Vol. 8. No. 3. 2019

Contents available at:
www.crdeepjournal.org

International Journal of Basic and Applied Sciences (ISSN: 2277-1921)

Full Length Research Paper

Clomiphene citrate versus Letrozole for Ovulation Induction in Patients with Polycystic Ovary Syndrome

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ARTICLE INFORMATION

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Article history:
Received: 06-03-2019
Revised: 09-03-2019
Accepted: 15-03-2019
Published: 16-03-2019

Key words:
Polycystic ovarian syndrome, clomiphene citrate, letrozole

ABSTRACT

PCOS has multiple reproductive, metabolic, and cardiovascular components, with health implications across a woman's life span. Approximately 75% of these women suffer from infertility due to anovulation. In women undergoing ovulation induction for the treatment of oligoanovulation, clomiphene citrate has long been the initial drug of choice for first-line therapy. Letrozole is an orally-active aromatase inhibitor, with good potential for ovulation induction. It has been in use for few years now. This present study aimed to compare the effect of Clomiphene Citrate and Letrozole in induction of ovulation in the treatment of infertile women with PCO. This prospective clinical trial was conducted at Al- Azhar university hospitals. The study was conduct on 100 women between 18 - 40 years old having PCOS with history of infertility. Patients are divided into two groups: Group I (Clomiphene Citrate group), Group II (Letrozole group). Each group involve 50 subjects. For Group I, women were received 50 mg of Clomiphene Citrate oral tablets twice daily from day 2 of the menses for 5 days and for up to three menstrual cycles, while in Group II, women were received 5 mg of Letrozole oral tablets daily from day 2 of menses for 5 days and the maximum daily dose of Letrozole 7.5 mg (three tablets), given for 5 days. Follicular monitoring was done by transvaginal sonography starting day 8 of menstrual cycle till a follicle attained 17-18 mm diameter. Letrozole showed to be effective in inducing ovulation than CC (84% vs 66%) and this difference is statistically significant. The mean endometrial thickness on the day of hCG administration (measured by transvaginal ultrasonography) was higher in Group (L) (8.71±2.13 mm) comparing with Group (C) (5.56 ± 1.61) thus the endometrium was of adequate thickness to allow implantation. The Ovulatory response was significantly better in Letrozole Group (L) compared to CC group at age of <30 years old, while the response decrease with advancement of the age >30 years denoting the age-related effect on female fertility. Pregnancy rate was significantly better in Letrozole than Clomiphene citrate group regardless the patient's age. Regarding to the early outcome of pregnancy by TVUS, induction with Letrozole results in 100% singleton pregnancy, while with using CC, two cases had twins' pregnancy & one case had ectopic pregnancy. In women with PCOS, induction of ovulation using Letrozole have a better ovulation rate with better follicular development and higher pregnancy rate that using CC beside less effect on the endometrial thickness and side effects.

Introduction

Polycystic ovarian syndrome (PCO) is one of the most common endocrinal disorder in female, and it is one of the leading causes of sub-infertility in female. About 5 - 10 % of females aged 18 - 44 years are affected by PCO [(1)]. Stein and Leventhal were the first who recognize the association between the presence of polycystic ovaries and signs of hirsutism, menstrual disturbances as amenorrhea and obesity [(2)]. According to Rotterdam Workshop Group in 2004,PCO women must have two out of following three criteria oligo-ovulation or anovulation, hyper- androgenism (clinical and /or biochemical), and polycystic ovaries on sonographic examination[(2)].

Infertility is one of the common problems that face the women with (PCOS) and the FSH and Clomiphene Citrate are the principle treatments used for anovulating women[(3)].Also lowering insulin levels by using insulin-sensitizing drugs such as biguanides and so may restore fertility. The laparoscopic ovarian surgery is used to induce ovulation in Clomiphene Citrate resistance women with anovulatory PCO. Other option for achieving pregnancy in women with PCOS is to use in

Vitro Fertilization (IVF)[4].Clomiphene Citrate is a non-steroidal selective estrogen receptor modulator (SERMs). The pharmacological goal of SERMs is to produce beneficial estrogenic action and antagonist activity in other tissues such as endometrium, where estrogenic actions (e.g., carcinogenesis) might be deleterious[5]. Letrozole is a member of the third-generation aromatase inhibitors (AIs) drugs, an oral non-steroidal agents which have been widely used in the treatment of postmenopausal women with early stage or advanced, hormone receptor positive breast cancer[6].

Aromatase converts androstenedione to estrone and testosterone to estradiol. Its activity can be demonstrated in several tissues, including the ovaries, brain, placenta, adipose tissue, muscle, liver, and breast and estrogen dependent breast cancer. This enzyme is mainly expressed in the ovaries of premenopausal women. And prevent the aromatase from producing estrogens by competitive binding to the heme of its cytochrome P450 unit[7]. Letrozole may be used for ovulation induction and hence may increase pregnancy rate in women with anovulatory PCOs and inadequate Clomiphene Citrate response and improving ovarian response to FSH in poor responders. Letrozole has less side effect than Clomiphene Citrate and gonadotropins such as multiple pregnancies and OHSS[8].

