Research Article

Clomiphene Citrate versus Letrozole for Induction of Ovulation in Infertile women having Polycystic Ovarian Syndrome (Randomized Controlled Trial)

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Abstract:

Background: Polycystic ovary syndrome is a disorder but with unclear etiology that its diagnosis depends on exclusion of other etiologies with ovulatory disorders and androgen excess as congenital adrenal hyperplasia, 21-hydroxylase deficient non classic congenital adrenal hyperplasia (NCAH), adrenal or ovarian androgen-secreting tumors, disorders of adrenocortical dysfunction as Cushing's disease, and abuse of androgenic or anabolic drugs. Polycystic ovary syndrome affects approximately 6-15% of women in reproductive age and constitutes 50% of the causes of infertility in women.

Aim of the Work: To compare the efficacy of letrozole on ovulation induction to that of clomiphene citrate in women suffering polycystic ovary syndrome and the effect on the follicular maturation, endometrial thickness and pregnancy rate. This study was carried in the outpatient infertility clinic of Ain-Shams Maternity Hospital during the period from November 2020 till April 2021.

Patients and Methods: This study included 80 infertile women diagnosed as having polycystic ovary syndrome. Women were randomized into two groups. Letrozole group (1) included 40 women who were given the aromatase inhibitor (Letrozole) orally in a 5mg dose daily from day 3 to day 7 of the menstrual cycle. While Clomiphene citrate group (2) included 40 women who were given the clomiphene citrate orally in 100mg dose daily from day 3 to day 7 of the menstrual cycle. All women were counseled and informed consent was obtained before recruitment.

Results: In this study, ovulation rate was significantly more frequent in the Letrozole group (82.5%, 33 women reached ovulation successfully) than in Clomiphene citrate group (60%, 24 women reached ovulation successfully) within P value=0.024. Clomiphene citrate at a dose of 100mg showed more efficacies in the number of follicle ≥18mm than Letrozole at a dose of 5mg. In Letrozole group, the number of follicles (≥18mm in diameter) ranged from 1 to 2 with a Mean±SD= 1.4±0.65 and in Clomiphene citrate group, the number of follicles (≥18mm in diameter) ranged from 1 to 3 with a Mean±SD= 1.9± 0.41 (P value=0.0001).

Conclusion: Letrozole can be considered as a first line treatment of anovulation in polycystic ovary syndrome. But, moreover studies including larger number of cases will further confirm the efficacy of letrozole versus clomiphene citrate in induction of ovulation, reaching to the optimum doses for aromatases inhibitors, more observation on endometrial thickness, incidence of pregnancy outcomes, incidence of abortion and incidence of congenital fetal malformations.

Keywords: polycystic ovary syndrome; androgen excess society; NICHD; ASRM; ESHRE

Introduction

Ovulation is a main event in reproduction cycle. Anovulatory dysfunction is common problem and is responsible for approximately 40% of female infertility (Baadwy et al., 2009).

Polycystic ovary syndrome (PCOS) considers a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries (Ndefo, 2013).

The National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) gathered a panel of experts who developed the first known criteria for PCOS in year 1991 and realized that ovarian morphology was a key component in the diagnosis.

After that, The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) sponsored a workshop in Rotterdam. Through the workshop, polycystic ovarian morphology on pelvic ultrasound was added to the NICHD/NIH criteria (Legro, 2013).

In year 2006, the Androgen Excess Society (AES) suggested that the NICHD/NIHS criteria might be used with modifications that contained the Rotterdam tool. The AES describes PCOS as a disorder primarily involving androgen excess, along with different combinations of phenotypic features (e.g., hyperandrogenemia, hirsutism, oligo-

ovulation/anovulation, and/or polycystic ovaries) that may promote a more accurate diagnosis (Dewailly, 2011).

Using the modified Rotterdam criteria in clinical diagnosis of polycystic ovarian syndrome is easily reached and most often treatment can be initiated following a few basic investigation and exclusion of the male factor problem (Azziz, 2007).

For more than four decades, clomiphene citrate has been used as the first line therapy for induction of ovulation in women with anovulatory infertility and for super-ovulation in couples with unexplained infertility. It's orally administrated, available and inexpensive (Palomba, 2004).

