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Effect of Letrozol in Primary and Secondary Infertile Patients: A Prospective Study

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Introduction: *Letrozole, is a third generation non-steroidal selective reversible and highly potent aromatase inhibitors which was used in breast cancer is a new drug used for ovulation induction. The present study aims to assess safety and efficacy of the use of letrozole in the patient undergoing ovulation induction, to determine ovulation rate, to evaluate the effect of letrozole on uterine endometrial thickness and to study the final success rate of treatment in terms of pregnancy rate*

Material and Methods: *A total 60 patients attending with primary and secondary infertility were included in the study. All women were given tablet letrozole 5mg daily from day 2 of the mensis for 5 day. Patients were followed up for maximum up to three cycles.*

Results: *60 women of the reproductive age group were studied. Mean age of the women was.27±3.47 years. 52 Women (86.66%) had primary infertility and eight women (13.33%) had secondary infertility. Mean number of follicles in first cycle was 1.47±0.66, mean number of follicles in second cycle was1.70±0.66, mean number of follicles in the third cycle was 1.62±0.66. Average number of dominant follicle was 1.58 ± 0.66. Out of 155 cycle total number of pregnancies was 10, pregnancy rate per cycle was(10/155) 6.45 % , pregnancy rate per ovulatory cycle was (10/129) 7.75% and cumulative pregnancy rate was(10/60) 16.66%.*

Conclusions: *Letrozole can be used as effective ovulation inducing agent, with no case of multiple pregnancy in the present study. However long-term multicenter randomized case controlled trials are needed with large sample size to conclude about the efficacy and safety of the drug, especially to study long term effect in fetal life, infancy and beyond.*

Keywords: *Letrozole, Primary infertility, Secondary infertility, Ovulatory cycles, Ovulation induction, Cumulative pregnancy rate.*

Introduction

"*Of all nature's gifts to the human race, what is sweeter to a man than his children*?" quoted by roman philosopher- Marcus Tullius Cicero.

Parenthood is undeniably one of the most universally desired goals in adulthood, and most people have life plans that include children. For

many couples, the inability to bear children is a tragedy. The conflux of personal, interpersonal, social, and religious expectations brings a sense of failure, loss, and exclusion to those who are infertile and will need medical help to resolve underlying fertility problems.

Infertility is generally defined as one year of unprotected regular intercourse without conception.[1] The American Society for Reproductive Medicine (2008) has recently revised its definitions of infertility - "Infertility is a disease, defined by the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years."[2]

Cycle fecundability is the probability that a cycle will result in pregnancy. Fecundity is the probability that a cycle will result in a live birth.[3] Approximately 85–90% of healthy young couples conceive within 1 year, most within 6 months[4,5] Infertility therefore affects approximately 10–15% of couples.[3] Among these couples, infertility is exclusively a problem in the female in about 30-40% of cases, exclusively in the men in about 10-30% of cases. In 15-30% of cases, both partners have detectable abnormalities.

Letrozole, is a third generation non-steroidal selective reversible and highly potent aromatase inhibitors which was used in breast cancer is a new drug used for ovulation induction. Although experience with it is limited, Letrozole is another potential option for Clomiphene resistant anovulatory women. Surprisingly Letrozole has been advocated as a possible first-line alternative to clomiphene treatment for ovulation induction. Whereas Clomiphene stimulates endogenous Follicle Stimulating Hormone (FSH) secretion by decreasing central negative feedback via estrogen receptor antagonism, Letrozole does so by inhibiting peripheral estrogen production.

Aims and Objectives

1. To study and determine the safety and efficacy of the use of letrozole in the patient undergoing ovulation induction.
2. To determine ovulation rate in study group.
3. To evaluate the effect of letrozole on uterine endometrial thickness.
4. To study the final success rate of treatment in terms of pregnancy rate.

Material and Methods

The study is conducted to evaluate the efficacy of letrozole as ovulation inducing agent in patients with anovulatory and unexplained infertility. It was a prospective study in primary and secondary infertility patients. A total 60 patients attending gynaecology outdoor patient department with primary and secondary infertility, who fulfilled the inclusion and exclusion criteria were included in the study.

