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Original Research Article

Low Dose-Extended Letrozole versus Double Dose-Short Letrozole Protocol for Induction of Ovulation in Women with Polycystic Ovary Syndrome

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Abstract

Background and Aim: The major factor for anovulatory infertility is polycystic ovarian syndrome (PCOS). As a new therapeutic option, letrozole and other aromatase inhibitors (AIs) may compete with clomiphene citrate (CC) to induce ovulation in this population. The purpose of the current study was to compare the effectiveness of the low dose-extended or long letrozole protocol and the double dose-short letrozole strategy in ovulation induction in individuals with polycystic ovarian syndrome.

Material and Methods: This study was done on the diagnosed cases of PCOS patients with subfertility in the department of obstetrics and gynecology for the period of 1 year. Letrozole 2.5 mg tablets were given daily for 10 days to the low dose-extended letrozole group or experimental group and tabs were given to the double dose-short letrozole group or control group. Starting on the second day of menstruation or the first day of withdrawal bleeding, take letrozole 5 mg once day for 5 days. On day 12 of the menstrual cycle, transvaginal sonography was used to quantify the endometrial thickness and count of developing follicles using a technique called folliculometry. On days 21 through 23, mid-luteal serum progesterone was tested to confirm ovulation.

Results: The mean LH levels of the two groups did not significantly differ from one another. In the third cycle, patients in the extended letrozole group (54.28%) and the short letrozole group (18.75%), respectively, achieved multifollicular development, bearing statistically significant differences. In the first cycle, group II had more patients grow dominant follicles (18 mm) than group I, however in the second and third cycles, group I patients had more patients generate dominant follicles (18 mm). While there was a higher percentage of ovulating patients in the low dose prolonged letrozole group (76.5% versus 71.9%), there was no statistically significant difference.

Conclusion: Low dose-extended letrozole protocol can be a better alternative to double dose-short letrozole protocol in respect to significant increase in the number of growing follicles with a higher trend to raise the ovulation rate and pregnancy rate though there were no significant differences in dominant follicle size, endometrial thickness, ovulation rate and pregnancy rate between two groups.

Keywords: Low dose-extended letrozole, Ovulation induction, Polycystic ovary syndrome, Pregnancy.

Introduction

One of the most typical causes of anovulatory infertility is polycystic ovary syndrome (PCOS), which affects 8-13% of reproductive-aged women. It was first identified more than 50 years ago, but the exact aetiology of this condition is still unknown. It is by far the most frequent cause of hyperandrogenic anovulatory infertility [1,2]. Chronic anovulation and elevated ovarian androgen production are the causes of the disease's typical symptoms. Menstrual dysfunction and hyperandrogenism are the two main clinical traits of polycystic ovarian syndrome [3,4]. Between five and ten percent of women in the population have this condition [5]. It accounts for 80% of all cases of anovulatory infertility [6]. This disorder's basic cause is still a mystery [7].

The aetiology of PCOS involves a combination of variables that include obesity, ovarian dysfunction, abnormalities in the hypothalamus-pituitary axis, and genetic and environmental causes of hormonal imbalances. It is a complicated illness with metabolic and reproductive issues [8,9]. Insulin resistance may develop as a result, causing PCOS and hyperandrogenism. Due to an innate stimulation of steroidogenesis that occurs even in the absence of trophic stimuli, theca of the ovary release large quantities of androgens [10,11]. Insulin resistance and hyperandrogenism can be brought on by oxidative stress in PCOS patients [12]. Many patients seek medical attention for conditions like infertility, irregular or nonexistent periods, hirsutism, and acne.

For the treatment of PCOS women with CC-resistant anovulation, aromatase inhibitors (AIs), such as letrozole or anastrozole, have been developed. It has been proposed that limiting ovarian aromatization would stop oestrogen production and relieve the hypothalamic-pituitary axis of estrogenic negative feedback. FSH secretion thus rises, promoting the growth of ovarian follicles. Aromatase inhibitors have been found to be effective in superovulation and ovulation induction, according to preliminary investigations [2,3]. Recently, we examined how letrozole dosages of 2.5 mg, 5 mg, and 7.5 mg affected ovulation [13]

Letrozole, an aromatase inhibitor, has been suggested as the first line treatment for anovulatory infertility due to its ability to induce monofollicular ovulation, improve endometrial thickness, and prevent the development of lag endometrium [14,15]. By preventing the conversion of androgens to oestrogens, letrozole exerts its peripheral action by reducing oestrogen production and relieving the HPO axis of oestrogen negative feedback.