In addition, predictors of the ovulatory response to clomiphene are body mass index, the free androgen index, ovarian volume and low concentrations of IGF-BP-I. On the other hand, pregnancy predictors with clomiphene are age and the severity of the cycle disorders, i.e. better responses occur in women of a younger age and with maintained oligomenorrhoea or amenorrhea, suggesting that FSH threshold (amount of FSH required to stimulate the follicular maturation and the ensuing ovulation) and oocyte quality are specifically regulated (Imani et al., 1999).

Because of its long half-life (two weeks), clomiphene citrate accumulates in the body and may have a negative effect on the quality and quantity of cervical mucus, endometrial development, which may cause implantation failure, luteal phase defect (LPD) and significant thinning of endometrium. Clomiphene citrate resistance together with side effects like multi-follicular development and cyst formation are areas of concern. The desire for an effective alternative persist (Kamath, 2010).

Clomiphene Citrate has drawbacks, including its overall poor efficacy, a nearly high multiple-pregnancy rate (3 to 8%) as compared with the rate associated with unassisted conception (<1%), and an unfavorable side effects profile, including mood changes and hot flushes. Failure either to ovulate (clomiphene resistance) (Legro R., 2007) or to conceive with ovulation (clomiphene failure) often results in the use of more expensive treatment options for infertility that may be associated with high multiple-pregnancy rate and an increased risk of the ovarian hyper-stimulation syndrome (Costello M., 2012).

Letrozole is a third generation selective aromatase inhibitor that was used as an ovulation inductor in anovulatory infertility women with more than 5mm endometrial thickness (Guang and Rezk, 2018).

Letrozole has been in use as an ovulation induction agent for more than a decade. Even though emerging evidence suggests that it's an effective ovulation induction agent, comparable if not better than clomiphene (Kamath & George, 2011).

Other studies also reported that letrozole is effective in clomiphene-resistant patients, and also resulted in ovulation of 62% cases, and pregnancy of 14.7% (Guang, 2018).

In contrast to clomiphene, letrozole at the customary dose of 2.5 mg elicits a mono-follicular response and doesn't adversely affect either the endometrial thickness or cervical mucus, due to an absence of a peripheral estrogen receptor blockage (Polyzos, 2008).

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AIM OF THE WORK

The aim of this study is to compare the efficacy of letrozole on ovulation induction to that of clomiphene citrate in women suffering polycystic ovary syndrome.

Research Question: In women with polycystic ovary syndrome, is Letrozole more effective than Clomiphene citrate in induction of ovulation?

Researcher Hypothesis: In women with polycystic ovary syndrome, letrozole may be as effective as Clomiphene citrate in induction of ovulation.

PATIENTS AND METHODS

Study design:

- Type of study: A randomized controlled trial / single blinded study.
- Study Setting: The study carried out in Ain-shams University Hospital, maternity hospital, infertility outpatient clinic, Cairo, Egypt. After being approved by the medical ethics committee.
- Study Duration: the study duration was 6 months from November 2020 till April 2021.
- Study population: 80 women distributed into two groups with randomization sheet:

Group (1): this group included 40 patients with polycystic ovarian syndrome took letrozole 5mg/day dose for 5 days starting on day 3 till day 7 of the menstrual cycle.

Group (2): this group included 40 patients with polycystic ovarian syndrome took clomiphene citrate 100 mg/day dose for 5 days starting on day 3 till day 7 of the menstrual cycle.

Inclusion Criteria: 1. Female aged from 18-35 years. 2. Had primary infertility (Period of infertility more than one year). 3. Diagnosis of (PCOS): Modified Rotterdam criteria used to diagnosis the polycystic ovarian syndrome which required the presence of two out of the following three variables: Oligo-ovulation (menses that occur at intervals greater than 35days) and/or an ovulation, Clinical or biochemical signs of hyperandrogenism : hirsutism (ESHRE/ASRM 2013) or an elevated testosterone level (LEGRO 2010) and Polycystic ovaries (12 follicles that were <10 mm in diameter) or an increased individual ovarian volume (>10 cm) in one ovary or both. 4. No treatment was taken for induction of ovulation during the last 2 month prior to the inclusion in the study. 5. Serum level of FSH (<10 mlU/mL) in the early follicular phase. 6. Two patent fallopian tubes and normal uterine cavity were documented by a recent (within 6 months) hysterosalpingiography or laparoscopy. 7. Recent (within 3 months) semen analysis of the husband with normal semen parameters.

