Journal of Medicine in Scientific Research

Volume 3 | Issue 4 Article 6

Subject Area:

Comparison between short and long letrozole therapy for ovulation induction in clomiphene.resistant women with polycystic ovarian syndrome

Mohamed A. El-Naggar
Banha Teaching Hospital, elnaggar662003@yahoo.com

Recommended Citation

El-Naggar, Mohamed A. (2020) "Comparison between short and long letrozole therapy for ovulation induction in clomiphene.resistant women with polycystic ovarian syndrome," *Journal of Medicine in Scientific Research*: Vol. 3: Iss. 4, Article 6.
DOI: https://doi.org/10.4103/JMISR.JMISR_43_20

Original Article

Comparison between short and long letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome

Mohamed A. El-Naggar
Department of Obstetrics and Gynecology, Banha Teaching Hospital, Met-Ghamr City, Eldaqahlia Governorate, Egypt

Abstract

Objective
The aim of this study is to compare the effect of the short and long letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome.

Design
This was a prospective study.

Patients and methods
Sixty infertile women were selected from the patients attending the outpatient clinic of Benha Teaching Hospital. All patients were diagnosed as having anovulation due to polycystic ovary syndrome.

Intervention
Patients were randomly allocated to treatment with either long letrozole therapy (n=30; three cycles) or short letrozole therapy (n=30; three cycles).

Main outcome measure
Number of growing, mature follicles and the occurrence of pregnancy.

Results
The number of ovulating patients was greater in the long letrozole group (73.3 vs. 56.7%) but without statistical differences. The total number of follicles during stimulation was greater in the long letrozole group. The number of follicles more than or equal to 18 mm was significantly greater in the long letrozole group. Pregnancy occurred in four (13.3%) in the short group and seven (23.3%) in the long letrozole group, and the difference was statistically insignificant.

Conclusion
The long letrozole protocol (10 days) can produce more mature follicles and subsequently more pregnancies than the short letrozole therapy (5 days).

Keywords: Clomiphene resistance, extended letrozole, ovulation induction, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by changes in hormonal levels. It is associated with increased prevalence of serious clinical problems including insulin resistance, hypertension, obesity, diabetes mellitus, dyslipidemia, depression, anxiety, cardiovascular

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/JMISR.JMISR_43_20

Correspondence to: Mohamed A. El-Naggar, MD, Department of Obstetrics and Gynecology, Banha Teaching Hospital, Met-Ghamr City, Eldaqahlia Governorate, Egypt.
E-mail: elnaggar662003@yahoo.com

Submitted: 26-Mar-2020 **Revised:** 26-May-2020. **Accepted:** 18-Jun-2020 **Published:** 23-Dec-2020

How to cite this article: El-Naggar MA. Comparison between short and long letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome. J Med Sci Res 2020;3:279-85.

risk, and reproductive implications that affect many women of reproductive age [1,2]. The most common reproductive symptoms of PCOS are high production of male hormones, menstrual irregularity, anovulatory infertility, and pregnancy complications [3,4].

High levels of insulin stimulate the ovaries to increase androgenic secretion and have inhibitory effects on the hepatic production of sex-hormone-binding globulin. Thus, insulin resistance can also affect ovulation and consequently increase the risk of infertility [5,6].

The diagnosis of PCOS can be made based on the 2003 Rotterdam criteria, the features of which are oligo-ovulation and/or anovulation, hyperandrogenism diagnosed either clinically (excessive hair growth, hirsutism) or biochemically (raised serum testosterone levels), and ovaries that appear to be polycystic on vaginal sonogram defined by the presence of 12 or more antral follicles in an ovary or an ovarian volume of more than 10 ml. Antral follicles are defined as measuring between 2 and 9 mm in diameter [7].

Clomiphene citrate is one of the selective estrogen receptor modulators that interferes with the negative feedback of the endogenous estradiol on the pituitary gland and the hypothalamus, leading to increased follicle-stimulating hormone (FSH) secretion and can be used for induction of ovulation in infertile women with PCOS [8].

Aromatase inhibitors are a newer class of drugs that were introduced for ovulation induction in 2001 with good pregnancy rate and lower incidence of multiple pregnancies [9]. Aromatase inhibitors are an alternative treatment to clomiphene citrate in ovulation induction, especially in patients with PCOS [10]. Aromatase inhibitors inhibit the aromatase enzyme by inhibition of aromatization of androgens to estrogens that in turn releases the hypothalamic–pituitary axis from negative feedback of estrogen [11]. Aromatase inhibitors are like clomiphene citrate administered orally, but due to their short half-life elimination time of 48 h, there are fewer adverse effects on estrogen target tissues such as the endometrium and the cervix compared with clomiphene citrate [12].