The aim of this study is to Compare the effect of Clomiphene Citrate and Letrozole in induction of ovulation and pregnancy rate in the treatment of infertile patients with PCOS.

Patients and methods

This is a prospective clinical trial will be conducted at Al-Azhar university hospitals. The study will conduct on 100 women between 18 - 40 years old; all of them had at least 2 out of 3 of Rotterdam criteria for diagnosis of PCO. Patients are divided into two groups: Group I (Clomiphene Citrate group), Group II (Letrozole group).

Group I (Clomiphene Citrate group):

This group will include 50 women receiving 50 mg of CC oral tablets (clomid; patheon France S.A) twice daily from day 2 of the menses for 5 days and for up to three menstrual cycles. The dose will increase in cases of non-response (progesterone level during the mid-luteal phase, <3 ng per milliliter) or poor ovulatory response. The maximum daily dose of Clomiphene Citrate 150 mg (three pills), given for 5 days

Group II (Letrozole group):

This group will include 50 women receiving 5 mg of Letrozole oral tablets (Femara; Novartis pharma AG,Basel, Swizerland) daily from day 2 of menses for 5 days and the maximum daily dose of Letrozole 7.5 mg (three pills), given for 5 days.

In women who were amenorrhoeic, withdrawal bleeding induced by using 10 mg of dehydrogesterone oral tablets daily for 10 days.

Inclusion criteria:

1- Age between 18- 40 years.
2- Diagnosed as PCO by U/S or laboratory.
3- Unable to achieve pregnancy in period of 12 months or more despite regular unprotected intercourse.
4- Had patent uterine cavity patent fallopian tubes proved by hysterosalpingography.
5- No male factor for infertility
6- No history of heart, liver or kidney diseases

Exclusion criteria:

1- Age below 18 or above 40 years.
2- Not diagnosed as PCO by U/S or laboratory.
3- Had closed fallopian tubes proved by hysterosalpingography.
4- Patient refusal.
5- Male factor of infertility.
6- Any diseases as heart, liver or kidney diseases.
7- History of recent administration of hormonal therapy.

Methods

All patients included in the study subjected to:

1- Full history taking including age, parity, last menstrual period, regulatory of the cycle and previous lab investigations for the patient and her husband.
2- General examination including blood pressure, pulse, temperature and BMI.
3- Abdominal examination including any surgical markings, palpable masses, hernia.
4- Local examination by sterile Cusco speculum.
5- Transabdominal U/S for congenital malformations of the uterus, for typical appearance of polycystic ovary, U/S for liver, spleen and kidney.
6- Hysterosalpingography for Congenital malformations of the uterus, patent uterine cavity, patent tubes, and masses or fibroma.
7- Laboratory investigations:
   - Routine lab investigations (e.g.; CBC, urine analysis, random blood sugar, creatinine... .etc.).
   - Hormonal study on day 2 of the menstrual cycle (FSH, LH, LH: FSH ratio, total testosterone, prolactin, TSH, estradiol).

All patients in two groups subjected to:

- ❖Measurement the number and size of the growing and mature follicles by transvaginal U/S.
- ❖Good response will achieve when at least one mature follicle becomes 17mm in diameter and the patients advised to have timed intercourse every other day, starting at least 24 hours after the leading follicular diameter reached 17mm in size and follow up pregnancy rate outcome.

Results

One-hundred patients were participated in this study, were the randomly allocated into 2 groups; Group (L)(Letrozole group) and Group (C)(Clomiphene citrate group) each group involve 50 patients. The mean age of Group (L) was a 25.26±3.8 year while for Group (C) was 24.58±3.296 years. Regarding the age group for the studied population, half of cases were in the age group 20-24 years. Most of subjects had a BMI of 18-25 [46 %for Group (L)and 42 %of Group (C)].The average body weight was 69.9±6.95 fir Group (L) and 70.160±3.296 for Group (C). Also BMI for each group was quiet similar 25.23±2.39 vs 25.454±2.6725. On the other hand most of cases had a history of infertility of 1.5-3 year. All values had no statistical difference regarding both groups as presented in table 1. On the basis of Rotterdam criteria for diagnosis of PCOS, 4 main items were taken in consideration for assessment, occurrence of Oligomenorrhea and Hirsutism, presentence of obesity, beside US criteria of PCOS. The