Exclusion Criteria: 1. History of pelvic surgery or previous laparoscopic intervention. 2. Women with infertility factors other than polycystic ovarian syndrome like hyperprolactinemia, cervical polyps, fibroids, pelvic inflammatory disease or endometriosis. 3. Male factor of infertility (by semen analysis) like genetic defects in sperm production, increase abnormal forms or varicocele.

All the participants were subjected to the following:

1- **Written informed consent.**
2- **History taking:** Personal history: name, age, occupation, marital status and duration, residence, special habits of medical importance and husband full history. History of present illness: duration of infertility, history of investigations and treatment and other system review.

Menstrual history: criteria and average number of menses for year and last normal menstrual period. Past history: including any medical disorder e.g Diabetes mellitus, hypertension or any surgical procedure. Sexual history: continued unprotected sexual intercourse, duration, frequency and pain.

3- **Physical examination:** measurement of body mass index (BMI ≥25).
4- **General examination:** for acne and hirsutism.
5- **Abdominal examination.**
6- Vaginal examination for enlarged for enlarged cystic ovaries.
7- **Investigations:** pelvic ultrasound, hormonal profile (basal FSH, LH, Prolactin and TSH), HSG and husband semen analysis.
8- Basaline transvaginal US day 2 or 3 of menstrual cycle to exclude presence of ovarian cyst.
9- Folliculometry by transvaginal US started from day 9 of the menstrual cycle then every other day.
10- hCG (10, 000 IU) were given IM when at least one follicle > 18mm.
11- Measurement of endometrial thickness on the day of hCG administrated.
12- Patients were advised to have intercourse 24 to 36 hours after hCG injection.
13- Measurement of mid luteal phase serum progesterone and estradiol serum level.
14- In case that no pregnancy repetitive of the schedule up to 3 cycles.

❖ **Statistical Analysis:**

- Sample size : Using PASS 11 program for sample size calculation, setting power at 80% and a-error at 0.05, and according to previous literature (Mohamed et al, 2020), it was expected that ovulation rate in Letrozole group=80% and Clomiphene citrate group=60%, so sample size of 40 patients could detect the difference between two groups with power 80%.
- Randomization: sample randomization was done by using (random allocation software version 1.0) prepared by independent statistician.
- Statistical Methods: Recorded data was analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data was expressed as mean± standard deviation (SD). Qualitative data was expressed as frequency and percentage.

The following tests were done:

1. Independent-samples t-test of significance was used when comparing between two means.
2. Mann Whitney U test: for two-group comparisons in non-parametric data.
3. Chi-square (x2) test of significance was used in order to compare proportions between qualitative parameters.
4. Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of cells, while Fisher's exact test was more accurate than the chi-squared test when the expected numbers were small.
5. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

Probability (p-value):
P-value <0.05 would be considered significant.
P-value < 0.001 would be considered as highly significant.

P-value > 0.05 would be considered insignificant.

RESULTS

Table 1: Comparison between Letrozole Group and Clomiphene Citrate Group according to their demographic data regarding age (years), type of infertility, duration of infertility (years) and BMI [Weight/Height^2].

Baseline Characteristics	Letrozole Group (n=40)	Clomiphene Citrate Group (n=40)	Test	p-value
Age Group				
<25 years	6 (15.0%)	6 (15.0%)		
25-<30 years	24 (60.0%)	19 (47.5%)	x2=1.581	0.454
≥30 years	10 (25.0%)	15 (37.5%)		
Age (years)				
Mean±SD	27.33±2.78	28.20±3.66	t=-1.205	0.232
Range	21-33	21-35		
primary Infertility	33 (82.5%)	31 (77.5%)	x2=0.31	0.576
Duration of infertility (years)				
At One year	5 (12.5%)	4 (10.0%)		
>1-2 years	13 (32.5%)	11 (27.5%)	x2=0.611	0.894
>2-4 years	12 (30.0%)	15 (37.5%)		
>4-6 years	10 (25.0%)	10 (25.0%)		
Duration of infertility (years)				
Mean±SD	2.90±1.42	3.15±1.55	z=0.565	0.455
Range	1-5	1-6		
BMI Group				
18-<25	9 (22.5%)	11(27.5%)		
25-<30	22 (55%)	15 (37.5%)	x2= 4.879	0.087
≥30	9 (22.5%)	14 (35%)		
BMI [wt/(ht)^2]				
Mean±SD	27.36±2.33	27.79±2.73	t=0.379	0.706
Range	24.1-31.8	22-33		

t-Independent Sample t-test; z-Mann-Whitney test; x^2: Chi-square test
*p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