Inclusion Criteria

1. Patient with primary and secondary anovulation
2. Patient with patent fallopian tube as diagnosed on hysterosalpingography or with laproscopy.
3. Clomiphene citrate failure/ resistant cases.
4. Unexplained infertility.

Exclusion Criteria

1. Infertility associated with endocrine abnormality of thyroid and prolactin disorders.
2. Patients with tubal factor for infertility or any other adnexal pathology.
3. Patients with partner having moderate to severe male factor infertility.
4. Patient with uncontrolled medical disorder.

Tablet letrozole 5mg was given orally for total five days to both primary and secondary infertility patients starting from day 2 of menses.

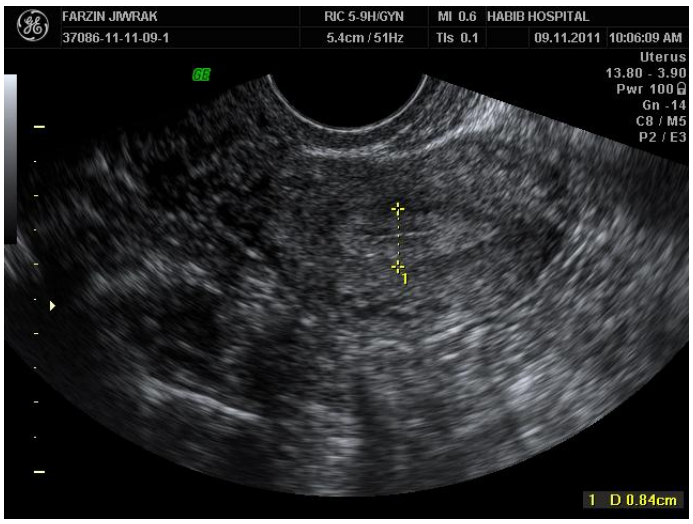
After approval by ethics committee, the study started in infertile patients attending gynaecology outpatient department. Patients were explained

about the type of study and the nature of the drug letrozole and how and why it is used. They were also told to report any untoward side effect they observe. Patients were included in the studies only after their informed consent was taken.

Detail history of patients were taken which included demographic data, age of both partners, occupation of both the partners, both present and past menstrual history, marital history, period of infertility and any treatment taken for the same in the past, obstetric history, past history of medical or surgical disorder, history of any addiction and any other personal history, etc. history and data collection was done with the preset questionnaire. Thorough general, physical and systemic examination was done to rule out any medical or surgical disorder. All women were investigated for complete blood count, blood group of both the partner, fasting and post prandial blood sugars, husband's semen analysis to rule out male factor infertility, hormonal investigation i.e. serum TSH, serum prolactin, to rule out endocrine disorder, ultrasonagraphy of the pelvis to rule out any adnexal and uterine pathology, hysterosalphingography, or diagnostic if required operative laproscopy to confirm tubal patency was done.

Patients who fulfill inclusion criteria were included in the study and proforma filled for all the women. All women were given tablet letrozole 5mg daily from day 2 of the cycle for 5 days. Patients were instructed to take tablet regularly and to inform immediately if any side effect seen. Serial ultrasonography was done on day from day 9 onwards every alternate day and more frequently if required for follicular monitoring in both the ovaries and for measuring endometrial thickness and its triple lining. All transvaginal ultrasonography was done on the same machine by the same observer (to avoid inter observer variation). At each transvaginal ultrasonography internal diameter of each visible follicle were measured in two dimensions and average diameter was then calculated.

Fig 1- Transvaginal ultrasound showing endometrial thickness



When atleast one dominant follicle had a diameter of 18 mm injection HCG 10,000 units was given intra muscularly as ovulation triggering agent and women were instructed to have planned relation. TVS was repeated on next day to look for evidence of ovulation i.e. disappearance of dominant follicle which was seen previously and presence of free fluid in cul-de-sac.