percentage of cases having each items for Group (L)or C was 70 % vs 64 %, 62 % for both, 54% vs 42% and 82% vs80% respectively. No statistical difference was observed between both groups regarding each previously mentioned item (table 2). Regarding the hormonal profile for both groups, level of FHS was 3.921-8.63mIU/mLfor Group (L) and 3.79-9.12 mIU/mL for Group (C). The level of LH, was 8.76-18.51 mIU/mL for Group (L) and 9.43-19.30 mIU/mL for Group (C). There was no statistically significant difference in basal FSH & LH, or ratio of LH to FSH among women of Group (L) and C as Shown in table 3. On the day of hCG triggering, ultrasonographic assessment for the size of the mature follicle & the endometrial thickness were done. The mean Follicles size for Group (L) was 19.83±2.72mm which was higher than Group (C) 17±1.44mm. The Endometrial Thickness was also higher in Group (L) comparing with Group (C)(8.71±2.13 vs 4.17±2.45 respectively) as showed in table 4.

We observed that the Ovulatory response was significantly better in Letrozole group compared to CC group at age of <30 years old, while the response decrease with advancement of the age >30 years. Women having BMI < 30 kg/m^2 showed better response to Letrozole group compared to CC group, with higher response with BMI 18-25 kg/m^2. Women with history of infertility <3 years showed an ovulatory response significantly better in Letrozole group compared to CC group with no significant difference in infertile cases (> 3 y) as presented in table 5. On the day of hCG administration, we observed that the Endometrial thickness was significantly better in Letrozole groups compared to CC group in women aged < 30 years. Also the Endometrial thickness on the day of hCG administration was significantly better in Letrozole than CC groups in women with BMI < 30. Regarding the duration of infertility, women with history of infertility <3 years showed a significantly better Endometrial thickness on the day of hCG administration in Letrozole than CC group (table 6).

The time needed for reaching the follicular maturity and to give hCG injection was shorter in the Group (L)(13.35±1.87 days) comparing with Group (C)(15.78±1.65 days). However, this difference was found to be statistically not significant (P=0.12) (table 7). The level of mid luteal phase serum progesterone was higher in Group (L) (17.3±1.88 ng/ml) while it was 12.54±1.47 ng/ml in Group (C) and this difference is statistically significant(P=0.001) as in table 8.

Letrozole showed to be effective in inducing ovulation than CC (84% vs 66%) and this difference is statistically significant. Regarding the number of recorded pregnancy in each group there was highly significant number of pregnancies as evidenced by positive pregnancy test and intrauterine gestational sacs in Group (L) than Group (C)(76 % versus 48 %respectively).The difference between Group (L) & C was statistically significant (P=0.02). The percentage of pregnancy per cycle was higher in Group (L) than Group (C) (17.8 % versus 11 %) the difference was also statistically significant (P=0.01) (table 9).

Pregnancy rate was significantly better in Letrozole than Clomiphene citrate group regardless the patient's age. Pregnancy rate was significantly better in Letrozole than CC groups in patients with BMI < 30 kg/m^2, while women with BMI > 30 kg/m^2 showed no significant difference in pregnancy rate. Moreover, Pregnancy rate was significantly better in Letrozole comparing to CC group regarding the duration of infertility < 5 years, while women with history of infertility > 5 years showed no significant difference in pregnancy rate for either letrozole nor CC (table 10).

Regarding to the early outcome of pregnancy by TVUS, induction with Letrozole results in 100% singleton pregnancy, while with using CC, two cases had twins' pregnancy & one case had ectopic pregnancy (figure 1). Regarding the side effects of Letrozole, the most frequent side effect was headache (5 cases) followed by hot flushes (4 cases). While in CC group, 4 cases suffered from ovarian hyper-stimulation & similar had headache. Other frequent side effects were nausea and fatigue (figure 2).

Table (1): Epidemiological data of study population.

		Group (L) Letrozole (n=50)				Group (C) Clomiphene citrate (n=50)				t-test	P value
		n	%	Range	Mean ± SD	N	%	Range	Mean ± SD		
Age (years)	20-24y	13	26 %	20-36	25.26±3.8	12	24 %	20-36	24.58±3.296	0.942	0.351
	>24-30	25	50 %			26	52 %				
	>30-35	10	20 %			9	18 %				
	>35	2	4 %			3	6 %				
Weight (kg)				56.5-83.5	69.9±6.95			56.5-83.5	70.160±3.296	-0.247	0.806
Height (meter)				1.58-1.73	1.66±0.03			1.58-1.73	1.6614±0.03270	0.387	0.700
BMI kg/m2	18-25	23	46 %	20.8-32.6	25.23±2.39	21	42 %	20.5-33.4	25.454±2.6725	-0.498	0.621
	>25-30	18	36 %			20	40 %				
	≥ 30-35	9	18 %			9	18 %				
Period of Infertility	1.5-3	31	62	1.50-10	2.91±1.6	28	56	1.5-5	2.630+0.9466	1.206	0.234