The two groups were comparable in age with the mean Age ±SD in each of Letrozole Group and Clomiphene Citrate Group was 27.33±2.78 compared to 28.20±3.66 respectively, there is no statistically significant difference between the two groups with p-value (p=0.232).

This table showed also Primary infertility that were comparable in each of Letrozole Group (were 33 patients (82.5%)) and Clomiphene Citrate Group (were 31 patients (77.5%)). there is no statistically significant difference between the two groups with p-value (p=0.567).

Also, the two groups were comparable in duration of infertility "years" with the mean in each of Letrozole Group and Clomiphene Citrate Group was 2.90±1.42 compared to 3.15±1.55 respectively, there is no statistically significant difference between the two groups with p-value (p=0.455).

Finally, the two groups were comparable in BMI with the mean in each of Letrozole Group and Clomiphene Citrate Group was 27.36±2.33 compared to 25.79±2.73 respectively, there is no statistically significant difference between the two groups with p-value (p=0.706).

Table 2: Comparison between Letrozole Group and Clomiphene Citrate Group according to their hormonal profile regarding FSH, LH and FSH/LH ratio.

Hormonal Profile	Letrozole Group (n=40)	Clomiphene Citrate Group (n=40)	t-test	p-value
FSH (mIU/mL)				
Mean±SD	6.78±1.09	8.15±9.60	-0.899	0.371
Range	4.5-9.8	4.7-67		
LH (mIU/mL)				
Mean±SD	14.90±1.57	14.85±2.13	0.114	0.910
Range	11.5-18	11-18.2		

FSH/LH ratio				
Mean±SD	2.33±0.45	2.35±0.42	-0.181	0.857
Range	1.4-3.4	1.8-3.5		

t-Independent Sample t-test; p-value>0.05 NS

The two groups were comparable in FSH with the mean ±SD in each of Letrozole Group and Clomiphene Citrate Group was 6.78±1.09 compared to 8.15±9.60 respectively, there is no statistically significant difference between the two groups with p-value (p=0.371).

This table shows also, the two groups were comparable in LH with the mean ±SD in each of Letrozole Group and Clomiphene Citrate Group was 14.90±1.57 compared to 14.85±2.13 respectively, there is no statistically significant difference between the two groups with p-value (p=0.910). While, the two groups were comparable in FSH/LH ratio with the mean ±SD in each of Letrozole Group and Clomiphene Citrate Group was 2.33±0.45 compared to 2.35±0.42 respectively, there is no statistically significant difference between the two groups with p-value (p=0.857).

Table 3: Comparison between Letrozole Group and Clomiphene Citrate Group according to number of women had follicles ≥18mm and <12mm, number of follicles ≥18mm, diameter of the dominant follicle, number of women received hCG, endometrial thickness (mm), mid-luteal phase serum progesterone level (ng/mL), estradiol serum level pg/ml) and number of pregnant women (in the first cycle).

First cycle	Letrozole Group (n=40)	Clomiphene Citrate Group (n=40)	Test	p-value
Number of women who had follicles ≥18mm **Number of women who had follicles < 12mm**	38 (95%) 2 (5%)	30 (75%) 10 (25%)	x2= 6.27	0.012*
Number of follicles ≥18mm Mean±SD Range	1.6± 0.7 1-2	2.5 ±0.5 1-3	t= 6.61	0.0001*
Diameter of the dominant follicle in mm Mean±SD Range	22.4 ± 1.32 20- 23	20.2± 1.15 19-21	t= 7.94	0.0001*
Number of women who received HCG	36 (95%)	24(80%)	x2=4.8	0.028*
Endometrial thickness (mm) Mean±SD Range	8.5±0.5 8-10	7.5±1.26 6-9	t= 4.66	0.0001*
Mid-luteal phase serum progesterone (ng/mL) Mean±SD Range	14.12±1.71 7-16	11.27±1.6 6-13.6	t= 7.69	0.0001*
Estradiol serum level (pg/mL) Mean±SD Range	168.8± 21.3 148 - 181	189.3±29.2 158- 195	t= 3.587	0.001*
Number of women became pregnant on first cycle	4 (10%)	1 (3%)	x2= 1.92	0.163