Fig 2 - Transvaginal ultrasound showing ruptured follicle

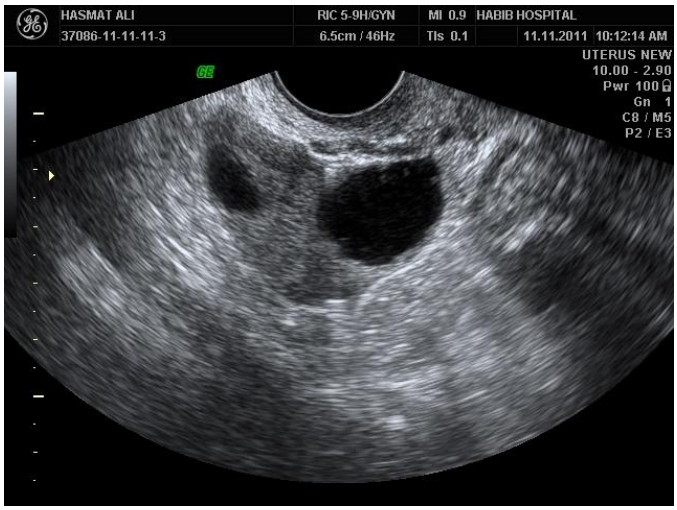
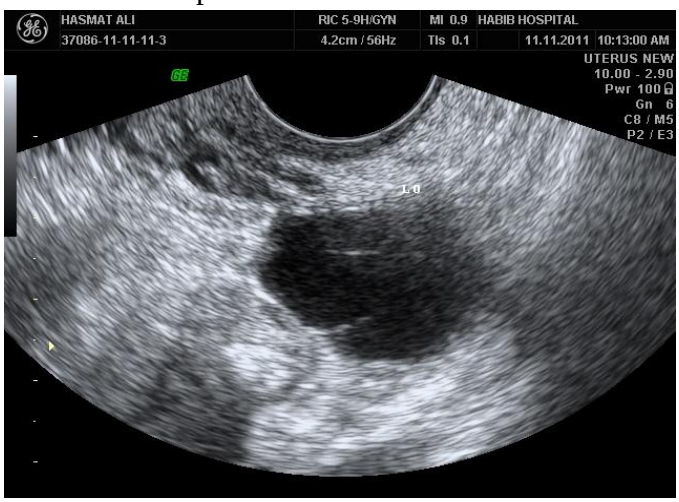


Fig 3 – Transvaginal ultrasound scan showing Lutinized Unruptured Follicle



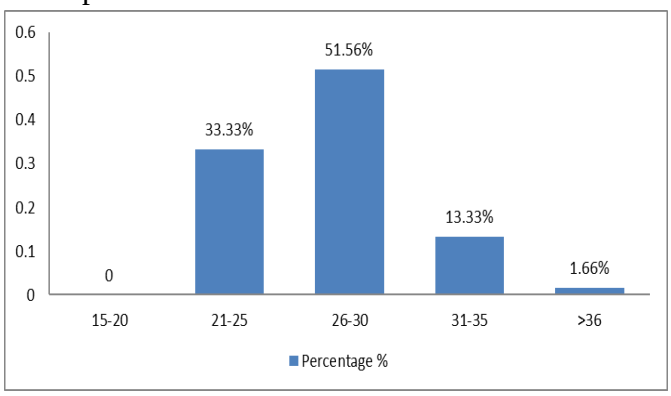
Women were instructed to follow up in next cycle or immediately after missed period. If patient is not pregnant, tablet letrozole was given in next cycle and similar protocol was followed. Before starting the ovulation in the next cycle all woman were taken for transvaginal ultrasonography on day 2 of menses to rule out the presence of any ovarian cyst. All women were followed up for total three cycles. Women who missed there period urinary pregnancy test or serum beta HCG level was done and pregnancy were calculated based on positive urinary pregnancy test or serum beta HCG >10 mIU/ml and presence of intra uterine gestational sac on ultrasonography. Primary outcome measured in the form of number of matured follicle (≥18mm) in both the ovaries in the endometrial thickness on the day of HCG injection, presence or absence of ovulation, pregnancy rate and any side effect of drug.