(years)			%		%		
	>3-5	16	32	18	36		
			%		%		
	>5	3	6 %	4	8 %		
Type of infertility	1ry	35	70%	36	72%	0.162	0.569
	2nry	15	30%	14	28%		

Table (2): Percentage of clinical signs of PCOS among studied groups

		Group (L) (Letrozole) "n=50"		Group (C)(cc) "n=50"		t	*P*
		N	%	n	%		
Menstruation	Normal	15	30	18	36	0.771	0.444
	Oligomenorrhea	35	70	32	64		
Hirsutism	Yes	31	62	31	62	0.00	1.00
	No	19	38	19	38		
Obesity (BMI)	> 25	27	54	29	42	-0.23	0.821
	<25	23	46	21	58		
US Criteria	Present	41	82	40	80	-.275	0.785
	Absent	9	18	10	20		

Table (3): Biochemical data of study population

	Group (L) Letrozole		Group (C) Clomiphene citrate (n=40)		t-test	P value
	Range	Mean ± SD	Range	Mean ± SD		
FSH (mIU/mL)	3.921-8.63	6.67±1.85	3.79-9.12	6.87±1.78	0.897	0.361
LH (mIU/mL)	8.76-18.51	12.82±6.42	8.52-19.32	13.45±3.57	1.461	0.149
LH/FSH	1.86-3.54	2.31±0.23	0.70-5.82	2.63±1.31	0.451	0.576

Table (4): the follicles size and endometrial thickness in each group on day of hCG administration

		Group (L)(letrozole) "n=50"	**Group(C)(CC) "n=50"**	***t***	***P***
Follicles size inmm	Range	17-23.0	16-20	-0.652	0.001
	Mean ± S.D	19.83±2.72	17±1.44		
Endometrial Thickness (mm	Range	5.0-13.0	3.0 – 8.0	-.845	0.000
	Mean ± S.D	8.71±2.13	4.17±2.45		

Table (5): Effect of age, BMI and duration of infertility on number of follicles ≥18 mm at day of hCG administration

	Group (L)		**Group (C)**		P value
	Range	Mean ± SD	Range	Mean ± SD	
Age (years)					
20-24	1-5	2.63±1.26	1-4	1.8±0.87	0.01*
> 24-30	1-5	2.27±1.43	1-3	1.71±0.81	0.01*
> 30-35	1-3	1.48±0.83	1-2	1.48±0.41	0.05
> 35	1-3	1.23±0.65	1-2	1.1±0.23	0.06
BMI kg/m2					
18-25	1-6	2.96±1.78	1-4	1.87±0.88	0.005*
> 25-30	1-5	2.88±1.67	1-3	1.96±0.79	0.03*
> 30-36	1-3	1.67±0.79	1-2	1.42±0.45	0.08
Duration of infertility (years)					
1.5-3	1-5	2.56±1.42	1-3	1.72±0.46	0.00*
> 3-5	1-5	2.34±1.23	1-2	1.64±0.84	0.05
> 5	1-3	1.42±0.25	1-2	1.47±0.51	0.12

* Statistically significant P<0.05

Table (6): Effect of age, BMI and duration of infertility on endometrial thickness (mm) on the day of hCG administration

	Group (L)		Group (C)		P value
	Range	Mean± SD	Range	Mean± SD	
Age (years)					
18-24	8-14	11.31±2.13	5-9	7.37±1.49	0.001*
> 24-30	6-14	8.92±2.66	4-10	6.16±1.72	0.005*
> 30-35	6-12	7.76±1.75	4-9	5.37±1.49	0.05
BMI					
18-25	8-14	10.23±2.64	5-9	6.75±1.52	0.001*
> 25-30	8-14	10.69±1.74	4-10	7.62±0.37	0.005*
> 30-36	7-12	8.75±1.67	4-9	6.36±1.32	0.05
Duration of infertility (years)					
1.5-3	8-14	10.94±2.87	5-9	7.75±1.64	0.01*
> 3-5	7-14	8.42±2.43	4-9	6.68±1.75	0.01*
> 5	7-10	8.24±1.74	4-9	6.43±0.73	0.05

* Statistically significant P<0.05

Table (7): The mean duration (days) till hCG injection in Letrozole group and Clomiphene citrate group

		Group (L) (Letrozole) "n=30	Group (C) (CC) "n=30"	P
Day of cycle on hCG Injection	Range	10.0 – 15.0	12.0-18.0	0.12
	Mean ± S.D	13.35±1.87	15.78±1.65	

Table (8): Mid luteal phase serum progesterone in Letozole group and Clomiphene citrate group

	Group (L) Letrozole		Group (C) Clomiphene citrate (n=40)		t	P
	Range	Mean± SD	Range	Mean± SD		
Mid luteal phase serum progesterone (ng/ml)	16-19	17.3±1.88	9.2-15.3	12.54±1.47	2.68	0.001