*x^2: Chi-square test; t-Independent Sample t-test; * p-value<0.05 HS*

There was a highly statistically significant difference between two groups according to Number of women who had follicles ≥18mm and women who had follicles <12mm (p= 0.012). The highest response was found in Letrozole Group 38 (95%) had follicles ≥18mm and 2 (5%) had follicles <12mm than Clomiphene Citrate Group 30 (75%) had follicles ≥18mm and 10 (25%) had follicles <12mm.

There was a highly statistically significant difference between two groups according to Number of follicles ≥18mm on the day of hCG administration (p=0.0001). The highest value was found in Clomiphene citrate Group with Mean±SD 2.5 ±0.5 compared to Letrozole Group with Mean±SD 1.6± 0.7.

Also, there was a highly statistically significant difference between both group according to Diameter of the dominant follicle (p=0.0001). The highest value was found in Letrozole Group with Mean±SD 22.4 ± 1.32 compared to Clomiphene Citrate Group with Mean±SD 20.2± 1.15.

There was a highly statistically significant difference between two groups according to Number of women who received HCG (p= 0.034). The highest response was found in Letrozole Group 36 (95%) than Clomiphene Citrate Group 24 (80%).

There was a highly statistically significant difference between two groups according to Endometrial thickness (mm) on the day of hCG administration (p=0.0001). The highest value was found in Letrozole Group 8.5±0.5 compared to Clomiphene Citrate Group 7.5±1.26.

There was a highly statistically significant difference between two groups according to Mid-luteal phase serum progesterone level (p=0.0001). The highest value was found in Letrozole Group 14.12±1.71 ng/mL compared to Clomiphene Citrate Group 11.27±1.6 ng/mL.

There was a highly statistically significant difference between two groups according to Estradiol serum level on the day of hCG administration (p=0.001). The highest value was found in Clomiphene Citrate Group 189.3±29.2 pg/mL compared to Letrozole Group 168.8± 21.3 pg/mL.

The two groups were comparable in Number of women became pregnant on the first cycle, in Letrozole Group 4 women became pregnant (10%) while in Clomiphene Citrate Group 1 became pregnant (3%), there is no statistically significant difference between the two groups with p-value (p=0.163).

Table 4: **Comparison between Pregnant and non-pregnant women in Letrozole Group according to their number of follicle(s) ≥18mm on the day of hCG administration, diameter of the dominant follicle, endometrial thickness (mm), estradiol serum level on the day of hCG administration (pg/ml) and mid-luteal phase serum progesterone level (ng/mL)**

Letrozole Group (n= 40)	Pregnant (n=15)	Non-pregnant (n=25)	Test	p-value
Number of follicles ≥18mm Mean±SD Range	2.03± 0.5 1-2	1±0.6 0-2	t=5.579	0.0001*
Diameter of the dominant follicle in mm Mean±SD Range	23.4± 0.9 21-24	17.3± 1.47 10-19	t=9.41	0.0001*
Endometrial thickness (mm) Mean±SD Range	8.85± 0.6 8-10	6.6±0.3 6-8	t= 9.16	0.0001*
Mid-luteal phase serum progesterone (ng/mL) Mean±SD Range	14.5± 0.6 13-15.4	9.2 ± 1.6 6 -10.3	t= 12.27	0.0001*
Estradiol serum level (pg/mL) Mean±SD Range	167.3±13.6 150- 185	100.1±17.8 70- 148	t=8.56	0.0001*

*t-Independent Sample t-test; *p-value<0.05 HS*

There was a highly statistically significant difference between two groups according to Number of follicles ≥18mm on the day of hCG administration (p=0.0001). The highest value was found in Pregnant Group with Mean±SD 2.03± 0.5 compared to Non-pregnant Group with Mean±SD 1±0.6.

