Journal of Biology and Today's World

Journal home page: http://journals.lexispublisher.com/jbtw

Received: 21 August 2017 • Accepted: 15 October 2017

Research

doi:10.15412/J.JBTW.01061103

Two Protocols of Letrozole Treatment in Polycystic Ovary Syndrome: Randomized Clinical Trial

Tahereh BehrouziLak[1], Masoomeh hajshafiha[1], Rogiieh Derogar[1], Fedyeh Haghollahi[2*]

[1] Maternal and Childhood Obesity Research Center, Shahid Motahari Hospital, Urmia University of Medical Sciences, Urmia, Iran

[2] Institute for Family Health, Vali-e-Asr Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran, Iran

*Correspondence should be addressed to Fedyeh Haghollahi, Institute for Family Health, Vali-e-Asr Reproductive Health Research Center, Tehran University of Medical Sciences; Imam Hospital, Keshavarz Blvd, Tehran, Iran, Iran; Tel: +982166581616; Fax: +982166581658; Email: Fedyeh_hagh@yahoo.com.

ABSTRACT

This study is a prospective randomized clinical trial that was conducted on 200 infertile patients with polycystic ovary syndrome (PCOS) in two groups (A and B). Group A (n=100) received Letrozole, 7.5 mg/day for 5 days (short-term group) from day 3 to 7 of menstruation. Group B (n=100) received Letrozole, 5 mg /day for 10 days (long-term group) from day 3 of menstruation. In both groups, the subcutaneous injections of human follicle stimulating hormone (Gonal-F) (75 IU) were applied on days of 5, 7, 9th menstrual cycles. When the follicle size was 18mm or more, human chorionic gonadotropin (hCG) (5000 IU) was injected intramuscular and after 34 to 36 hours, intrauterine insemination (IUI) was performed. The number of follicles and days to reach mature follicle, endometrial thickness, pregnancy and abortion were evaluated. The pregnancy and abortion rate were no differences in two groups. Endometrial thickness and number of mature follicles in group A (short-term) letrozole group are higher than the second group ($p<0.05$). The results of this small series suggest that short-term with totally low doses of letrozole offers benefit results, regarding number of mature follicles, endometrial thickness and could be the first line treatment for induction of ovulation in PCOS patients.

Key words: Polycystic ovary syndrome, Letrozole, Ovulation induction, Recombinant FSH.

Journal of Biology and Today's World is published by *Lexis Publisher*; Journal p-ISSN 2476-5376; Journal e-ISSN 2322-3308.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disorder among reproductive age women and is characterized by hyper androgenism, polycystic ovaries and ovulation disorders (1, 2). This syndrome affects women of childbearing age from 8 to 18% (3). The pathogenesis of PCOS is not known exactly, but it seems a series of genetic and environmental factors are responsible for this syndrome (4-6). Symptoms of this syndrome start after the onset of menarche and continue till menopause (7).

Polycystic ovaries are defined as the presence of 12 or more follicles with 2–9 mm in diameter, and/or increased ovarian volume greater than 10 mL (8). Clomiphene citrate (CC) is a selective estrogen receptor modulator with a long half-life (2 weeks) and long lasting estrogen receptor (ER) depletion, that is prescribed as the first medicine for ovulation induction in these patients with 73% and 36% of success in ovulation and occurrence of pregnancy, respectively (9). Patients who do not ovulate with taking 150 mg CC for 5 days are considered as CC- resistant patients (10). Prolonged ER reduction may have an opposing effect on the cervical mucus and endometrium in 15–50% of patients (11, 12) causing a difference between ovulation and conception rates, and higher incidence of miscarriage (13-15). In addition, prolonged estrogen receptor down regulation can lead to multiple follicular growths and increased risk of multiple pregnancies and ovarian hyper stimulation syndrome. One study showed that obese women and women who have insulin resistance (IR) and elevated androgen levels are more at the risk of CC- resistance (9). If pregnancy does not occur for up to 6 cycles after to taking CC, it is defined to CC failure (16). Aromatase is a cytochrome P450 enzyme that converts androstenedione and testosterone to estrone and estradiol by hydroxylation (17). The aromatase inhibitors especially letrozole and anastrozole are mainly used to treat