Table (9): Ovulatory response and Pregnancy rate

	Group (L)Letrozole (n = 50)		Group (C)CC (n = 50)		X2	P
	n.	**%**	**n.**	**%**		
Ovulation	42	84	33	66	3.541	0.01*
Pregnancy	38	76	24	48	5.84	0.02*
Total number of cycles	213		219		6.859	0.952
Percentage of pregnancy/cycle		17.8		11	3.74	0.01*

* Statistically significant P<0.05

Table (10): Effect of age, BMI and Duration of infertility on pregnancy rate

	Group (L) n=38		**Group (C) n=24**		**P value**
	n	%	N	%	
Age (years)					
a) 20-24	22	57.89	17	70.83	0.05 *
b) > 24-30	11	28.94	5	20.86	0.01 *
c) > 30-35	5	13.15	2	8.33	0.02 *
BMI (kg/m2)					
a) 18-25	20	52.63%	16	66.6%	0.01*
b) > 25-30	12	31.57%	5	20.83%	0.00*
c) > 30-36	6	15.78%	3	12.5%	> 0.05
Duration of infertility (years)					
a) 1.5-3	29	76.13	18	75	0.01*
b) > 3-5	7	18.42	5	20.83	0.04 *
c) > 5	2	5.26	1	4.16	0.21

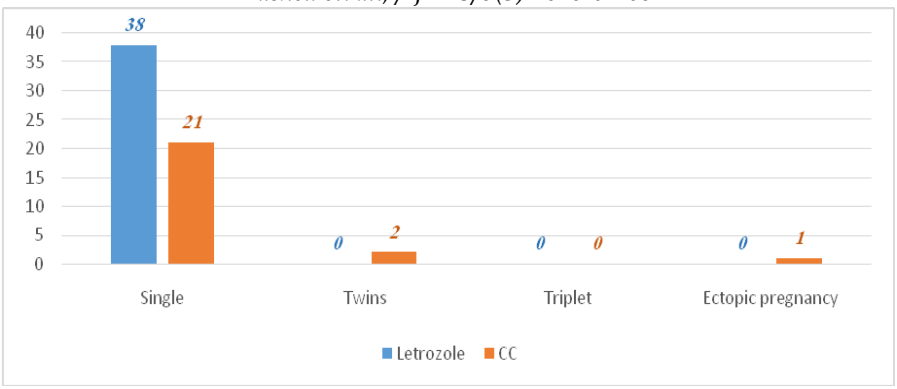

Fig (1): Early outcome of pregnancy by TVUS

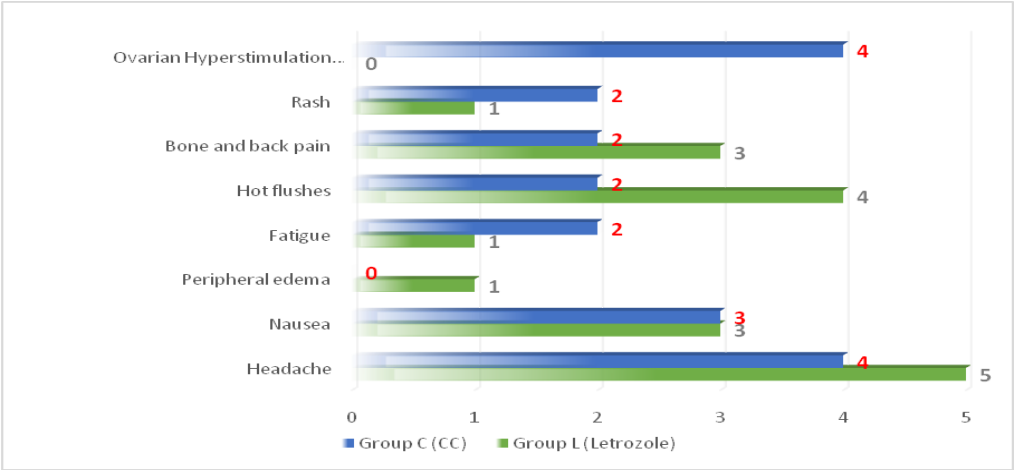

Fig (2): Side effects to letrozole and CC between women of Group L and C

Discussion

PCOS is a common endocrinologic disorder in women characterized by chronic anovulation, hyperandrogenemia, and infertility and associated with insulin resistance and obesity. Clomiphene citrate (CC) is routinely used by many gynecologists to treat infertile anovulatory PCOS because of the low costs and the simplicity of administration and management. Letrozole, an aromatase inhibitor, was reported to be effective in inducing ovulation with better pregnancy rate, endometrial development, and favorable cervical mucus as compared with CC[9].