Also, there was a highly statistically significant difference between both group according to Diameter of the dominant follicle (p=0.0001). The highest value was found in Pregnant Group with Mean±SD 23.4± 0.9 compared to Non-pregnant Group with Mean±SD 17.3± 1.47.

There was a highly statistically significant difference between two groups according to Endometrial thickness (mm) on the day of hCG administration (p=0.0001). The highest value was found in Pregnant Group 8.85± 0.6 compared to Non-pregnant Group 6.6±0.3.

There was a highly statistically significant difference between two groups according to Mid-luteal phase serum progesterone level (p=0.0001). The highest value was found in Pregnant Group 14.5±0.6 ng/mL compared to Non-pregnant Group 9.2±1.6 ng/mL.

There was a highly statistically significant difference between two groups according to Estradiol serum level on the day of hCG administration (p=0.0001). The highest value was found in Pregnant Group 167.3±13.6 pg/mL compared to Non-pregnant 100.1±17.8 pg/mL.

DISCUSSION

Polycystic ovary syndrome (PCO) is a disorder but with unclear etiology. For that, it became a diagnosis of exclusion, by exclusion of other etiologies with androgen excess and ovulatory disorders. For example, Androgen excess disorders should be excluded are 21-hydroxylase deficient non classic congenital adrenal hyperplasia (NCAH), adrenal or ovarian androgen-secreting tumors, disorders of adrenocortical dysfunction as Cushing's disease, and abuse of androgenic or anabolic drugs. Although not true androgen excess, namely idiopathic hirsutism, should be excluded (Azziz, 2007).

According to Rotterdam criteria, diagnosis of polycystic ovary syndrome needs two of three characteristics: oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries according to pelvic ultrasound (Dunaif, 2013; Lawrenson, 2014; Escobar-Morreale, 2018).

Clomiphene citrate is a non-steroidal selective estrogen-receptor modulator that binds to estrogen receptors and makes agonist effects in some tissues and antagonist effect on other tissue (Grese, 1997; Barroso, 2006).

The main mechanism of action of clomiphene citrate is to induce ovarian stimulation through the anti-estrogenic effect on the hypothalamus and pituitary leading to increase the pulse frequency and concentration of the FSH and LH within increase of ovarian follicles to reach the ovulation (Casper & Mitwally, 2006; Porter, 2008).

Aromatase inhibitors are three generations that might be steroidal or non-steroidal inhibitors (Bhatnagar, 1990 and Brodie, 1996) which block estrogen synthesis affect directly hypothalamic pituitary ovarian axis function and that theoretically may increase pregnancy rate (Casper & Mitwally, 2006).

Letrozole is a triazole derivative (antifungal) which is potent, reversible, competitive, non-steroidal, and highly selective aromatase inhibitor (Badawy, 2009). It prevents androgen to estrogen conversion in the ovary and leads to decrease in estrogen level providing negative feedback in hypothalamus which stimulates the pituitary gland to secrete FSH and development of follicle (Stafeno, Legro et al., 2014). Letrozole is rapidly absorbed from GIT and completely bioavailable up to 99.9% after oral administration (Sioufi, 1997). It's available in two doses (2.5 and 5mg)

(Al Fozan, 2004), has short half-life (approximately 2 days) and excreted mainly by kidneys (Novartis Pharmacoceutical, 2014).

Advantages of Letrozole over Clomiphene citrate include:

•   High rate of mono-follicular development which theoretically will reduce the risk of multiple pregnancies.

•   No direct anti-estrogenic side effects on the endometrial thickness because of absence of peripheral estrogen receptor blockage.

•   Short half-life (48 hours versus two weeks for clomiphene citrate) which could predict a lower risk of teratogenicity.

•   Lower serum estradiol (E2) levels, this is a special advantage for women with breast cancer undergoing ovarian stimulation prior to gonadotoxic therapy (Al-Obaidi, et al., 2019).

•   Letrozole makes endometrium thicker than clomiphene citrate because it may be due to improve vascularization as reported by Doppler study done by (Baruah, et al., 2009).

•   Letrozole administration in the early part of menstrual cycle could release the pituitary hypothalamic axis from the estrogenic negative feedback as the effect of clomiphene citrate but without estrogen receptors down-regulation and the resulting increase in gonadotropin secretion might stimulate ovarian follicle development (Lidor, et al., 2000).