Data was entered in Microsoft Office Excel work sheet and the results were analyzed in number and percentage.

Results

In the present study, maximum women i.e. 31 women (51.56%) were in the age group of 26-30 years. 20 women (33.33%) were between 21-25 years, 8 women(13.33%) in the age group of 31-35 years. And only one women were above 35 years. Mean age of women in the study was 27.27±3.47 years. (Figure 4)

Figure 4: Bar diagram showing age distribution of the patients



86.66% patients in the present study were of primary infertility while 13.33% were of secondary infertility. (Figure 5)

Figure 5: Pie chart showing distrubution of type of infertility

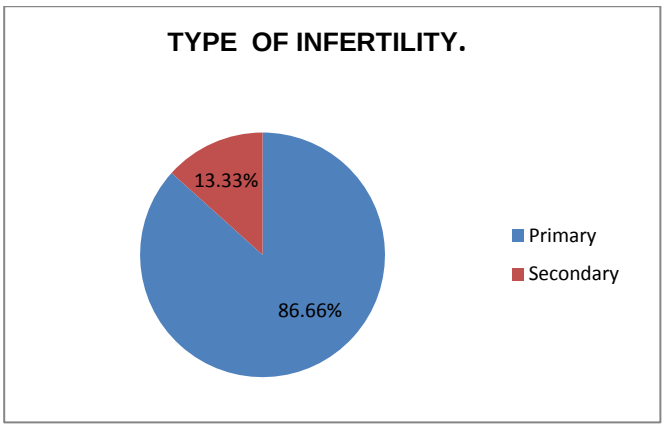


Table 1: Distribution of patients according to number of dominant follicles of 18 mm size or more

Number of follicles >18mm	Cycle 1	Cycle 2	Cycle 3
	Number %	Number %	Number %
0	6 (10%)	1 (1.88%)	2 (4.76%)
1	22 (36.66%)	15 (28.30%)	15 (35.71%)
2	30 (50%)	36 (67.92%)	22 (52.38%)
3	2 (3.33%)	1 (1.88%)	3 (7.14%)
Total	60 (100%)	53 (100%)	42 (100%)
Mean (no. of dominant follicles) with S.D	1.47±0.66	1.70±0.66	1.62±0.66

Sixty patients received first cycle, 53 patients received second cycle and 42 patients received third cycle. This was because of pregnancy and poor follow up of patients. As shown in Table 1, in the first cycle 30 women were (50%) developed two follicles >18mm in size, 22 women (36.66%) developed only one follicle and two women

(3.33%) developed three dominant follicles. Six women (10%) did not develop any dominant follicle. None of the women had developed more than three follicles ≥18mm in size in any of 3 cycle. Mean number of follicles developed in first cycle was 1.47±0.66.

In second cycle, 53 women were included. 2 lost to follow up (five conceived) and similar protocol were followed .Out of 53, 36 women (67.12%) developed two dominant follicles. 15 women (20.30%) developed single dominant follicle, one woman (1.88%) developed three dominant follicles. One woman did not develop any dominant follicle .None of them developed more than three follicles of≥ 18mm in size. Mean number of follicles developed were 1.7±0.66 in the second cycle.

In third cycle, 42 women were included. Six women lost to follow up and 5 concieved. Out of 42 women, 22 women (52.38%) developed two dominant follicle ≥18mm in size. 15 women developed (28.30%) one dominant follicles. Three women (7.14%) develop three dominant follicle. 2 women (4.76%) did not developed ant dominant follicle. In this study none of the patient develop ≥4 dominant follicles. Mean number of dominant follicles were 1.62±0.66 in the third cycle. (Table-1)

Table 2: Distribution of patients according to endometrial thickness on the day of ovulation trigger

Endometrial Thickness	Cycle 1	Cycle 2	Cycle 3
	Number %	Number %	Number %
<8	3(5%)	2(3.77%)	1(2.38%)
8-9	47(78.33%)	33(62.26%)	24(57.14%)
9.1-10	10(16.66%)	18(33.96%)	17(40.47%)
≥10.1	0	0	0
Total	60(100%)	53(100%)	42(100%)
Mean (endometrial thickness)with S.D	8.74 ±0.59	8.94±0.61	9.01±0.61