Aim

This study aims to compare the effect of the short and long letrozole therapy for ovulation induction in clomiphene-resistant women with PCOS.

Patients and methods

Patients

This randomized study was done with 60 infertile women in the infertility clinic of Benha Teaching Hospital during the period since October 2018 to September 2019). Sixty infertile women were selected from the patients attending the outpatient clinic of Benha Teaching Hospital and written consent was obtained from patients. All patients were diagnosed as having anovulation due to PCOS. Inclusion criteria were age: between 18 and 35 years, the period of infertility more than or equal to 2 years and all patients suffered from primary infertility, diagnosis of PCOS according to the Rotterdam criteria with at least two of the following three criteria having been met [13]: (a) oligo-ovulation and/or an ovulation. (b) Clinical and/or biochemical signs of hyperandrogenism. Clinical hyperandrogenism includes hirsutism, acne, or androgenic alopecia; biochemical hyperandrogenism (or hyperandrogenemia) includes raised level of circulating androgens (testosterone, androstenedione, and DHEA-S). (c) Polycystic ovaries on ultrasound (defined as the presence of 12 or more follicles in either ovary measuring 2–9 mm in diameter, and/or increased ovarian volume greater than 10 ml). Two patent fallopian tubes and a normal uterine cavity had to be documented by a recent (within 6 months) hysterosalpingography and recent (within 3 months) semen analysis of the husband with normal semen parameters according to WHO criteria (2005) had to be documented: volume more than or equal to 2 ml, sperm concentration more than or equal to 20 million/ml, motility more than or equal to 50% in the first hour, morphology more than or equal to 30% normal forms , and patients with PCOS who had failed to ovulate or become pregnant after 4–6 months of 150 mg clomiphene citrate. Exclusion criteria were a history of pelvic surgery and women with infertility factors other than anovulation. All participating patients had full history taking, complete general, abdominal, and local examination and investigations: fasting blood sugar (FBS) level less than 100 mg/dl (5.6 mmol/l) is normal [14], fasting insulin: normal less than 25 mIU/l, androgens [15], normal: 15–70 ng/dl, gonadotropins [16] with FSH (follicular third day) being normal (3.5–12.5), and luteinizing hormone (LH) (follicular third day) being normal (l2.4–12.6).

Methods

This study comprised 60 clomiphene-resistant women with PCOS among those attending the gynecology outpatient clinic in Benha Teaching Hospital. The diagnosis of PCOS can be made based on the ‘Rotterdam criteria’ 2003. By clomiphene resistance in this study, we meant the failure of ovulation after 150 mg clomiphene citrate for 5 days for 4–6 months.

Patients had randomly allocated using a computer-generated random table into two treatment groups: short letrozole group (30 patients) and long letrozole group (30 patients).

Patients in the short letrozole group had taken 5 mg of letrozole daily for 5 days starting day 1 of spontaneous or progesterone inducing menstrual bleeding using norethisterone acetate, which will be prescribed 10 mg/day for 5 days to induce withdrawal bleeding in patients with amenorrhea.

Patients in the long letrozole group had taken 2.5 mg of letrozole daily for 10 days starting day 1 of spontaneous or progesterone inducing menstrual bleeding using norethisterone acetate, which will be prescribed 10 mg/day for 5 days to induce withdrawal bleeding in patients with amenorrhea.

All patients had been monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on days 10, 12, and 14 of the cycle.

The HCG injection (5000 IU intramuscular) will be given when at least one follicle measured more than or equal to 18 mm. Patients will be advised for intercourse 24–36 h after HCG injection. Serum HCG will be determined 2 weeks after HCG injection in the absence of menstruation for diagnosis of pregnancy, followed by 1 week later transvaginal ultrasound for demonstration of the gestational sac.

Statistical analysis

The statistical analysis of data was done by using Excel program (Microsoft Office 2013) and the Statistical Package for the Social Sciences program (SPSS Inc., Chicago, Illinois, USA), version 20. Kolmogorov–Smirnov test was done to test the normality of data distribution. Qualitative data were presented as frequency and percentage. Quantitative data were presented as mean and SD or median and range.

Results

This prospective, randomized study was to evaluate the efficacy of the short and long course of letrozole therapy in the induction of ovulation in 100 clomiphene-resistant infertile women with PCOS.