This study was a randomized controlled single blinded clinical trial. The objective of this study was to compare the efficacy of letrozole on ovulation induction to that of clomiphene citrate in women suffering polycystic ovary syndrome and the effect on the follicular maturation, endometrial thickness and pregnancy rate.

The current study was carried out at Ain-Shams University Maternity Hospital, infertility out-patient clinic during the period from November 2020 till April 2021.

The study included 80 infertile women at the age group of 18-35 years who diagnosed as having PCOS. The polycystic ovary syndrome was defined according to Modified Rotterdam Criteria (oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries according to pelvic ultrasound) other causes of infertility were excluded.

Women were randomly divided into two groups, Letrozole group (1) received 5mg/day dose for 5 days starting on day 3 till day 7 of the menstrual cycle (n=40) and clomiphene citrate group (2) received 100mg/day dose for 5 days starting from day 3 till day 7 of the menstrual cycle (n=40).

In this study, in Letrozole group, the range of age was 21 to 33 years and Mean±SD 27.33±2.78 was while in the Clomiphene citrate group, the range of age was 21 to 35 years and Mean±SD was 28.20±3.66. This is in agreement with (Chakravorty, et al., 2016) study that reported no statistically difference between both Letrozole group (Mean±SD was 27.3 ± 1.9) and Clomiphene citrate group (Mean±SD was 26.9 ± 2.1) in the mean of age.

In this study, in the Letrozole group, (82.5%) of women had primary infertility while in the Clomiphene citrate group was (77.5%). This result showed no significant difference with p value= 0.576 and agreed with (Hussain, et al., 2013) study that reported no statistically difference between both Letrozole group (76% had primary infertility) and Clomiphene citrate group (78.7% had primary infertility) with P value=0.660.

In this study, all women in both Letrozole and clomiphene citrate groups showed menstrual regularities, 6 women (15%) showed amenorrhea in Letrozole group and the rest of women 34 (85%) showed oligomenorrhea. In Clomiphene citrate group 9 women (22.5%) had amenorrhea and 31 women (77.5%) had oligomenorrhea.

In this study, the overall incidence of oligomenorrhea was 81.25% (65 out of 80 cases) and the incidence of hirsutism was 48.75% (39 out of 80 cases), which is in agreement with (Jungari M., 2020) that reported 83.3% had oligomenorrhea and hirsutism was 43.1%.

In this study, the mean value of FSH and LH in day 3 of menstrual cycle were about 6.78±1.09 mIU/mL and 14.90±1.57 mIU/mL in Letrozole group, respectively, while the mean value of FSH and LH in day 3 of the menstrual cycle were about 8.15±9.60 mIU/mL and 14.85±2.13 mIU/mL in Clomiphene citrate group, respectively. So, there were no significant differences in the mean FSH or LH values of women in both groups. This is agreed with (Al-Shoraky Mohamed, et al., 2020) which reported that circulating levels of LH are increased nearly 40% to 70% of women with clinical diagnosis of PCOS. In spite of increased LH is generally considered important pathophysiology of PCOS, LH/FSH ratio is not necessary for PCOS diagnosis due to the lack of agreement as regards to what constitutes an abnormal result in FSH/LH ratio as diagnostic criteria for PCOS (Lewis, 2001; Cho, et al., 2006).

In this study, ovulation rate and ovulation/cycle were significantly more frequent in the Letrozole group (ovuation rate was 82.5%, 33 women reached ovulation successfully and ovulation/cycle was 91%) than in Clomiphene citrate group (ovulation rate was 60%, 24 women reached ovulation successfully and ovulation/cyclw was 61%) within P value< 0.024 and <0.0001, respectively.

Also, in the Letrozole group, the number of women who received HCG in the first, second and third cycles were 36 (95%), 32 (97%) and 30 (97%), respectively while in Clomiphene citrate group were 24 (80%), 23 (82%) and 24 (86%), respectively.

In this study, in Letrozole group, the mean endometrial thickness on the day of hCG administration which measured by transvaginal ultrasound ranged from 6 to10 mm with a Mean±SD= 8.91±1.5 mm therefore the endometrium was of adequate thickness to allow implantation and in Clomiphene citrate group, the mean endometrial thickness ranged from 5 to 9 mm with Mean±SD= 7.54±0.9 mm (P value<0.0001). Also, in Letrozole group, the mean of endometrial thickness in first, second and third cycles were 8.5±0.5 , 8.7±1.4 and 8.6±0.7, respectively while in clomiphene citrate were 7.5±1.26, 7.6±1.02 and 7.6±0.6, respectively.