This induces stimulation of the ovarian follicle and increases gonadotropin (both FSH and LH) output. It promotes monofollicular development and ovulation while maintaining the HPO axis and preventing the body's oestrogen receptors from becoming depleted [15]. The action of letrozole also diminishes during the late follicular phase as a result of the shorter half-life, which causes the amount of estradiol produced by developing follicles to rise. The elevated estradiol level suppresses the release of FSH. The drop in FSH levels causes atresia of small follicles and even selection of dominant follicle is impaired [16]. Letrozole has no adverse effect on endometrium. Due to its short half-life (45 hours) and the lack of

downregulation of estrogen receptors letrozole has less negative effects on the endometrium and cervix in the late follicular phase [17]. Moreover, another important observation about letrozole was that letrozole administration in infertile ovulatory women was associated with in-phase histological dating of endometrium and normal pinopode expression [18]. Extended letrozole protocol maintains the continuous production of FSH for a longer duration. As a result, more tiny follicles are recruited early on in the cycle and help the mature follicles (18 mm) to form. The group receiving extended letrozole had a higher pregnancy rate.

In PCOS individuals, the 5-day letrozole treatment can occasionally fail to stimulate ovulation, necessitating the use of gonadotropins or laparoscopic ovarian drilling instead. This forces them to incur additional costs, which frequently becomes a burden for many underprivileged PCOS sufferers. In light of this, the current study was carried out to assess the effectiveness of the low dose-extended or long letrozole protocol and the double dose-short letrozole protocol in the induction of ovulation in patients with polycystic ovary syndrome.

Material and Methods

This study was done on the diagnosed cases of PCOS patients with subfertility in the department of obstetrics and gynecology for the period of 1 year.

Age between 18 and 35 years, infertility, PCOS diagnosed using Rotterdam criteria, and a body mass index between 18 to 30 kg/m2 were all inclusion criteria. Other causes of hyperandrogenism, endometriosis, bilateral tubal obstruction, decreased ovarian reserve, male factor, endocrine disorders (hypothyroidism, hyperprolactinemia), medical conditions (like diabetes mellitus, hypertension), a history of taking an insulin sensitizer (metformin, myoinositol), and a history of taking an ovulation-inducing drug (clomiphene, letrozole,

A computer-generated random table was used for the randomization. Randomization was done between the low dose-extended letrozole group (54 patients) and the double dose-short letrozole group for eligible women who provided their informed consent (52 patients). Treatment was started from the 2nd day of menstruation after the baseline visit and investigations in the remaining patients. 50 patients total took part in the low dose extended letrozole group during the first cycle, while 50 patients took part in the double dose short letrozole group.

The PCOS women's double dose-short letrozole group received letrozole 5 mg daily for 5 days beginning on the second day of menstrual cycle or withdrawal bleeding for three consecutive cycles, while the low dose-extended letrozole group received letrozole 2.5 mg for 10 days beginning on the second day of menstrual cycle or withdrawal bleeding for three consecutive cycles.

Every patient was told not to take any additional medications without first talking with us. We referred to the double dosage short letrozole group as "group II" and the low dose extended letrozole group as "group I." On the 12th day of the cycle, transvaginal follicle growth was monitored for the emergence of preovulatory follicles (mean diameter 18 mm) and endometrial thickness 7 mm or greater.

In the current study, follicles with a size of 10 mm or greater that were found by TVS folliculometry after administering ovulation induction were considered to be developing follicles. The total number of growing or developing follicles was calculated by adding the number of follicles in each ovary. During transvaginal sonography, the largest follicle's size was determined by averaging the two largest internal follicular diameters recorded in two parallel planes. In the fundal region,

endometrial thickness was measured at the largest diameter perpendicular to the mid sagittal plane.