Table 1 shows that the mean age of the short letrozole group was 24.97 years, and 24.87 years in long therapy; age was insignificant between two groups; the *P* value is 0.928.

Table 1 shows that the mean weight in the short therapy group was 77.37 and 78.53 kg in the long therapy group. The weight of the patients was insignificant between two groups; the *P* value is 0.515.

Mean height of the short therapy group was 166.63 and 165.82 cm in the long therapy group; height was insignificant between two groups, *P* value is 0.504.

Mean BMI in the short therapy group was 27.86 and 28.59 kg/m^2 in the long therapy group. BMI was insignificant between two groups, *P* value is 0.215.

Table 2 shows that the mean FSH level in the short therapy group was 5.16 mIU/ml and in the long therapy group was 6 mIU/ml. FSH level was insignificant between two groups; the *P* value is 0.093.

Mean LH level in the short therapy group was 9.88 mIU/l, and in the long therapy group was 9.45 mIU/l. LH level was insignificant between two groups; the *P* value is 0.363.

Mean LH/FSH level in the short therapy group was 2.08 and 1.69 in the long therapy group, and there was a significant difference between two groups regarding LH/FSH ratio; the *P* value is 0.011.

Table 3 shows that the mean testosterone level in the short therapy group was 0.39 ng/ml and in the long therapy group was 0.42 ngl/ml. The testosterone level was insignificant between two groups; the *P* value is 0.159.

Table 4 shows that the mean FBS in the short therapy group was 88.37 mg/dl, and in the long therapy group was 99.63 mg/dl. FBS was significant between two groups with the long therapy groups showing high FBS; the *P* value is 0.001.

The mean insulin level in the short therapy group was 12.09 IU/ml, and in the long therapy group was 13.11 IU/ml. The insulin level was insignificant between two groups; the *P* value is 0.056.

Table 5 shows that in the short therapy group 43.3% of patients had no ovulation and 56.7% had ovulation in the long therapy group; in the 73.3% of patients who had ovulation there was insignificant difference between two groups regarding ovulation but in the long therapy group ovulation was higher; *P* value is 0.176.

Table 6 shows that the mean number of follicles in the short therapy group was 8.17 and 8.2 in the long therapy group; the

Table 1: Comparison between the two studied groups according to basic criteria

	Short letrozole therapy (*n*=30)	Long letrozole therapy (*n*=30)	*t*	*P*
Age (years)			0.091	0.928
Minimum-maximum	19.0-32.0	19.0-34.0		
Mean±SD	24.97±4.26	24.87±4.22		
Median	25.0	25.0		
Weight (kg)			0.654	0.515
Minimum-maximum	67.0-90.0	65.0-90.0		
Mean±SD	77.37±6.48	78.53±7.30		
Median	75.0	79.50		
Height (cm)			0.672	0.504
Minimum-maximum	158.0-173.0	158.70-175.0		
Mean±SD	166.63±4.45	165.82±5.13		
Median	167.50	165.0		
BMI (kg/m^2)			1.254	0.215
Minimum-maximum	23.18-31.51	21.55-33.62		
Mean±SD	27.86±1.91	28.59±2.56		
Median	28.08	28.71		

Table 2: Comparison between the two studied groups according to levels of sex hormones

	Short letrozole therapy (n=30)	Long letrozole therapy (n=30)	t	P
FSH (mIU/ml)			1.709	0.093
Minimum-maximum	3.14-7.54	3.25-9.42		
Mean±SD	5.16±1.61	6.0±2.14		
Median	5.23	6.38		
LH (mIU/l)			0.919	0.363
Minimum-maximum	7.21-11.81	5.24-13.52		
Mean±SD	9.88±1.14	9.45±2.33		
Median	9.71	9.73		
LH/FSH			2.629*	0.011*
Minimum-maximum	1.29-3.26	1.21-2.88		
Mean±SD	2.08±0.60	1.69±0.52		
Median	1.83	1.41		

FSH, follicle-stimulating hormone; LH, luteinizing hormone; * = significant

Table 3: Comparison between the two studied groups according to the level of testosterone hormone

	Short letrozole therapy (n=30)	Long letrozole therapy (n=30)	Z	P
Testosterone (ng/ml)				
Minimum-maximum	0.24-0.81	0.23-0.67	0.170	0.159
Mean±SD	0.39±0.23	0.42±0.20		
Median	0.38	0.49		

Table 4: Comparison between the two studied groups according to fasting blood glucose and insulin levels