postmenopausal women with breast cancer, but since 2001, these Medications particularly letrozole have been prescribed for ovulation induction in patients who do not respond to CC (18). So that this enzyme inhibitor Medications inhibit the estrogen production and consequently the pituitary gland is stimulated to secrete FSH and ovarian follicle grows larger followed by FSH (19). Several studies used letrozole as first line of treatment in PCOS patients (20-25), and other compared it with CC in PCOS patients resistant as the first line treatment (26-30). However, treatment period and ideal dosage of letrozole is not known exactly in PCOS patients (21). There are several studies comparing 2.5mg x 5.0mg for 5days (15, 20-25). By the way, most of them show no differences in terms of pregnancy, or live birth rates. What the literature lack are studies comparing 7.5mg doses and studies comparing different durations of treatment (5 or 10days). The authors compare the different doses and duration of two protocols of letrozole treatment in PCOS. The aim of this research was assessment of two different doses and timing protocols of letrozole administration for ovulation induction in PCOS patients.

2. MATERIALS AND METHODS

2.1. Population

This randomized clinical trial study was performed among PCOS patients who referred to Kosar infertility center of Urmia, Iran in May 2013 to May 2014. Due to sample size calculation formula and data from previous similar studies, the sample size was calculated 188 patients (94 patients in each group) based on a 95% confidence and a power of 80%. But for reaffirmation 200 patients were selected (100 patients in each group). Inclusion criteria were; age between 18 to 38 years, proven PCOS (based on Rotterdam criteria) (8) and the presence of normal laboratory tests of thyroid and prolactin function. Exclusion criteria included; age more than 38 years, a history of underlining disease (Cushing's syndrome, hyperprolactinemia, congenital adrenal hyperplasia, or other diseases of the adrenal gland, thyroid disorders, galactorrhea) impaired glucose tolerance or type 1/type 2 diabetes, hypertension, hyperlipidemia, active or chronic liver or renal failure, or congestive heart failure; a history of coronary artery disease, acute infection , presence of any chronic inflammatory and autoimmune disease; known malignancy; and body mass index (BMI) >35 kg/m^2. Abnormal hysterosalpingography (HSG), male infertility, patients with history of ovarian hyper stimulation syndrome (OHSS) (31).

2.2. Study design and treatments

The study participants were divided into two groups by using random numbers table; group A (n=100) or short-term letrozole group and group B (n=100) or long-term letrozole group. The name of study treatment regimens were put in two closed envelopes (A and B).The study participants were selected randomly into two groups and an informed consents were obtained from patients before initiation of study (Figure 1).