In first cycle 57 women had endometrial thickness ≥8mm with triple lining of endometrium, among them maxium 47 women (78.33%) had endometrium between 8-9mm. Mean endometrial thickness was 8.24±0.59mm. During second cycle, out of 53, total 51(96.22%) have ≥8mm of endometrium. Among them 33(62.26%) had endometrial thickness between 8-9mm with triple lining of endometrium. Mean endometrial thickness was 8.94±0.61 mm in the second cycle. During the third cycle, out of 42, 41 women (97.61%) had endometrial thickness ≥8mm with triple lining of endometrium, with maxium 24 (57.14%) have endometrial thickness between 8-9mm. Mean endometrial thickness was 9.01±0.61 mm. (Table-2)

Figure 6: Bar diagram showing ovulation and pregnancy rate after each cycle of letrozole

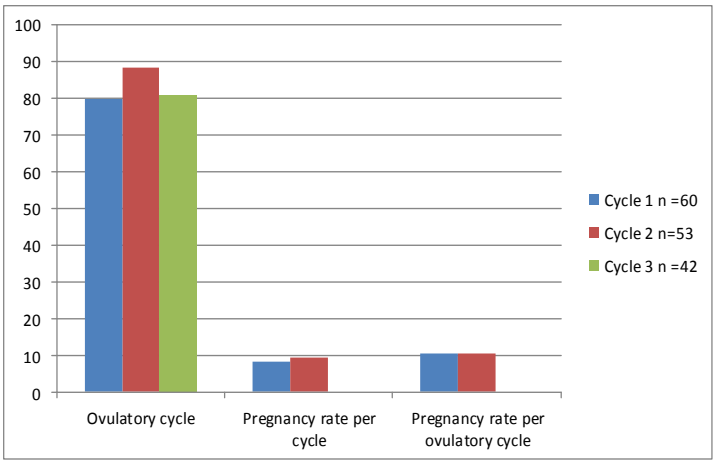


Table 3: Distribution according to total pregnancy and cumulative pregnancy rate

Total pregnancy	10
Total patients	60
cumulative Pregnancy rate	16.66%

From 155 cycle total number of pregnancies was 10, pregnancy rate per cycle was (10/155) 6.45 %, pregnancy rate per ovulatory cycle was (10/129) 7.75% and cumulative pregnancy rate was (10/60) 16.66%.

Discussion

Clomiphene citrate is the most commonly prescribed medication for ovulation induction when women are anovulatory. Despite the high rate of ovulation by CC, pregnancy rate per cycle remains relatively low. The antiestrogenic effect of CC produces cervical mucus thickening and thinning of the endometrium.It has been noted that 15%–50% of women on CC develop a thin endometrium <8 mm, with a tendency toward a nontrilaminar pattern at mid-cycle[6,7,8].

Inappropriate development of the endometrium is associated with low implantation rate and early pregnancy loss due to luteal phase defect [6,9]. 20% to 25% of patients do not respond to CC in spite of high doses. In CC unresponsive cases the next step for induction of ovulation is the use of gonadotropins, which increases both the cost and risks associated with treatment. Letrozole, which is an aromatase inhibitor, has the same role as CC in initiating gonadotropin release through the withdrawal of its negative feedback on the pituitary by reducing blood estrogen levels. Letrozole, however, has an added positive effect, because peripherally it may increase follicular sensitivity to FSH through amplification of FSH receptor gene expression [10,11,12,13].

Although, it creates an E-deficient environment, it has no negative effect on the endometrium and cervix due to its short (45 hours) half-life. Therefore, ovulation induction by letrozole is superior to CC in terms of follicular growth and endometrial development, which is essential for competent or proper implantation of embryo.[1]

Tehrani et. al (2008)[14], compared efficacy of letrozole and clomiphene citrate gonadotropins in controlled ovarian stimulation. In this prospective simply randomized clinical trial, women were given either letrozole (**5mg**) or clomiphene citrate (100 mg) on days 3-7 of the menstrual cycles. In the letrozole group they found, the number of mature follicles was 1.8±0.7, endometrial thickness 9.7±1.6mm, and clinical pregnancy rates of 32.8%.

