (2).

Table [2]: Distribution of studied females as regard to type of infertility

		group				Total	
		CC		Letrozole			
		n	%	n	%	n	%
Infertility	Primary	53	75.7%	55	78.6%	108	77.1%
	Secondary	17	24.3%	15	21.4%	32	22.9%
Statistics		X^2=0.16 , p =0.68					

In the present work, the duration of infertility extended from 1.5 to 6 years; and there was no statistically significant difference between CC and letrozole groups as regard to infertility duration [it was 2.80±0.93 vs 2.92±0.95 in CC and letrozole groups respectively] Table (3).

Table [3]: Distribution of studied females as regard to duration of infertility [year]

	Mean	S. D	Minimum	Maximum	Statistics	
					t	p
CC	2.80	0.93	1.50	5.00	0.77	0.44
Letrozole	2.92	0.95	1.50	6.00		
Total	2.86	0.92	1.50	6.00		

As regard to menstruation, 9 females [6.4%] had amenorrhea and 131 [93.6%] had oligomenorrhea and there was no significant difference between CC and letrozole groups Table (4).

Table [4]: Distribution of studied females as regard to menstruation

		group				Total	
		CC		Letrozole			
		n	%	n	%	n	%
Menstruation	Amenorrhea	4	5.7%	5	7.1%	9	6.4%
	Oligomenorrhea	66	94.3%	65	92.9%	131	93.6%
Statistics		X^2=0.11 , p =0.73					

As regard to hyperandrogenism, it was reported in 113 females [50.7%], while 27 females [19.3%] had no hyperandrogenism; and there was no significant difference between CC and letrozole groups Table (5).

Table [5]: Distribution of studied females as regard to hyperandrogenism

		group				Total	
		CC		Letrozole			
		n	%	n	%	n	%
HA	Positive	54	77.1%	59	84.3%	113	80.7%
	Negative	16	22.9%	11	15.7%	27	19.3%
Statistics		X^2=1.14 , p =0.28					

As regard to FG score [for hirsutism], it ranged from 4 to 8 with mean value of 6.92±0.80; and there was no significant difference between CC and letrozole groups [6.87±0.58 vs 6.97±0.97 respectively] Table (6).

Table [6]: Distribution of studied females as regard to FG score

	Mean	S.D	Minimum	Maximum	Statistics	
					t	p
CC	6.87	0.58	5.00	8.00	0.73	0.47
Letrozole	6.97	0.97	4.00	8.00		
Total	6.92	0.80	4.00	8.00		

As regard to hormonal profile in studied females, there was no statistically significant difference between both groups, except statistically significant decrease of mid cycle E2 in letrozole group when compared to CC group [212.20±15.57 vs 456.7±56.76 respectively] Table (7).

Table [7]: Distribution of studied females as regard to hormonal profile.

	CC		Letrozole		Statistics	
	Mean	S D	Mean	S D	t	p
FSH [mIU/ml]	5.56	0.60	5.61	0.64	0.51	0.60
LH [mIU/ml]	5.71	0.60	5.71	0.65	0.03	0.97
LH/FSH ratio	1.03	0.06	1.01	0.03	1.34	0.18
Mid cycle E2 [Pg/ml]	456.7	56.76	212.20	15.57	*34.7*	*<0.001**
Testosterone [ng/dl]	99.21	35.34	103.89	31.45	0.81	0.41
TSH [microgram/ml]	1.13	0.22	1.14	0.20	0.44	0.66
Prolactin [ng/ml]	9.35	0.68	9.18	0.69	1.34	0.15

Fasting blood sugar ranged from 93 to 112 mg/dl; and there was statistically non-significant difference between CC and letrozole groups Table (8).

Table [8]: Distribution of studied females as regard to fasting blood glucose levels

	Mean	SD	Minimum	Maximum	Statistics	
					t	p
CC	106.00	3.37	95.00	111.00	1.18	0.23
Letrozole	105.22	4.28	93.00	112.00		
Total	105.61	3.86	93.00	112.00		

Table [9]: Distribution of studied females as regard to ovarian volume and endometrial thickness [mm]

		Mean	S. D	Minimum	Maximum	Statistics	
						t	p
Ovarian volume	CC	15.50	1.81	12.00	19.00	1.26	0.21
	Letrozole	15.11	1.79	11.00	20.00		
	Total	15.30	1.80	11.00	20.00		
ET [mm]	CC	7.82	1.58	5.00	12.00	*9.43*	*<0.001**
	Letrozole	10.27	1.47	7.00	15.00		
	Total	9.05	1.95	5.00	15.00		

As regard to ovarian volume, it ranged from 11 to 20 and there was no significant difference between CC and letrozole groups. On the other hand, endometrial thickness [ET] ranged from 5 to 15 mm; and there was statistically significant increase of ET in letrozole when compared to CC groups [10.27±1.47 vs 7.82±1.58 respectively] Table (9).