	Short letrozole therapy (n=30)	Long letrozole therapy (n=30)	t	P
Fasting blood glucose (mg/dl)			3.584*	0.001*
Minimum-maximum	70.0-110.0	79.0-115.0		
Mean±SD	88.37±11.28	99.63±13.01		
Median	89.0	105.0		
Insulin (IU/ml)			1.961	0.056
Minimum-maximum	10.23-14.54	10.33-18.21		
Mean±SD	12.09±1.53	13.11±2.40		
Median	11.84	12.54		

* = significant

Table 5: Comparison between the two studied groups according to ovulation

	Short letrozole therapy (n=30) [n (%)]	Long letrozole therapy (n=30) [n (%)]	χ^2	P
Ovulating			1.832	0.176
No	13 (43.3)	8 (26.7)		
Yes	17 (56.7)	22 (73.3)		

number of follicles was insignificant between two groups; P value is 0.951.

Follicle size more than 14 mm in the short therapy group: 23.3% had zero follicle, 53.3% one follicle, 23.3% has two follicles, and 0% had three follicles. In the long therapy group, 20% had zero, 50% had one, 26.7% had two, and 3.3% had three follicles. There was insignificant difference between the two groups regarding follicles more than 14 mm; the P value is 1.000.

Follicles size was more than or equal to 18 mm in the short therapy group with 46.7% having zero follicles and 53.3% having one, and in the long therapy group 33.3% had zero, 36.7% had one, and 30% had two; there were significant differences between two groups regarding follicles more than or equal to 18 mm as in the long therapy group there were more follicles with size more than or equal to 18 mm; the P value is 0.005.

Table 7 shows that in the short therapy group, 86.7% was nonpregnant and 13.3% got pregnant in the long therapy group; 76.7% was nonpregnant and 23.3% got pregnant. The pregnancy rate was insignificant between two groups with a P value of 0.317.

Positive US criteria were 73.3% in the short therapy group, and in long therapy group 83.3% had positive US criteria; there

Table 6: Comparison between the two studied groups according to the nature of follicles

Follicles	Short letrozole therapy ($n=30$) [n (%)]	Long letrozole therapy ($n=30$) [n (%)]	Test of significance	P
Total number			t=0.061	0.951
Minimum-maximum	5.0-11.0	5.0-11.0		
Mean±SD	8.17±2.04	8.20±2.19		
Median	8.50	9.0		
>14 mm			χ^2=1.179	^{MC}P=1.000
0	7 (23.3)	6 (20.0)		
1	16 (53.3)	15 (50.0)		
2	7 (23.3)	8 (26.7)		
3	0 (0.0)	1 (3.3)		
≥18 mm			χ^2=11.399*	^{MC}P=0.005*
0	14 (46.7)	10 (33.3)		
1	16 (53.3)	11 (36.7)		
2	0 (0.0)	9 (30.0)		

* = significant

Table 7: Comparison between the two studied groups according to pregnancy/cycle and positive US criteria

	Short letrozole therapy ($n=30$) [n (%)]	Long letrozole therapy ($n=30$) [n (%)]	χ^2	P
Pregnancy/cycle			1.002	0.317
Nonpregnant	26 (86.7)	23 (76.7)		
Pregnant	4 (13.3)	7 (23.3)		
Positive US criteria			0.884	0.347
Negative	8 (26.7)	5 (16.7)		
Positive	22 (73.3)	25 (83.3)		

were insignificant differences between two groups regarding US criteria; the P value is 0.347.

Discussion

PCOS is an etiology of menstrual irregularity, infertility, and androgen excess in women. The definition of PCOS has varied over the years. Based on the Rotterdam criteria, the diagnosis of PCOS requires two of the three potential characteristics: oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (on pelvic ultrasound). Other causes of these signs or symptoms, such as late-onset congenital adrenal hyperplasia or Cushing's syndrome, must also be excluded [17].

In this study, we aimed to evaluate the efficacy of short and long letrozole therapy for ovulation induction in clomiphene-resistant women with PCOS.

Reproductive age is the most critical factor in determining the outcome of female infertility treatment. A significant decline in fecundity occurs in women starting at the age of 35 years. Several factors account for obstacles and failures of fertility treatment with advancing female age including poor oocyte quality, reduction in follicular response to internal and external gonadotropins, and the decline in endometrial receptivity [18].

In this study, we found that the mean age of the short letrozole group was 24.97 and 24.87 years in long therapy; age was insignificant between two groups; the P value is 0.928.