Injection Women with follicular sizes less than 18 mm received 5000 IU of HCG, and timing of sexual activity was advised every other day starting on the day the HCG was delivered. To measure serum progesterone between days 21 and 23, doctors advised their patients. Normal ovulation is often indicated by blood progesterone levels of 3 ng/ml on days 21 to 23. 19 Mid luteal serum progesterone (3 ng/ml) was used as a marker for ovulation at a subsequent visit. 19 Ultrasonography, urine pregnancy test kits, or serum beta-HCG were all used to determine whether a woman was pregnant.

Number of developing and mature follicles, largest follicular size, serum progesterone (ng/ml), and endometrial thickness were the main outcome indicators (mm). Ovulation rate was the primary outcome, whereas pregnancy and miscarriage rates were the secondary outcomes.

Statistical Analysis

Microsoft Excel 2007 was used to compile and enter the data collected, which was then exported to the data editor page of SPSS version 15 for analysis (SPSS Inc., Chicago, Illinois, USA). The level of significance and confidence level for each test were set at 5% and 95%, respectively.

Results

A total of 100 women participated in the study and were included in analysis. Table 1 shows important baseline characteristics of both groups which revealed that most of the patients belonged to similar age group that is less than 27 years in both extended (group I) and short letrozole (group II) group. There was no significant difference in mean duration of infertility and BMI. The hormonal status of the patients revealed normal mean FSH and LH values that supported PCOS patient's normogonadotropic characteristics. There was no significant difference between mean LH levels of both groups. All the patients of both groups were in euthyroid state and had normal prolactin level. Table 2 displays that the number of patients that developed more than one follicular growth in first and second cycle was more or less double in extended letrozole group compared to short letrozole group but this difference could not meet the statistical significance level. On the other hand, 54.28% versus 18.75% patients attained multifollicular growth in extended and short letrozole group respectively in n third cycle which bore statistically significant difference.

In the first cycle, group II had more patients grow dominant follicles (18 mm) than group I, however in the second and third cycles, group I patients had more patients generate dominant follicles (18 mm). None of the cycles, however, revealed a discernible difference. Regarding the mean number of developing follicles, there was a significant difference between groups I and II, with group I showing the greater rate. As a result, group I grew multifollicularly more than group II. However, there were no appreciable changes between the two groups in terms of the dominant follicle's average size, endometrial thickness, or mid-luteal serum progesterone levels.

The ovulation rate was greater in group I than group II in second and third cycles but the result was reverse with a little difference in first cycle. Cumulative ovulation rate was almost similar in both groups however, none of the differences proved significant statistically (Table 3). There was no significant difference between the two groups in terms of pregnancy rate in any of the cycles and in cumulative pregnancy rate as well. In terms of side effects, letrozole was generally well tolerated by patients in both the prolonged and short letrozole groups; 88%

and 96% of patients in each group had no adverse effects, respectively. In both groups, headache was the most commonly reported side effect that only affected a very small percentage of patients.

Table 1: Age wise Distribution of study participants

Variable	Extended letrozole group I N=50		Short letrozole group II N=50		P value
	Number/Mean±SD	Percentage	Number/Mean±SD	Percentage	
Age(Years)	24.20±2.15		25.12±3.20		0.54
18-24	17	34	21	42	0.12
24-27	23	46	19	38	
>27	10	20	10	20	

Statistically significance at p≤0.05

Table 2: Total number of growing follicles in study population

Number of growing follicles	Extended letrozole group I N=50		Short letrozole group II N=50		P value
	Number	Percentage	Number	Percentage	
1st cycle	**N=50**		**N=50**		
0	11	22	10	20	0.05*
1	15	30	28	56	
>1	24	48	12	24	
2nd cycle	**N=47**		**N=44**		
0	10	21.27	11	25	0.54
1	17	36.17	18	40.90	
>1	20	42.55	15	34.09	
3rd cycle	**N=35**		**N= 32**		
0	0	0	4	12.5	0.03*
1	16	45.71	22	68.75	
>1	19	54.28	6	18.75	