As regard to cumulative ovulation rate [one or more follicles with size ≥ 18 mm], it was reported in 51.4% of CC group and in 68.6% in letrozole group, with statistically significant increase of cumulative ovulation rate in letrozole when compared to CC group Table (10).

Table [10]: distribution of studied females as regard to cumulative ovulation rate

		Group				Total	
		CC		Letrozole			
		n	%	n	%	n	%
Follicle ≥ 18mm	Positive	36	51.4%	48	68.6%	84	60.0%
	Negative	34	48.6%	22	31.4%	56	40.0%
Statistics		$X^2 = 4.28,\ p = 0.038^*$					

As regard to number of mature follicles in studied females, it ranged from 1 to 2 follicles; and there was no significant difference between CC and letrozole groups [1.72±0.45 vs 1.60±0.49 respectively] Table (11).

Table [11]: Distribution of studied females as regard to number of follicles

	Mean	S D	Minimum	Maximum	Statistics	
					t	p
CC	1.72	0.45	1.00	2.00	1.12	0.26
Letrozole	1.60	0.49	1.00	2.00		
Total	1.65	0.47	1.00	2.00		

As regard to cumulative pregnancy rate, it was reported in overall 37 females [26.4%] and there was statistically significant increase of pregnancy rate in letrozole when compared to CC group [34.3% vs 18.6% respectively] (Table 11).

Table [12]: Distribution of studied females as regard to cumulative pregnancy rate

		group				Total	
		CC		Letrozole			
		n	%	n	%	n	%
Pregnancy	Positive	13	18.6%	24	34.3%	37	26.4%
	Negative	57	81.4%	46	65.7%	103	73.6%
Statistics		$X^2 = 4.44,\ p = 0.02^{**}$					

4. Discussion

The development of effective, simple, and safe treatments for polycystic ovary syndrome [PCOS] as a cause of infertility is an important public health goal **[Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008].**

Polycystic ovary syndrome [PCOS] is a common cause of reproductive endocrinopathy in women and is characterized by hyperandrogenism, chronic oligo-anovulation, and insulin-resistance **[Legro et al., 2007].**

For an infertile woman with PCOS, clomiphene citrate [CC] remains the first-line treatment; however, 15–40% of women do not resume ovulation following CC treatment, which is defined as CC-resistance. The most common treatments for CC-resistant PCOS are laparoscopic ovarian drilling [LOD] and gonadotropin treatment. Successful pregnancy outcomes for both treatments have been reported **[Palomba et al., 2009].**

However, the main disadvantages of LOD are the need for hospitalization, general anesthesia and may lead to pelvic adhesion and ovarian function decrease, which would hinder any subsequent pregnancies. Due to the high sensitivity of the ovaries to gonadotropin stimulation, treatment with human menopausal gonadotropin or pure follicle-stimulating hormone [FSH] is challenging to control and is individually administered to induce several ovulatory follicles, which incurs a substantially increased risk of multiple pregnancies and ovarian hyperstimulation syndrome [OHSS] **[Bayram et al., 2004].** In addition, the cost of gonadotropin treatment could add a financial burden to the infertile patient; therefore, a convenient, economic and safe treatment method for CC-resistant PCOS is required **[Farquhar et al., 2002].**

Letrozole [LE] is a potent and selective third-generation aromatase inhibitor [AI], which can effectively and highly selectively block the production of estrogen without disturbing other steroidogenic pathways. LE was first used to treat breast cancer and was found to be superior to the previous gold standard tamoxifen, and more effective than others **[Ibrahim et al., 2017].**

Also, **Mitwally and Casper [2003],** introduced LE to the ovulation induction field; since then, numerous investigations in LE-induced ovulation have been performed.

According to the reports, the ovulation rate in women with CC-resistant PCOS is between 54.6 and 84.4% **[Wang et al., 2015].**

The present study was designed to investigate the possible role of letrozole in comparison to clomiphene citrate in treatment of irregularities of females with polycystic ovary syndrome especially in treatment of anovulation and infertility.

All included females were submitted to full history taking, clinical examination, laboratory investigations and ultrasono-graphy examination. They were divided into two groups [those who received clomiphene citrate and those who received letrozole for successive 3 months]. In each month, ovulation and pregnancy rates were documented.