This present study aimed to compare the effect of Clomiphene Citrate and Letrozole in induction of ovulation in the treatment of infertile women with PCO. This is a prospective clinical trial was conducted at Al- Azhar university hospitals. The study was conduct on 100 women between 18-40 years old having PCOS with history of infertility. Patients are divided into two groups: Group I (Clomiphene Citrate group), Group II (Letrozole group). Each group involve 50 cases.

Regarding the basal demographic data of the study population, about half of cases were in the age group 20-24 years. The mean age of Group (L) was 25.26±3.8 while for Group (C) was 24.58±3.296. Most of cases had a BMI of 18-25 (46 % for Group (L) and 42 % of Group (C)).The average body weight was 69.9±6.95 Kg for Group (L) and 70.160±3.296 kg for Group (C). Also BMI for each group was quiet similar 25.23±2.39 vs 25.454±2.6725. On the other hand most of cases had a history of infertility of 1.5-3 year and about 70% Group (C) of and 72% Group (L) had 1ry infertility. No statistical difference between both groups as all subjects were allocated randomly in each group.

Sixty-seven % of women had Oligomenorrhea (70% of Group (L) and 64 % of Group (C) , 62 % of women had Hirsutism , 65 % of women had BMI > 25 kg/m^2, and 81% had US criteria of PCOS (82% of Group (L) and 80% of Group (C). No statistical difference was observed between both groups regarding each previously mentioned items.

Regarding the hormonal profile for both groups, level of FHS was 3.92-8.63 mIU/mL for Group (L) and 3.79-9.12 mIU/mL for Group (C). The level of LH, was 8.76-18.51 mIU/mL for Group (L) and 8.52-19.32 mIU/mL for Group (C). There was no statistically significant difference in basal FSH & LH, or ratio of LH to FSH among women of Group (L) and (C).

For Group I, women were received 50 mg of Clomiphene Citrate oral tablets (clomid; patheon France S.A) twice daily from day 2 of the menses for 5 days and for up to three menstrual cycles. The dose had increased in cases of nonresponse (progesterone level during the mid-luteal phase, <3 ng per milliliter) or poor ovulatory response. The maximum daily dose of Clomiphene Citrate is 150 mg given for 5 days. While in Group II, women were received 5 mg of Letrozole oral tablets (Femara; Novartis pharma AG,Basel, Swizerland) daily from day 2 of menses for 5 days and the maximum daily dose of letrozole 7.5 mg (three tablets), given for 5 days.

Follicular monitoring was done by transvaginal sonography starting day 8 of menstrual cycle till a follicle attained 17-18

mm diameter. A single injection of HCG 10,000 IU was given if at least one follicle attained 17-18 mm. The time needed for reaching the follicular maturity assessed by ultrasonography and when to give hCG injection was shorter in the Group (L) (13.35±1.87 days) comparing with Group (C) (15.78±1.65 days). However, this difference was found to be statistically not significant (P=0.12).

On the day of hCG triggering, ultrasonographic assessment for the size of the mature follicle & the endometrial thickness were done. The mean Follicles size for Group (L) was 19.83±2.72 mm which was higher than Group (C) 17±1.44 mm. Mosammat et al.[10] reported that average follicular diameter by day 16 of the cycle was 18.84 ± 3.17mm (range 14-23mm) in the letrozole group and 16.19 ± 3.47mm (range 12-22mm) in the Clomiphene citrate group. There is a significant difference infollicular development in both the groups ($p < 0.05$).

In our study letrozole showed to be effective in inducing ovulation than CC (84% vs 66%) and this difference is statistically significant (P=0.001). Several studied reported same finding that Ovulation rate was better with using Letrozole for induction of ovulation that CC as reported in the study of Badawy et al.[11] [61.5% vs 70.9%], Begum et al.[12] [62.5% vs37.5%], Dehbashi et al.[13] [60% vs 32%], Kar[14] (73.08% vs 60.78%) and M. Zeinalzadeh et al.[15] [86 % vs 72%]. Badawg et al.[16] reported that CC was superior than Letrozole in ovulation rate [CC 70.9%, Let 67.5%]. Ganesh et al.[17] found no statistically significant difference between CC and Letrozole in ovulation rate. However, Letrozole has been shown to have good ovulation rate in CC-resistant PCOS women. The mean endometrial thickness on the day of hCG administration (measured by transvaginal ultrasonography) was higher in Group (L) comparing with Group (C) thus the endometrium was of adequate thickness to allow implantation. In Group (L) endometrial thickness ranged from 5 to 13 with a mean ± SD of 8.71±2.13 mm while in group C, the endometrial thickness ranged from 3 to 8 with a mean ± SD of 4.17 ± 2.45 mm (P=0.00).

Begum et al.[12] reported that using Letrozole is associated with a thicker endometrium compared with CC. However, Badawg et al.[16], in their study of 438 patients with 1063 cycles, one of the largest studies comparing CC and Letrozole, reported statistically significantly higher endometrial thickness in CC group (9.2 ± 0.7) vs. Letrozole (8.1 ± 0.2, P = 0.021).