*** indicates statistically significance at p≤0.05**

Table 3: Comparison of ovulation rate in study participants in three cycles

Ovulation rate	Extended letrozole group I N=50		Short letrozole group II N=50		P value
	Number	Percentage	Number	Percentage	
1st cycle	**N=50**		**N=50**		**0.47**
Yes	32	64	36	72	
No	18	36	14	28	
2nd cycle	**N=47**		**N=44**		**0.32**
Yes	37	78.72	29	65.90	
No	10	21.27	15	34.09	
3rd cycle	**N=35**		**N=32**		**0.10**
Yes	26	74.28	22	68.75	
No	9	25.41	10	31.25	

Statistically significance at p≤0.05

Discussion

One of the most common conditions affecting women of reproductive age is polycystic ovarian syndrome (PCOS), which frequently results in infertility. Hyperandrogenism, oligomenorrhea, and polycystic ovaries on ultrasonography are used to diagnose it [20,23] According to the various diagnostic criteria, its prevalence has been observed to range from 6.8% to 18%. PCOS patients frequently have psychological difficulties as a result of its symptoms. These ailments frequently include anxiety, irregular periods, sadness, and even infertility. For women with PCOS who are infertile, various managements have been suggested. The best management strategy, however, has not yet been satisfactorily addressed [24].

Even though numerous treatments, such as ovarian cauterization, clomiphene citrate, metformin, weight loss, and gonadotropins, have been reported to treat this problem, there is still inadequate data to support their effectiveness [25] For decades, clomiphene citrate has been used for this indication. It is a selective estrogen-receptor modulator that blocks the hypothalamic effects of oestrogen and increases the stimulation of the ovaries by endogenous gonadotropin. Since being introduced into clinical practise in the 1960s, clomiphene citrate (CC) has been the most often prescribed medication for the treatment of infertility.

The downsides of clomiphene include its generally low efficacy (only 22% of live births occurred with up to six cycles of clomiphene in our prior study) [26] a relatively high multiple-pregnancy rate (3 to 8%) as compared with the rate associated with unassisted conception (<1%) and an undesirable side-effect profile, including mood changes and hot flushes. Failure to ovulate (clomiphene resistance), which happened in 25% of patients treated with clomiphene, or to become pregnant when treated for ovulation by CC, was also linked to greater frequencies of multiple pregnancies and an elevated risk of ovarian hyperstimulation syndrome [27].

Letrozole has been used successfully over the past ten years to induce ovulation in people with polycystic ovarian syndrome (PCOS) and to speed up ovulation in women who are already ovulating. Letrozole has no negative effects on endometrium or the endocervix, unlike clomiphene citrate, which is swiftly removed from the body and does not deplete oestrogen receptors. Letrozole is preferred above clomiphene citrate for superovulation in PCOS patients, according to several studies. The optimal dose and duration of letrozole administration for superovulation in patients with PCOS are still not clear [18-20].

The mean age of the prolonged letrozole group (group I) and the short letrozole group (group II) in our study was 24.20 2.15 and 25.12 3.20, respectively. There was no discernible distinction between the two groups. Patients from a similar age group were chosen by Badawy and Hassanein [28].

In the current study, there was no discernible difference between the two groups' study participants, who were all normogonadotropic. In the Long and Short letrozole groups, the average LH levels were 6mIU/ml, respectively. Several study participants had luteinizing hormone levels that were somewhat greater than this. Patients having LH levels above 10 mIU/ml were included in the investigations by Salama *et al*., Badawy *et al*., and Hassanein *et al*.; the respective values were 12 mIU/ml and 9 mIU/ml [28-30]. The mean number of growing follicle was 1.40±0.90 versus 0.94±0.50 in group I and group II respectively generating p value of 0.001. These results came in agreement with the results of study done by Badawy *et al*, Aziz

et al, Hassanein *et al*, Yadav *et al*, and Salama *et al* [28-31].

In the second and third cycles, more patients in group I than group II had dominant follicles (18 mm), with the exception of the first cycle, where this was more common in group II than group I. Hence, more patients in group I than in the other acquired dominating follicles (18 mm). None of the cycles, however, revealed a discernible difference.