Results of the present work revealed that, the cumulative ovulation rate was statistically significantly increased in letrozole group when compared to CC group [68.6% vs 51.4%]. However,

the mean number of matured follicles was increased in the CC group, but the difference was statistically non-significant. In addition, the cumulative pregnancy rate was significantly increased in letrozole group when compared to CC group [34.3% vs 18.6%]. Furthermore, endometrial thickness [ET] revealed statistically significant increase in letrozole when compared to CC groups [10.27±1.47 vs 7.82±1.58 respectively]. Finally, there was statistically significant decrease of mid cycle E2 in letrozole group when compared to CC group [212.20±15.57 vs456.7±56.76 respectively]. Otherwise, both groups were comparable for other studied variables.

Results of the present work are in accordance with the study done by **Begum et al. [2009]** who reported that, characteristics of age, duration of infertility, and basal hormone levels were similar in both groups of patients. Mean age was 25.47±3.98 years and 26.09±3.62 years, duration of infertility was 2.66 ±1.11 years and 2.58±1.10 years in the letrozole and CC groups, respectively.

In addition, results of the present study are in agreement with a recent meta-analysis where, **Roque et al. [2015]** reported that, use of letrozole for ovulation induction followed by timed intercourse in patients with PCOS significantly improved the live birth and pregnancy rates when compared to CC. They added, when considering the pregnancy rates, all seven studies included in their meta-analysis evaluated this outcome revealed a statistically significant increase in these rates, favoring the letrozole group [RR=1.38; 95% CI: 1.05–1.83].

Furthermore, results of the present work are in accordance with the study published by **Franik et al. [2014]** who done a Cochrane review and found that, the use of aromatase inhibitor [letrozole] in subfertile women with polycystic ovary syndrome was associated with better overall outcome than the use of CC.

Furthermore, results of the present work are in agreement with those reported by **Begum et al. [2009]** who reported that, in their study ovulation was significantly more frequent in the letrozole group [62.5%; 20 patients] than in the CC group [37.50%; 12 patients]. Pregnancy rate [PR] was also higher in the letrozole group [40.62%] in comparison with the CC group [18.75%].

Mitwally and Casper [2001] using 2.5 mg/day of letrozole achieved 75% and 100% ovulation in anovulatory and ovulatory patients, respectively. Other studies also showed higher ovulation with letrozole **[Mitwally and Casper, 2002; Fisher et al., 2002].**

Ovulation rate was also higher [98%] in our previous study with 5 mg of letrozole for patients who did not respond to 100–150 mg of CC in their previous cycles **[Begum et al., 2006].**

Fozan et al. [2004] showed significantly higher number of mature follicles with 7.5 mg of letrozole in comparison with 100 mg of CC in randomly selected cases.

For interpretation of favoring pregnancy rate with letrozole, **Roque et al. [2015]** hypothesized that these improved live birth and pregnancy rates observed among the patients that used letrozole would be explained by differences in the pharmaco-dynamics between the two drugs, as well as by the differential alterations in endometrial gene expression.

The half-life of letrozole is 45 h **[Pavone and Bulun, 2013]** and it features rapid clearance, preventing accumulation of the drug with repeated cycles. This is in contrast to CC, which has a longer plasma and tissue retention time [plasma levels are measurable up to 1 month after a single 50 mg dose of CC] **[Young et al., 1999],** leading to prolonged depletion of the estrogen receptors. This depletion may lead to the development of adverse effects, such as endometrial thinning as well as poor quality and quantity of the cervical mucus **[Casper and Mitwally, 2006].**

In the present work, results confirm the thinning of endometrial thickness in CC group when compared to letrozole group. In addition, the mid-cycle E2 was significantly increased in CC group. In favor of this, **Begum et al. [2009]** assumed that, because of the much shorter life span of letrozole and absence of anti-estrogenic effects in the late follicular phase, estradiol concentration increased and consequently the endometrium grew faster, and thus a greater endometrial thickness on the day of HCG administration, in favor of nidation, and a higher pregnancy rate was to be expected.

In accordance with the results of the current study, a greater endometrial thickness was detected in the letrozole group compared with the clomiphene citrate group in two previous studies **[Atay et al., 2006; Aygen et al., 2007].** However, the result in **Badawy et al. [2009]** was the opposite: the endometrial thickness was greater in the clomiphene citrate group.

Mitwally et al. [2005] and Sohrabvand et al. [2006] studied the endometrial thickness at the day of HCG administration which was significantly increased in the Letrozole group than the clomiphene citrate group which was in line with the results obtained by **Samani et al. [2009]** but they compared it in women with polycystic ovarian. This endometrial effect may be due to an effect on endometrial vascularity which is more evident in Letrozole.