In a study by Banerjee et al.[18], 147 Indian women with PCOS were compared between Letrozole (2.5 mg) vs. clomiphene (100 mg). Mean endometrial development was 8.72 ± 11.41 mm in Letrozole and 8.78 ± 1.16 mm in CC group (P = 0.004).

Increased endometrium thickness may attributed to improved vascularization as reported by a recent Doppler study. One of the main drawbacks of clomiphene citrate is that the Anti-estrogenic effect of CC leads to prolonged depletion of estrogens receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus, which results in thinning of the later. As a result, it may decrease the implantation events. Letrozole has the potential to enhance FSH release, not by the inhibiting estradiol-receptor interaction, but rather by inhibition of estradiol synthesis, so it has no adverse effect on endometrium and cervical mucus.

We also observed that the Ovulatory response was significantly better in Letrozole Group (L) compared to CC group at age of <30 years old, while the response decrease with advancement of the age >30 years. The age-related effect on female fertility has also been shown in numerous reports on the results of IVF treatment in infertile couples. It was observed that the probability of live birth obtained through IVF treatment clearly decreases after the age of 35 and the same has been shown to be true for the implantation rate per embryo[19]. Women having BMI < 30 kg/m^2 showed better response to Letrozole Group (L) compared to CC group, with higher response with BMI 18-25 kg/m^2. Women with history of infertility < 3 years showed an ovulatory response significantly better in Letrozole Group (L) compared to CC group with no significant difference in infertile cases (> 3 y).

Letrozole resulted in mono-folliculogenesis in 79.49% of cases, which is optimal for ovulation induction in PCOS women. However, where multiple follicular development was needed, Letrozole may be inadequate[20].On the day of hCG administration, we observed that the Endometrial thickness was significantly better in Letrozole groups compared to CC group in women aged < 30 years (For age group 18-24: 11.31±2.13 vs 7.37±1.49 & for age group > 24-30: 8.92±2.66 vs 6.16±1.72). Also the Endometrial thickness on the day of hCG administration was significantly better in Letrozole than CC groups in women with BMI < 30 (For BMI=18-25: 10.23±2.64 vs 6.75±1.52, P=0.00 & for BMI > 25-30: 10.69±1.74 vs 7.62±0.37, P=0.005). Regarding the duration of infertility, women with history of infertility <3 years showed a significantly better Endometrial thickness on the day of hCG administration in Letrozole than CC group (P=0.01).

The level of mid luteal phase serum progesterone was higher in Group (L) (17.3±1.88, range: 16-19) while it was 12.54±1.47 (range: 9.2-15.3) in Group (C) and this difference is statistically significant (P=0.001). Regarding the number of recorded pregnancy in each group there was highly significant number of pregnancies as evidenced by positive pregnancy test and intrauterine gestational sacs in Group (L) than Group (C) (76 % versus 48 % respectively). The difference between Group (L) & C was statistically significant (P=0.02). The percentage of pregnancy per cycle was higher in Group (L) than Group (C) (17.8 % versus 11 %) the difference was also statistically significant (P=0.01). Although 60% to 85% of patients will ovulate on CC, only about one half will conceive. Approximately 50% of conceptions will occur on 50 mg, with another 20% to 25% and 10% occurring on 100 mg and 150 mg, respectively [21].

Pregnancy rate per cycle was astonishingly high with Letrozole in the study of Kar[20] (21.56%) comparing with the results of Badawy et al.[11] who reported that pregnancy rate was slightly better pregnancy rate in CC group (17.9%) than Letrozole (15.1%) group). Zeinalzadeh et al.[15] reported slightly better pregnancy rates with Letrozole; however, no statistically significant difference between the two groups.

This observation may be as results of the pharmacodynamics of letrozole that ensures improved endometrial thickness, cervical mucus, monofollicular, and better folliculogenesis. Therefore, these factors may lead to higher pregnancy rates and greater likelihood of singleton pregnancy[22]. Kar[20] concluded that letrozole has excellent pregnancy rates compared to clomiphene citrate (Let 21.56%, CC 7.84%, P=0.0125) and

Letrozole should be considered at par with clomiphene citrate as first line drug for ovulation induction in infertile PCOS women.

Pregnancy rate was significantly better in Letrozole than Clomiphene citrate group regardless the patient's age. Pregnancy rate was significantly better in Letrozole than CC groups in patients with BMI < 30 kg/m^2, while women with BMI > 30 kg/m^2 showed no significant difference in pregnancy rate. Moreover, Pregnancy rate was significantly better in Letrozole comparing to CC group regarding the duration of infertility < 5 years, while women with history of infertility > 5 years showed no significant difference in pregnancy rate for either letrozole nor CC. Regarding to the early outcome of pregnancy by TVUS, induction with Letrozole results in 100% singleton pregnancy, while with using CC, two cases had twins' pregnancy & one case had ectopic pregnancy.