This study's findings were consistent with those of Aziz *et al*., who found that patients in the extended letrozole group had follicles that were somewhat larger than the other group's, but not significantly larger. Their findings were equivalent to those of Badawy *et al* [28]. The mean size of the dominant follicle was insignificantly greater in group I than group II. This result is consistent with Aziz *et al* and Salama *et al* studies.

There was no significant difference in mean endometrial thickness on day 12 between two groups in present study but it was slightly lower in extended letrozole group than short letrozole group. That came agree with Badawy *et al* [28] and Ramezanzadeh *et al* [32] Similar to this study, there were no significant differences in mean endometrial thickness at HCG between two groups in Badawy *et al*, Aziz *et al*, Salama *et al* and Yadav *et al* studies. This decrement of endometrial thickness in this study might be due to considering the endometrial thickness by transvaginal sonography at day 12 of menstrual cycle irrespective of follicular size instead of taking the endometrial thickness at HCG by following the patients by serial transvaginal sonography. Another discrepancy of this result is that extended letrozole group had slightly lower endometrial thickness.

One of the explanations of this deviation might be that in extended letrozole group, the antiestrogenic effect of letrozole continues up to day 12 or 13 which lowers the intrafollicular estrogen level as well as estrogen production in other sites that might affect the endometrial development. Contrary to this, in short letrozole group, due to shorter half-life of letrozole, this antiestrogenic influence cannot persist for long enough to affect endometrial development adversely. However, serum estradiol measurement which was not done in this study might be helpful in clarifying this issue.

The ovulation rate was greater in extended letrozole group than short letrozole group in second and third cycles but the result was reverse with a little difference in first cycle. This outcome came in similar with the consequences of Badawy, Aziz, Hassanein and Salama. Nonetheless, the ovulation rates were lower in both groups in Badawy *et al*, Aziz *et al* and Salama *et al* study than this one. Comparing two groups in terms of cumulative pregnancy rate, it was manifested that pregnancy rate was somewhat higher in group I than group II.

However, cumulative pregnancy rate between two groups were not significant statistically. These findings were comparable to those of Badawy *et al* [28]. whose study found that pregnancy occurred in 28 of 225 cycles for the short-letrozole group and 38 of 219 cycles for the long-letrozole group, with a statistically significant difference between the two. Contrary to these findings, Fouda *et al* [9] demonstrated that there was no significant difference in the clinical pregnancy rate between the two groups (22.06% vs. 16.18%, respectively). Ramezanzadeh *et al* [32] also disagreed, demonstrating that the pregnancy rate was 25.8% in group 1 and 21.2% in group 2 without a significant difference.

Conclusion

Low dose-extended letrozole protocol can be a better alternative to double dose-short letrozole protocol in respect to significant

increase in the number of growing follicles with a higher trend to raise the ovulation rate and pregnancy rate though there were no significant differences in dominant follicle size, endometrial thickness, ovulation rate and pregnancy rate between two groups.

References

1. Franks S, Adams J, Mason H, Polson D. Ovulatory disorders in women with polycystic ovary syndrome. Clin Obstet Gynecol. 1985;12: 605–32.
2. Mitwally MFM, Casper RF. Aromatase inhibition: a novel method of ovulation induction in women with polycystic ovarian syndrome. Reprod Technol. 2000; 10:244–7.
3. Mitwally M, Casper R. Use of aromatase inhibitor for ovulation induction in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001; 75:305–9.
4. Taylor HS, Pal L, Seli E. Female Infertility. In: Speroff's Clinical Gynecologic Endocrinology and Infertility. 9th ed. Wolters Kluwer, Philadelphia: Lippincottt Williams and Wilkins. 2020:990-991.
5. Dumont A, Robin G, Catteau-Jonard S, Dewailly D. Role of anti-müllerian hormone in pathophysiology, diagnosis and treatment of polycystic ovary syndrome: a review. Reprod Biol Endocrinol. 2015;13(1):1-10.
6. Committee Opinion No. 738. American College of Obstetricians and Gynecologists. Aromatase inhibitors in gynecologic practice. Obstet Gynecol. 2018;131(6):194-9.
7. March W. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25(2):544-51.
8. Legro RS, Strauss III JF. Molecular progress in infertility: polycystic ovary syndrome. Fertil Steril. 2002;78(3):569-76.
9. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010;8(1):1-10.
10. De Zegher F, Ibanez L. Early Origins of polycystic ovary syndrome: hypotheses may change without notice. J Clin Endocrinol Metab. 2009;94(10):3682-5.
11. Priya M, Nanthini A, Bini K. Polycystic ovary syndrome: An updated review. Int J Health Allied Sci. 2019;8(4):229.
12. Victor VM, Rocha M, Banuls C, Sanchez-Serrano M, Sola E, Gomez M, *et al*. Mitochondrial complex I impairment in leukocytes from polycystic ovary syndrome patients with insulin resistance. J Clin Endocrinol Metab. 2009; 94(9): 3505-12.
13. Badawy A, Metwally M, Fawzy M. Randomized controlled trial of three doses of letrozole for ovulation induction in patients with unexplained infertility. Reprod Biomed Online 2007; 14:559–62.
14. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, *et al*. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2018;33(9):1602-18.
15. Garg N, Vanitha VG. A Comparative study of letrozole versus clomiphene citrate as first line for anovulatory infertility- an institutional experience. Asian Res J Gynaecol Obstet. 2019; 2(1): 1-8.
16. Fouda UM, Sayed AM. Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: a randomized