In the Al-Fadhli *et al.* [19] randomized, controlled trials of two different doses of letrozole, the mean age in the letrozole 2.5 mg group was 31.8 years and in the letrozole 5 mg was 31.8 years. In the Elnashar *et al.* [20] study, the mean age in group I responders to letrozole was 26.7 years and in the nonresponder group the mean age was 28.35 years.

In agreement with this study, another study compared the effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation by Noriega-Portella *et al.* [21]. They found that there were no statistically significant differences in chronological age, infertility time, or BMI. Similarly, the baseline serum hormone levels were not statistically significantly different among the study groups.

In the study, we found that the mean weight in the short therapy group was 77.37 and 78.53 kg in the long therapy group. The weight of the patients was insignificant between two groups; the P value is 0.515. The mean height of the short therapy group was 166.63 and 165.82 cm in the long therapy group. Height was insignificant between two groups; the P value is 0.504.

Mean BMI in the short therapy group was 27.86 and 28.59 kg/m^2 in the long therapy group. BMI was insignificant between two groups; the P value is 0.215.

In the study by Quintero *et al.* [22] that compared letrozole versus FSH in clomiphene failure, weight and height in the letrozole group was 60.5 kg and 162 cm and in another group was 66.4 kg and 162 cm, respectively, and there were insignificant differences between two groups regarding weight and height, P value 0.11, 0.63, respectively.

In this study, we found that was seen in oligo-ovulation 73.3% of the short therapy group was and anovulation in 26.7%. In the long therapy group 73.3% had oligo-ovulation and 26.7% had anovulation, and there was an insignificant correlation between oligo/anovulation in the two groups; the *P* value is 1.000.

In the Quintero *et al.* [22] study, duration of infertility in the letrozole group was 2 years and in the gonadotropin group was 2 years. There were insignificant differences between two groups regarding the duration of infertility; the *P* value is 0.79.

In this study, we found that the mean FSH level in the short therapy group was 5.16 mIU/ml and in the long therapy group was 6 mIU/ml. The FSH level was insignificant between two groups; the *P* value is 0.093.

Mean LH level in the short therapy group was 9.88 mIU/l, and in the long therapy group was 9.45 mIU/l; LH level was insignificant between two groups with a *P* value of 0.363.

Mean LH/FSH level in the short therapy group was 2.08 and 1.69 in the long therapy group, and there was a significant difference between two groups regarding LH/FSH ratio with a *P* value of 0.011.

Badawy *et al.*[18] agree with our result as they found that mean FSH and LH level in the short therapy group was 5.1 and 11.9 IU/ml and in the long therapy group was 4.9 and 12.1 IU/ml, respectively. There were insignificant differences between the two groups regarding FSH and LH level with a *P* value of 0.20 and 0.09, respectively.

In this study, we found that the mean number of follicles in the short therapy group was 6.17 and 8.2 in the long therapy group. The number of follicles was insignificant between two groups with a *P* value of 0.951.

Follicle size was more than 14 mm in the short therapy group: 23.3% had zero follicles, 53.3% was with one follicle, 23.3% with two follicles, and 0% with three follicles. In the long therapy group 20% had zero follicles, 50% had one follicle, 26.7% had two follicles, and 3.3% had three follicles. There was insignificant difference between two groups regarding follicles more than 14 mm with a *P* value of 1.000.

Follicles size more than or equal to 18 mm in the short therapy group with 46.7% having zero follicles, 53.3% with one follicle and in long therapy group 33.3% had zero follicles, 36.7% had one follicle, and 30% had two follicles. There were significant differences between two groups regarding follicles more than or equal to 18 mm as in the long therapy group there were more follicles with size more than or equal to 18 mm with a *P* value of 0.005.

In the Noriega-Portella *et al.* [21] study in comparing between letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins they found that the number of follicles with diameter more than 8 mm was similar in the groups of study ($P>0.05$). The number of ovarian follicles with diameter more than 14 mm was statistically significantly ($P<0.05$) higher in the recombinant FSH-only group compared with the recombinant FSH þ 5.0 mg letrozole group.

In this study, we found that 86.7% of the short therapy group was nonpregnant and 13.3% got pregnant; in the long therapy group 76.7% was nonpregnant, and 23.3% got pregnant. The pregnancy rate was insignificant between two groups with a *P* value of 0.317.

Positive US criteria were 73.3% in the short therapy group, and in long therapy group 83.3% had positive US criteria. There were insignificant differences between two groups regarding US criteria with a *P* value of 0.347.