Fozan et al. [2004] found an insignificant increase in endometrial thickness on the day of HCG

administration in the letrozole group but this while they were using a higher dose of Letrozole [7.5 mg].

ElKattan [2013] concluded that, letrozole [5 mg] showed a significantly better endometrial response than 100 mg of clomid. They added, there was a significant difference in the endometrial thickness, endometrial volume, and spiral artery Doppler indices between the two groups one week after HCG administration. The pregnancy rate was higher in the letrozole group.

In addition, there are numerous proteins that can be used as biomarkers of endometrial receptivity [ER], and integrin is one of the most well-established markers of ER **[Franasiak et al., 2014].** Some previous studies have shown that letrozole might improve integrin expression, resulting in improvements in ER **[Miller et al., 2012].**

Furthermore, letrozole may increase the gene expression of some important genes during implantation, improving the results of women undergoing ovulation induction with this drug rather than CC **[Wallace et al., 2011].**

The mean no. of mature follicles >17 mm in treated groups is in agreement with that found by **Bayar et al. [2006]** study in which it was [1], and it is lower than to that found by **Sohrabvand et al. [2006]** study which was [1.8], while it disagrees with that found by **Atay et al. [2006]** and **Badawy et al. [2009]** studies in which the mean no. of mature follicles were [2.4] and [3.1] respectively.

On the other hand, **Misso et al. [2012] and He and Jiang [2011]** in their meta-analysis did not show differences in the pregnancy rates between the letrozole and CC groups.

However, **He and Jian [2011]** themselves reported that, their meta-analysis had many limitations; as first, most trials were conducted in Asia. Second, the dose of letrozole administered was not completely the same in all trials included in the meta-analysis, which could influence the results of the meta-analysis. Third, it is possible that studies with negative results, which showed no trend in favor of either intervention, may remain unpublished, leading to publication bias.

They added, one study **[Aygen et al., 2007]** was really small. Based on sample size calculation, the current study recommends that at least 52 participants are included for a proper RCT to compare both drugs.

Finally, **Al-Shaikh et al. [2017]** reported that, for women given Letrozole as an ovulation inducing agent been claimed to have several advantages including, rapid clearance from the body so less likely to have antiestrogenic effect on endometrium and cervical mucus quality resulting in high pregnancy rate, mono-follicular ovulation resulting in lesser chance of ovarian hyperstimulation syndrome [OHSS] and multiple gestation, no accumulation of the medicine or its metabolite. As have been proposed as both first and secondary treatment for ovulation induction in women with PCOS especially after CC failure, and also for unexplained infertility. They added, in order to enhance its activity, letrozole should be combined with another medication of infertility like low dose of FSH as found by **Healey et al. [2003], Garcia-Velasco et al. [2005]** studies in which rate of pregnancy per cycle were [21.6%], [22.2%], [22.4%] and [19%] respectively, letrozole combined low-dose gonadotropins therapy offers a higher rate of ovulation, monofollicular development, with a significantly lower risk of OHSS or it combined with metformin as in **Sohrabvand et al. [2006]** study in which pregnancy rate per cycle was [19%].

In conclusion, results of the present work are in favor of letrozole for treatment of anovulation and subfertility in females with PCOS.

Summary

The present study was designed to investigate the possible role of letrozole in comparison to clomiphene citrate in treatment of irregularities of females with polycystic ovary syndrome especially in treatment of anovulation and infertility.

All included females were submitted to full history taking, clinical examination, laboratory investigations and ultrasono-graphy examination. They were divided into two groups [those who received clomiphene citrate and those who received letrozole for successive 3 months]. In each month, ovulation and pregnancy rates were documented.

Results of the present work revealed that:

The cumulative ovulation rate was statistically significantly increased in letrozole group when compared to CC group [68.6% vs 51.4%].

The mean number of matured follicles was increased in the CC group, but the difference was statistically non-significant.

The cumulative pregnancy rate was significantly increased in letrozole group when compared to CC group [34.3% vs 18.6%]. Endometrial thickness [ET] revealed statistically significant increase in letrozole when compared to CC groups [10.27±1.47 vs 7.82±1.58 respectively]. Finally, there was statistically significant decrease of mid cycle E2 in letrozole group when compared to CC group [212.20±15.57 vs 456.7±56.76 respectively].

Otherwise, both groups were comparable for other studied variables.

Conclusion

Results of the present work revealed that, letrozole is superior to clomiphene citrate for induction of ovulation in polycystic ovary syndrome as regard to response rate and overall pregnancy rate.

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