controlled trial. Reprod Biol Endocrinol. 2011;9(1):1-7.
17. Baruah J, Roy KK, Rahman SM, Kumar S, Sharma JB, Karmakar D. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. ArchGynecol Obstet. 2009;279(3):311-4.
18. Cortínez A, De Carvalho I, Vantman D, Gabler F, Iñiguez G, Vega M. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. Fertil Steril. 2005;83(1):110-5.
19. Gardner DK, Weissman A, Howles CM, Shoham Z. Initial investigation of infertile couple. Volume 2: Clinical Perspectives. In: Textbook of Assisted Reproductive Techniques. 5th edn. CRC Pres: Taylor and Francis Group; 2018: 476.
20. Marciniak A, Lejman-Larysz K, Nawrocka Rutkowska. Polycystic ovary syndrome-current state of knowledge. Pol Merkur Lekarski, 2018; 44: 296–301.
21. Tanbo T, Mellembakken J, Bjercke S. Ovulation induction in polycystic ovary syndrome. Acta Obstet Gynecol Scand., 2018; 97:1162–7.
22. Kamboj MK, Bonny AE. Polycystic ovary syndrome in adolescence: diagnostic and therapeutic strategies. Transl Pediatr. 2017; 6:248–55.
23. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010; 8:41.
24. Zhou J, Yang L, Yu J. Efficacy of acupuncture on menstrual frequency in women with polycystic ovary syndrome: Protocol for a randomized, controlled trial. Randomized controlled trial. Medicine (Baltimore). 2017; 96: e8828.
25. Fouda UM, Sayed AM. Extended high dose letrozole regimen versus short low dose letrozole regimen as an adjuvant to gonadotropin-releasing hormone antagonist protocol in poor responders undergoing IVF-ET. 2011.
26. Legro RS, Barnhart HX, Schlaff WD (2007): Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med., 356:551– 566.
27. Kamphuis EI, Bhattacharya S, van der Veen F *et al*. Are we overusing IVF? BMJ., 2014;348:252.
28. 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. Fertil Steril. 2009;92(1):236-9.
29. Hassanein MS, Hegab MH, Attia AM, Zayed MA. Extended letrozole therapy for ovulation induction in clomiphene resistant women with polycystic ovary syndrome. Egypt J Hosp Med. 2018; 73(7):7032-6.
30. Salama KM, Sakr BE, Azab SA. Short letrozole therapy versus extended (long) letrozole therapy for induction of ovulation in women with polycyst
31. Yadav P, Agarwal M, Agarwal V, Verma U, Agarwal R. To study the efficacy on fertility outcome by short term letrozole versus extended letrozole regimen in clomiphene citrate resistant PCOS Women. J Med Sci Clin Res. 2018; 6(6): 340-5.
32. Ramezanzadeh F, Nasiri R, Sarafraz Yazdi M *et al*. A randomized trial of ovulation induction with two different doses of Letrozole in women with PCOS., 2011; 284:1029–1034.