In the Badawy *et al.* [23] study, they found that pregnancy occurred in 28 of 225 cycles in the short letrozole group (12.4%) and 38 of 219 cycles (17.4%) in the long letrozole group, and the difference was statistically significant ($P<0.05$). One twin pregnancy occurred in the long letrozole group, and no ovarian hyperstimulation syndrome was reported in either group.

Ethical approval statement

Informed consent will be obtained from all women after full explanation of benefits and risks, Privacy of all women data is granted and there will be code number for every woman file that includes all investigations, all women is voluntary and may discontinue participation at any time without penalty or loss of benefits. The use of safety methods either on taking the blood sample or on discard them after laboratory examination minimizes the risks, any unexpected risks appeared during the course of the research will be cleared to the women and the ethical committee on time.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human reproduction. 2018 Sep 1;33:1602-18.
2. Azziz R. Polycystic ovary syndrome. Obstet Gynecol 2018; 132:321–336.
3. Moghadam ZB, Fereidooni B, Saffari M, Montazeri A. Measures of health-related quality of life in PCOS women: a systematic review. International journal of women's health. 2018;10:397.
4. Almenning I, Rieber-Mohn A, Lundgren KM, Løvvik TS, Garnæs KK, Moholdt T. Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. PLoS One. 2015 Sep 25;10:e0138793.
5. Rojas J, Chávez M, Olivar L, Rojas M, Morillo J, Mejías J, Calvo M, Bermúdez V. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. International journal of reproductive medicine. 2014 Jan 28;2014.
6. Spritzer PM. Polycystic ovary syndrome: reviewing diagnosis and management of metabolic disturbances. Arq Bras Endocrinol Metabol 2016; 58:182–187.
7. Jayasena CN and Franks S. The management of patients with polycystic

ovary syndrome. Nat Rev Endocrinol 2014; 10:624–636.
8. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008; 89:505–522.
9. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2014(2).
10. Davar R, Javedani M, Fallahzadeh MH. Metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistance PCOS patients undergoing IUI. Iran J Reprod Med 2011; 9:31–36.
11. Chimento A, Sirianni R, Casaburi I, Pezzi V. Role of estrogen receptors and g protein-coupled estrogen receptor in regulation of hypothalamus-pituitary-testis axis and spermatogenesis. Front Endocrinol (Lausanne) 2014; 5:1.
12. Casper RF, Mitwally MF. Review: aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab 2006; 91:760–771.
13. Costello MF. The treatment of infertility in polycystic ovary syndrome: a brief update. Aust N Z J Obstet Gynaecol 2005; 52:400–403.
14. American Diabetes Association. Standards of medical care in diabetes-2016: summary of revisions. Diabetes Care 2016; 39(Supp l1):S4–S5.
15. Miller KK, Rosner W, Lee H, Hier J, Sesmilo G, Schoenfeld D, Neubauer G, Klibanski A. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. The Journal of Clinical Endocrinology & Metabolism. 2004 Feb 1;89:525-33.
16. Bowen R. Gonadotropins (2004):Luteinizing and Follicle Stimulating Hormones.jan;78:56-89.
17. Goldberg J M, Falcone T, Eckler T. (2016) Laparoscopic surgery for ovulation induction in polycystic ovary syndrome.UpToDate.apr.;6:765-769.
18. Badawy A, Aal IA, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertility and sterility. 2009 Sep 1;92:849-52.
19. Al-Fadhli R, Sylvestre C, Buckett W, Tan SL, Tulandi T. A randomized trial of superovulation with two different doses of letrozole. Fertility and sterility. 2006 Jan 1;85:161-4.
20. Elnashar A, Fouad H, Eldosoky M, Saeid N. Letrozole induction of ovulation in women with clomiphene citrate–resistant polycystic ovary syndrome may not depend on the period of infertility, the body mass index, or the luteinizing hormone/follicle-stimulating hormone ratio. Fertility and sterility. 2006 Feb 1;85:511-3.
21. Noriega-Portella L, Noriega-Hoces L, Delgado A, Rubio J, Gonzales-Castañeda C, Gonzales GF. Effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination. Fertility and sterility. 2008 Nov 1;90:1818-25.
22. Quintero RB, Urban R, Lathi RB, Westphal LM, Dahan MH. A comparison of letrozole to gonadotropins for ovulation induction, in subjects who failed to conceive with clomiphene citrate. Fertility and sterility. 2007 Oct 1;88:879-85.
23. Badawy A, Mosbah A, Tharwat A, Eid M. Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol. Fertility and sterility. 2009 Jul 1;92:236-9.