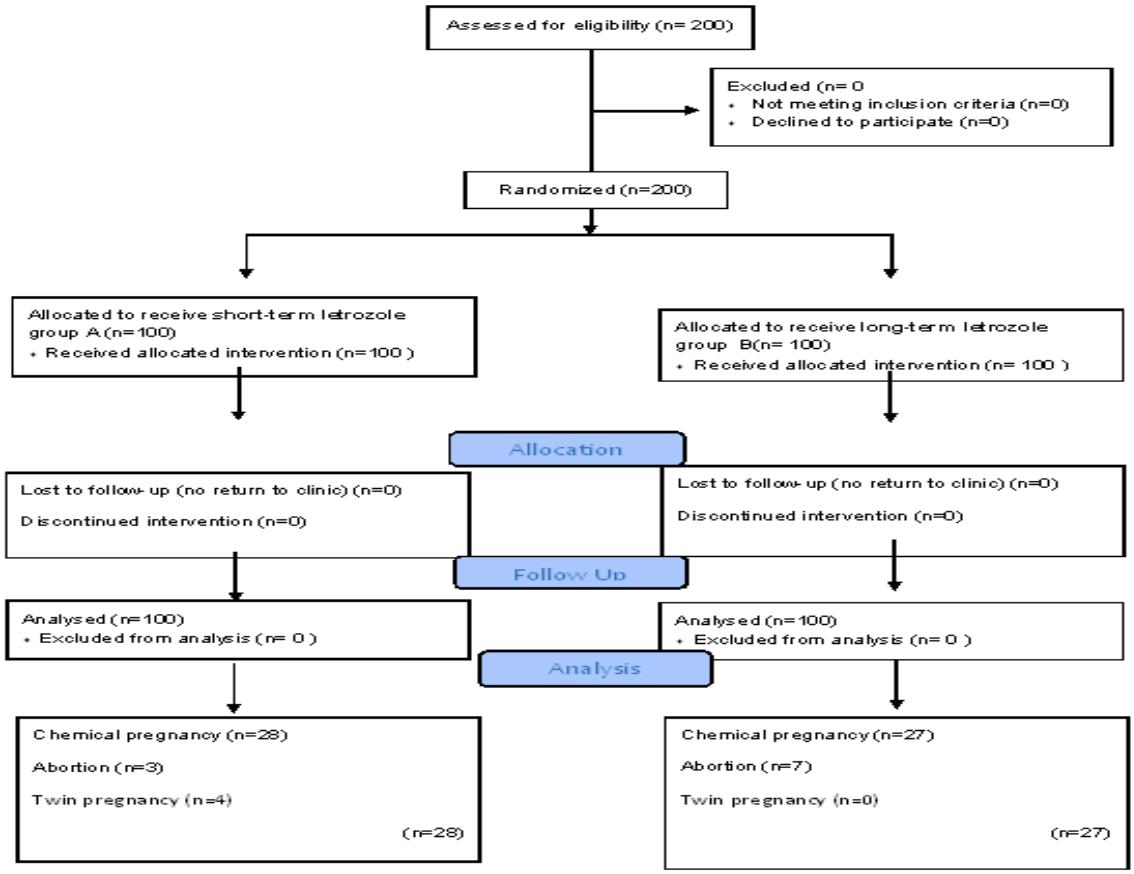

Figure 1. Consort flow diagram

A base transvaginal ultrasound was performed in all participants in 2 or 3nd day of cycle, and if it was normal, then patients received their treatment protocol according to their group. In group A (short-term letrozole group), participants received oral letrozole (Femara®; Novartis pharma AG, Basle, Switzerland) (37.5 mg – 7.5 mg/day for 5 days, from day 3 to 7 of menstruation). However, in group B (long-term letrozole group), patients received 5mg oral letrozole (Femara®; Novartis pharma AG, Basle, Switzerland), (50mg -5 mg /day) for 10 days from day 3 of menstruation. In both groups, the subcutaneous injections of Gonal-F (75 IU) were applied on days of 5, 7, 9th menstrual cycles. In order to continue of treatment, follicles size and their endometrial thickness on the 11th day of the menstrual cycle were assessed. In the presence of a mature follicle (the follicle is greater than 18mm), intra muscular HCG (5000 IU) was injected and intrauterine insemination (IUI) was done 34 to 36 hours after injection. Finally, two weeks after IUI, BHCG test was done in the absence of menstruation. Pregnancy was diagnosed on the basis of a b-HCG concentration greater than 10 IU/L and a positive gestational sac viewed by the ultrasound. The duration of treatment was continued with the presence of mature follicle. The number and size of mature follicles, endometrial thickness, the timing of HCG injection and pregnancy rate, miscarriage, multiple pregnancies, and ectopic pregnancy were assessed in both groups. The primary outcomes were mature follicles, and endometrial thickness (mm) measures and Secondary outcome were the Chemical pregnancy, abortion, multiple pregnancies, and ectopic pregnancy measures. Mature follicle (the follicle is greater than 18mm) were monitored by transvaginal ultrasound on days 10, 12, and 14 of the cycle.

2.3. Statistical Analysis

For continuous variables, data were presented as means ± standard deviation (SD) and for categorical variables, as number with frequency. The comparisons of variables between the two groups were made using the Fisher's exact test for categorical variables and independent t-test for continuous variables. Statistical analysis was performed using SPSS version 17. Kolmogorov-Smirnov test for normality quantitative data was reviewed. T test was used for normally distributed data.

2.4. Ethical Considerations

The study was approved by the ethics committee of Urmia University of Medical Sciences. All participants were notified about study objective and its procedure. Also subjects were informed that their participation was voluntary and written consent was obtained from all participants. The study was submitted to the Iranian health ministry website for clinical trials (www.IRRCT.IR; Registration number: IRCT201603092692 N2).