In this study, in the Letrozole group, the range of mid-luteal phase (21day) serum progesterone level was 6 to 16.4 ng/mL and Mean±SD was14.2±2.25 and in Clomiphene citrate was 5 to13.6 ng/mL and Mean±SD was 11.6±1.26 with P value<0.0001. Also, in Letrozole, the mean of mid-luteal phase serum progesterone level in the first, second and third cycles were 14.12±1.71, 13.3± 1.91 and 13.92± 2.7, respectively while in Clomiphene citrate were 11.27±1.6, 10.4 ± 1.06 and 11.03± 1.3, respectively.

In this study, in the Letrozole group, the range of estradiol serum level was 70 to 185 (pg/mL) and Mean±SD=156.6±17.9 and in Clomiphene citrate was 83 to 195 (pg/mL) and Mean±SD=178.1±24.7 with P value<0.001.Also, in Letrozole, the mean of estradiol serum level in the first, second and third cycles were 168.8± 21.3, 159.8±15.4 and 166.5±19.2, respectively, while in Clomiphene citrate were 189.3±29.2, 186.8±22.5 and 189.3± 29.2, respectively.

These findings showed that Clomiphene citrate had a significantly higher level of estradiol serum level than Letrozole group and in agreement with (Aletebi & Alaa, 2013) study which showed that the estradiol serum level was significantly higher in Clomiphene citrate group with Mean±SD=755±101 than Letrozole group with the Mean±SD=425.7±94 (P value= 0.0001)

In this study, pregnancy occurred in 20 out of 80 cases (25%). The number of pregnancies as evidenced by pregnancy test and intrauterine gestational sacs & % of pregnancy/ cycle were highly significant better in Letrozole Group (15 women became pregnant (37.5%) and 14% of pregnancy/cycle) than in Clomiphene Citrate Group (5 women became pregnant (12.5%) and 4% of pregnancy/cycle) with P value=0.01. Also, in Letrozole, the pregnancy rate in the first, second and third cycles were 10%, 11% and 22%, respectively, while in Clomiphene citrate were 3%, 3% and 8%, respectively.

This is in agreement with (Sharief &Nafee,2015) that found a pregnancy rate of 21.6% after receiving 2.5 mg Letrozole and 9.1% after receiving 100 mg Clomiphene citrate, which was statistically significantly different. Also in agreement with (Al-Shoraky Mohamed, et al., 2020) that reported

a higher pregnancy rate in Letrozole group (19 women became pregnant (38%)) than Clomiphene citrate group (8 women became pregnant (16%)). Also this study is agreed with (Sakar M., 2020) that reported 58 women (33.1%) became clinically pregnant in the Letrozole group which included 175 women compared with 31 pregnant women (20.9%) in the Clomiphene citrate group, which included 148 women and this was statistically significant (p=0.027) as pregnancy rate was better in Letrozole group than Clomiphene citrate group.

The result of pregnancy rate in this study is in contrast with (Nahid, 2012) study that included 100 infertile women with PCOS divided into Letrozole group (50 women received 2.5mg) and Clomiphene citrate (50 women received 100mg).That study showed no significant statistically difference in pregnancy rate between both Letrozole and Clomiphene citrate group. Also, it's in contrast to (Ershadi, 2017) that showed no significant difference between Letrozole group (50%) and Clomiphene citrate group (45%) with P value=0.65, although the pregnancy rate in Letrozole group was slightly higher than Clomiphene citrate. Also in (Akbari, et al., 2012) study, showed no significant statistically difference between Letrozole group (17 women (21.3 %)) and Clomiphene citrate (11 women (13.8%)) with P value= 0.146, although the pregnancy rate in Letrozole group was higher than Clomiphene citrate group.

CONCLUSION

Letrozole has efficacy as that of clomiphene citrate in induction of ovulation in polycystic ovary syndrome. Within 5mg daily dose of letrozole, women can achieve ovulation in about (82.5%) and pregnancy in about (37.5%).

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