Conclusion

In women with PCOS, induction of ovulation using Letrozole have a better ovulation rate with better follicular development and higher pregnancy rate that using CC beside less effect on the endometrial thickness and side effects.

References

1- Trivax B, Azziz R. Diagnosis of polycystic ovary syndrome, Clin. Obst. Gynecol 2007; 50 (1): 168-177.

2- Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Leppert PC, Myers ER. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome, N. Engl. J. Med 2007; 256 (6): 551-566.

3- Stadtmauer LA, Wong BC, Oehninger S. Should patients with polycystic ovary syndrome be treated with metformin? Benefits of insulin sensitizing drugs in polycystic ovary syndrome-beyond induction. Hum Reprod. 2002; 17(12):3016-26.

4- Hendriks J.C, Ket JC, Hompes PG, Homburg R, Lambalk CB. Why does ovarian surgery in PCOS help? Insight into the endocrine implications of ovarian surgery for ovulation induction in polycystic ovary syndrome. Hum Reprod Update. 2007; 13(3):249-64.

5- David S. Loose, George M. Stancel. Estrogen and Progestins (11th ed.)Laurence L. Brunton, John S. Lazo, Keith L. Parker (Eds.), Goodman and Gilman's. The Pharmacological Basis of Therapeutics, vol. 57, McGraw-Hill Companies Inc., USA 2006; 1541-1571

6- Baruce A, Chabner, Phlip C. Amrein, Brain J. Druker, M. Dror and Michaelson. The pharmacological Basis of therapeutics, 11th ed., Vol 51, McGraw-Hill Companies Inc 2006, 1541-1571.

7- Haynes, M. Dowsett, W.R. Miller, J.M. Dixon and Bhatngar A.S. The pharmacology of Letrozole, J. Steroid, Mol 2003; 87(1): 35-45.

8- 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(2): 305–309.

9- Kucuk M, Kilic-Okman T. Hormone profiles and clinical outcome after laparoscopic ovarian drilling in women with polycystic ovary syndrome. Med Sci Monit 2005; 11: CR29-34.

10- Mosammat, R.; Jannatul, F.; Anowar, B. and Ehsan Q. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Fertil Steril 2009; 92(3): 853-857.

11- Badawy A, Abdel Aal I, Abulatta M, Caballero AE. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial, Fertil Steril 2009; 92(3):849-52.

12- Begum MR, Khanam NN, Quadir E, Ferdous J, Begum MS, Khan F, Begum A. Prevention of gestational diabetes mellitus by continuing metformin therapy throughout pregnancy in women with polycystic ovary syndrome. J Obstet Gynaecol Res 2009; 35(2): 282-6.

13- Dehbashi S, DehbashiS, Kazerooni T, Robati M, Alborzi S, Parsanezhad ME, Shadman A. Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome, Iran J Med Sci 2009; 34(1): 23-28.

14- Kar S. Current evidence supporting "letrozole" for ovulation induction. Journal of Human Reproductive Sciences 2013; 6(2):93-98

15- Zeinalzadeh M, Basirat Z, Esmalpour M. Efficacy of letrozole in ovulation indication compared to that of clomiphene citrate in patients with polycystic ovarian syndrome. J Reprod Med. 2010; 55:36–40

16- Badawg A, Aal IA, Abulalta M. Climiphene Citrate or Letrozole for ovulation induction in women with polycystic ovarian syndrome: A prospective randomized trial. Fertil Steril 2009; 92: 849–52.

17- Ganesh A, Goswami SK, Chattopadhyay R, Choudhury K, Chakravarty BN. Comparison of letroz with continuous gonadotropins and clomiphene gonadotropin combination for ovulation induction. In 1387 PCOS women after clomiphene citrate failure: A randomized prospective clinical trial. J Assist Reprod Genet. 2009; 26: 19–24

18- Banerjee Ray P, Ray A, Chakroborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Arch Gynecol Obstet 2012; 285: 873–7.

19- Van Kooij RJ, Looman CW, Habbema JD, Dorland M and te Velde ER. Age-dependent decrease in embryo implantation rate after in vitro fertilization. Fertility and Sterility 1996; 66: 769–775.

20- 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): 262–265.

21- Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility, 7th ed. Pennsylvania: Lippincott Williams & Wilkins, 2005.

22- Legro RS, Kunselman AR, Brzyski RG, Casson PR, Diamond MP, Schlaff WD, Christman GM, Coutifaris C, Taylor HS, Eisenberg E, Santoro N, Zhang H. The Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial: rationale and design of a double-blind randomized trial of clomiphene citrate and letrozole for the treatment of infertility in women with polycystic ovary syndrome. Contemp Clin Trials 2012; 33(3): 470-81.