3. RESULTS AND DISCUSSION

The mean age in groups I and II were 27.88 ± 5.18 and 26.59 ± 5.31 years, respectively. There was no significant difference between in two groups (P = 0.08). There were no statistically significant differences regarding age, BMI, duration of infertility, basal hormone level and Type of infertility in both groups (Table 1).

Table 1. Characteristics of patients in two groups (A and B)

Variables	Group A (mean ± SD) n=100	Group B (mean ± SD)n=100	P value
Age (years)	27.88 ± 5.18	26.59 ± 5.31	0.08
BMI (kg/m^2)	27.96 ± 3.90	27.35 ± 3.35	0.23
Duration of infertility(Years)	4.27 ± 2.70	4.26 ± 2.8	0.96
FSH (mIu/ml)	5.72± 1.93	5.74 ± 4.69	0.96
LH (mIu/ml)	9.36 ± 4.71	8.14 ± 4.69	0.69
*Type of infertility (N,%)	No. (%)	No. (%)	
-Primary	66 (66%)	74 (74%)	0.217
- secondary	34 (34%)	26 (26%)	

T-Test
* Q-square
BMI.body mass index
FSH .Follicle stimulating hormone
LH.luteinized Hormone
Group A: Group A (n=100) received, Letrozole, 7.5 mg/day for 5 days or short – term group) from day 3 to 7 of menstruation.
Group B: group B (n=100) received Letrozole, 5 mg /day for 10 days (long term group) from day 3 of menstruation

The ovulation induction data for both groups are given in Table 1. There were significant statistical differences in the endometrial thickness (p=0.003), this is in group A (7.89 ± 0.87mm) and in group B (7.51 ± 0.88mm) (Table 2).

Table 2. Treatment outcomes in patient in two groups (A and B)

Variables	Group A (mean ± SD) n=100	Group B(mean ± SD) n=100	P value
No. of mature follicles	2.09 ± 0.84	1.70 ± 0.68	**0.001**
endometrial thickness(mm)	7.89± 0.87	7.51± 0.88	**0.003**
day of HCG administration	13.47±0.02	14.35± 2.25	**0.005**
day of IUI performing	15.33± 2.06	16.21± 2.24	0.006
Chemical Pregnancy (n.%)	28 (28%)	27 (27%)	0.874
			0.13
			0.111
*Abortion (n.%)	3 (10.3%)	7 (25.9%)	
*Twin pregnancy (n.%)	4 (**%**14)	0(0.0%)	

T-Test
* Fisher's exact test
Group A: Group A (n=100) received, Letrozole, 7.5 mg/day for 5 days or short – term group) from day 3 to 7 of menstruation.
Group B: group B (n=100) received Letrozole, 5 mg /day for 10 days (long-term group) from day 3 of menstruation.

The numbers of mature follicles are significantly different. (p=0.001) (2.09 ± 0.84 vs 1.70 ± 0.68), that in the group A is higher. The mean day of HCG administration in the group A was 13.47±0.02 days and in the group B was 14.35± 2.25, which there was significantly difference between the two treatment groups (P =0.005). The mean IUI performing days were 15.33± 2.06 in group A and 16.21± 2.24 day in the groups B. There was a significant difference between the two treatment groups regarding the day of IUI performing (P =0.006). The incidence of pregnancy in first cycle after treatment was 28 women (28%) in the group A, and 27 women (27%) in the group B. According to Fisher Exact test, there was no significant difference between two groups regarding pregnancy occurrence (P=0.874). In addition, the incidence of abortion was 3 cases (10.3%) in the group A and 7 cases (25.9%) in the group B. There was no significant difference between two groups regarding abortion rates in the first trimester of pregnancy (p=0.13). In group A; 4 of cases (14%) twin pregnancy has been reported while in the group B; there was not reported twin pregnancy. There were no cases of OHSS or ectopic pregnancy in our study. In view of the studies, in ovulation induction and pregnancy rates in PCOS patients, Letrozole is at least as higher effective than clomiphene with additional benefits including reduced risk of multiple pregnancies and OHSS (32) and without of dangerous role on cervical mucus and endometrial growth (27), and less monitoring during ovarian stimulation (33). Also, Sun and et al in the retrospective study determined the clinical pregnancy rate was significantly higher in the letrozole plus gonadotrophin group than the letrozole group in women undertaking letrozole ovarian stimulation and artificial insemination by donor (AID)(34). Athwal showed in the

prospective study showed the rate of pregnancy was slightly greater in the letrozole+FSH group (17.85% versus 13.33%), although not statistically significant and it appears to be a suitable ovulation inducing agent versus CC with FSH in PCOS (35). Arya S assess the effect of letrozole in combination with low dose gonadotropins for ovulation induction in PCOS, endometriosis, and unexplained infertility and the pregnancy rates per cycle were not statistically significant difference between the groups (36). Clinical investigation of Letrozole in infertile women has been generally limited to 5 days of treatment at doses of 2.5–7.5 mg daily.Yang et al compared two different doses of 2.5 and 5 mg of letrozole in women candidates for IUI, the follicle diameter and endometrial thickness were similar in the two groups. In their study; pregnancy rate and the number of mature follicles were significantly higher in the group who received 5 mg letrozole (37). Their conclusion showed that the dose of 5mg letrozole leads to higher pregnancy rates (32). Randomized trial of ovulation induction with two different doses(5 or 7.5 mg) of Letrozole in PCOS patients in the day of 3-7 of menstruation period were performed and showed that there were no significant statistical differences in endometrial thickness and the number of mature follicles on the day of 12–14th menstrual periods in two groups (37). A study, comparing 2.5 mg, 5 mg, and 7.5 mg, found that the number of mature follicles was significantly greater by increasing drug dose (1.0, 1.4, and 3.4, resp.) (38). A Prospective randomized controlled study was performed with two protocols of short and long letrozole treatment that in short group administrated 5 mg of daily starting day 1 of the menses for 5 days, and patients in the long letrozole group had 2.5 mg of letrozole daily starting day 1 of the menses for 10 days and results showed that long letrozole protocol (10 days) can produce more mature follicles and subsequently more pregnancies than the short letrozolethrapy (5 days) (39). In our study, mature follicles, endometrial thickness and the number of gonadotropin 75 IU used showed significant difference in both groups and in group A is higher, But there was no significant difference between pregnancy or abortion rates in both groups. The group taking 7.5 mg Letrozole (short – term or group A) have higher number of mature follicles, endometrial thickness on the days of 12–14 and the duration of stimulation day, compared to other group. (Long term or group B). In the present study the doses of letrozole in short term group (group A) (15 tablets for 5 days which totally dose is 37.5 mg) is less than other group (20 tablets for 10 days which totally dose is 50 mg). We can conclude that 7.5 mg Letrozole (short – term group) did not increase pregnancy rate but increase number of mature follicles and endometrial thickness. Thus, there is a reason to believe that the lower total dose of short-term administration than other group could be more efficient in stimulating the release of FSH, that resulting in greater follicular development. This is the first study that compares two different doses in short and long duration of Letrozole use in PCOS. There are several limitations on the present study:

1. Lack of comparison with lower doses of letrozole, for one, 2.5 mg/day for 5 days.
2. Lack of live birth rates.
3. We had no other study that compares the different doses and duration of two protocols of letrozole treatment in pcos, also we do not check testosterone and estrogen levels in these patients.

It is suggested that comprehensive study is clearly needed, including basic investigation into estradiol and androgen levels with these doses in reproductive age women. However, the superiority of letrozol in ovulation induction and pregnancy rates in PCOS with normal weight were mentioned in different studies, in our study, there was no significant difference between pregnancy rates. Although , one of the main goals of therapy -for patients and physicians- is treatment within a shorter time, and protocol used in the group I (15 tablets for 5 days that equally dose are 37.5 mg) seems more affordable among PCOS patients. We believe that short –term of Letrozole would be superior, particularly in the first line of letrozole therapy in PCOS with higher BMI and also high-dose letrozole may be of value in women who fail to respond adequately to lower doses.

4. CONCLUSION

The results of this small series suggests that compared with the daily dose, 7.5 mg of Letrozole in 5 days offers benefit regarding number of mature follicles, endometrial thickness and first line treatment for induction of ovulation in general PCOS patients. We suggest that shortening the duration of Letrozole therapy (short -term) may result in higher number of follicles and may be beneficial in special conditions like higher BMI.

ACKNOWLEDGMENT

We are grateful to the Kosar department of obstetrics and gynecology of Shahid Motahhari hospital affiliated to Urmia University of Medical Sciences for helping us. It should be noted that there was no association between the authors and any organization or institution.

FUNDING/SUPPORT

Not mentioned any Funding/Support by authors.

AUTHORS CONTRIBUTION

Study concept and design: Tahere Behrouzi lak; Analysis and interpretation of data: Tahere Behrouzi lak and Masoomeh hajshafiha; Drafting of the manuscript: Tahere Behrouzi lak and Fedyeh Haghollahi; Data collection: Rogieh Derogar and Masoomeh hajshafiha; Statistical analysis: Fedyeh Haghollahi.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with

respect to the authorship and/or publication of this paper.

REFERENCES

1. Khomami MB, Tehrani FR, Hashemi S, Farahmand M, Azizi F. Of PCOS symptoms, hirsutism has the most significant impact on the quality of life of Iranian women. PloS one. 2015;10(4):e0123608.
2. Nam H, Kim C-H, Cha M-Y, Kim J-M, Kang B-M, Yoo H-W. Polycystic ovary syndrome woman with heterozygous androgen receptor gene mutation who gave birth to a child with androgen insensitivity syndrome. Obstetrics & gynecology science. 2015;58(2):179-82.
3. Musmar S, Afaneh A, Mo'alla H. Epidemiology of polycystic ovary syndrome: a cross sectional study of university students at An-Najah national university-Palestine. Reproductive Biology and Endocrinology. 2013;11(1):47.
4. Xiang S-K, Hua F, Tang Y, Jiang X-H, Zhuang Q, Qian F-J. Relationship between serum lipoprotein ratios and insulin resistance in polycystic ovary syndrome. International journal of endocrinology. 2012;2012.
5. Goodarzi MO, Jones MR, Li X, Chua AK, Garcia OA, Chen Y-DI, et al. Replication of association of DENND1A and THADA variants with polycystic ovary syndrome in European cohorts. Journal of medical genetics. 2011:jmedgenet-2011-100427.
6. Merkin SS, Azziz R, Seeman T, Calderon-Margalit R, Daviglus M, Kiefe C, et al. Socioeconomic status and polycystic ovary syndrome. Journal of Women's Health. 2011;20(3):413-9.
7. Uysal S, Zeki Isik A, Eris S, Yigit S, Yalcin Y, Ozun Ozbay P. Correlation of endometrial glycodelin expression and pregnancy outcome in cases with polycystic ovary syndrome treated with clomiphene citrate plus metformin: a controlled study. Obstetrics and gynecology international. 2015;2015.
8. Lauritsen M, Bentzen J, Pinborg A, Loft A, Forman J, Thuesen L, et al. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Müllerian hormone. Human reproduction. 2014;29(4):791-801.
9. Kuang H, Li Y, Wu X, Hou L, Wu T, Liu J, et al. Acupuncture and clomiphene citrate for live birth in polycystic ovary syndrome: study design of a randomized controlled trial. Evidence-Based Complementary and Alternative Medicine. 2013;2013.
10. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. New England Journal of Medicine. 2007;356(6):551-66.
11. Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. Human Reproduction. 1990;5(6):670-4.
12. Sereepapong W, Suwajanakorn S, Triratanachat S, Sampatanukul P, Pruksananonda K, Boonkasemsanti W, et al. Effects of clomiphene citrate on the endometrium of regularly cycling women. Fertility and sterility. 2000;73(2):287-91.
13. Homburg R. Clomiphene citrate—end of an era? A mini-review. Human Reproduction. 2005;20(8):2043-51.
14. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertility and sterility. 2004;82(6):1561-3.
15. Franks S, Adams J, Mason H, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. Clinics in obstetrics and gynaecology. 1985;12(3):605-32.
16. Misso ML, Wong JL, Teede HJ, Hart R, Rombauts L, Melder AM, et al. Aromatase inhibitors for PCOS: a systematic review and meta-analysis. Human reproduction update. 2012;18(3):301-12.
17. EL-Gharib MN, Mahfouz AE, Farahat MA. Comparison of letrozole versus tamoxifen effects in clomiphen citrate resistant women with polycystic ovarian syndrome. Journal of reproduction & infertility. 2015;16(1):30.
18. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertility and sterility. 2006;85(2):277-84.
19. Hussain NHN, Ismail M, Zain MM, Yeu PC, Ramli R, Mohammad WMZW. Randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience. Open Journal of Obstetrics and Gynecology. 2013;3(05):11.
20. Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility: lippincott Williams & wilkins; 2005.
21. Zadehmodares S, Niyakan M, Sharafy SA, Yazdi MH, Jahed F. Comparison of treatment outcomes of infertile women by clomiphene citrate and letrozole with gonadotropins underwent intrauterine insemination. Acta Medica Iranica. 2012;50(1):18.
22. Begum MR, Ferdous J, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Fertility and sterility. 2009;92(3):853-7.
23. Sohrabvand F, Ansari S, Bagheri M. Efficacy of combined metformin–letrozole in comparison with metformin–clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. Human Reproduction. 2006;21(6):1432-5.
24. Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B. Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. Journal of assisted reproduction and genetics. 2009;26(1):19-24.
25. Hashim HA, Shokeir T, Badawy A. Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Fertility and sterility. 2010;94(4):1405-9.
26. Baruah J, Roy K, Rahman S, Kumar S, Sharma J, Karmakar D. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. Archives of gynecology and obstetrics. 2009;279(3):311-4.
27. 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;92(3):849-52.
28. Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. Journal of International Medical Research. 2006;34(1):73-6.
29. Bayar Ü, Basaran M, Kiran S, Coskun A, Gezer S. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. Fertility and sterility. 2006;86(5):1447-51.
30. Zeinalzadeh M, Basirat Z, Esmailpour M. Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome. The Journal of reproductive medicine. 2009;55(1-2):36-40.
31. Chen C-D, Wu M-Y, Chao K-H, Lien Y-R, Chen S-U, Yang Y-S. Update on management of ovarian hyperstimulation syndrome. Taiwanese Journal of Obstetrics and Gynecology. 2011;50(1):2-10.
32. Mitwally MF, Biljan MM, Casper RF. Pregnancy outcome after the use of an aromatase inhibitor for ovarian stimulation. American journal of obstetrics and gynecology. 2005;192(2):381-6.
33. Yang M, Quan S, Li H, Song Y, Xing F. Effect of two different doses of letrozole in promoting ovulation in infertile women with polycystic ovarian syndrome. Nan fang yi ke da xue xue bao= Journal of Southern Medical University. 2008;28(11):2060-1.
34. Sun X, Jiang L, Ji L, Nie R, Chen H, Jin L, et al. A retrospective analysis of ovarian stimulation with letrozole in women undergoing artificial insemination by donor. Reproductive BioMedicine Online. 2017;34(4):354-60.
35. Athwal A, Chakravorty R, Sur D, Saha R. Use of letrozole versus clomiphene citrate combined with gonadotropins for ovulation induction in infertile women with polycystic ovary syndrome: a pilot study. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017;6(9):4098-101.
36. Arya S, Kupesic-Plavsic S, Mulla ZD, Dwivedi AK, Crisp Z, Jose J, et al. Ovulation Induction and Controlled Ovarian Stimulation Using Letrozole Gonadotropin Combination: A Single Center Retrospective Cohort Study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017.
37. Ramezanzadeh F, Nasiri R, Yazdi MS, Baghrei M. A randomized trial of ovulation induction with two different doses of Letrozole in women with PCOS. Archives of gynecology and obstetrics. 2011;284(4):1029.
38. Badawy A, Metwally M, Fawzy M. Randomized controlled trial of three doses of letrozole for ovulation induction in patients with unexplained infertility. Reproductive biomedicine online. 2007;14(5):559-62.
39. 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;92(1):236-9.