Begum et al[15] (2006) studied role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate in a prospective clinical trial.35 Patient were treated by aromatase inhibitor **2.5-5** mg/day from day 3-7 of the menstrual cycle. 27(90%) patients developed mature follicles by day 12. The majority (77.77%) developed single follicle. Except for one cycle of one patient, the follicles of all patient were ruptured in all cycles and seven (25.94%) got pregnant.

Al-fadhil R et al[16]evaluted the effects of either a 2.5-mg or a 5-mg daily dose of letrozole in women undergoing superovulation and intrauterine insemination.

With 5 mg letrozole they found higher number of follicle 1.3±0.1, without any difference in ET 7.8 ± 0.3 mm and statistically higher pregnancy rate (26.3 %)

Badawy A et al[17] studied extended letrozole therapy for ovulation induction in clomiphene resistant women with polycystic ovaries syndrome. They used the drug 2.5 mg dose for 10 days. Total number of follicles and pregnancy rates were greater than standard regimen. Clinical pregnancy rates were significantly greater (17.4% Vs 12.4%) than the standard regimen.

Our results of mean number of follicle, average endometrial thickness, ovulation rate (83.22%) and pregnancy rate of (16.66%) are comparable to the above mention studies. **Mitwally et al[18] (feb 2005**) studied the **outcome of pregnancies** achieved after ovarian stimulation, including the use of of the aromatse inhibitor (2.5mg and 5 mg) reported that pregnancies conceived after letrozole treatments were associated with similar miscarriages and ectopic pregnancy rates compared with all other groups. In addition, letrozole use was associated with a significantly lower rate of multiple gestation compared with clomiphene citrate. They concluded that the favourable pregnancy outcome and low multiple gestation rate of aromatase inhibitors for ovarian stimulation in encouraging for the development of these agents as first- line ovulation induction agents.

Conclusion

From our study, we found that the drug letrozole can be used as effective ovulation inducing agent. There was no case of multiple pregnancy in our study. However longterm multicenter randomized case controlled trials are needed with large sample size to conclude about the efficacy and safety of the drug, especially to study long term effect in fetal life, infancy and beyond.

References

1. Speroff L, Fritz MA. Female Infertility In: Clinical Gynecologic Endocrinology and infertility. Eds: speroff L, Fritz MA, Lippincott William and Wilkins, Philadelphia pp1013-67.
2. Jacky Boivin, LauraBunting, John A Collins International estimates of infertility prevalence & treatment seeking: potential need and demand for infertility medical care. Human Reproduction pp1-7, 2007.
3. Kurl RN, Morris Id. Differential depletion of cytoplasmic high affinity oestrogen receptors after the in vivo administration of the antioestrogens, clomiphene, MER-25 and tamoxifen. BR J Pharmacol 1978;62:487-493.
4. Robert f.Casper and Mohamed F.M. Mitwally REVIEW: Aromatase inhibitors for ovulation induction the Journal of Clinical Endocrinology & Metabolism 91(3): 760-771.
5. Greenblatt RB, barfield We, Jugack EC Ray AW, Induction of ovulation with MRL/41, preliminary report, JAMA 178:255, 1961.
6. Mitwally MFM, Casper rf. Aromatase inhibition: a novel method of ovulation induction in women with polycystic ovarian syndrome. ReprodTechnol 2000;10:244-247.
7. Branigan Ef, Estes MA: A randomised clinical trial of treatment of clomiphene citrate resistant anovulation with the use of oral contraceptives ovarian suppression and repeated clomiphene citrate treatment. Am journal of obstet Gynecol.
8. Nestler Je, Jakubowicz DJ, Evans Ws, pasquali R effects of metformin on spontaneous and clomiphene induced ovulation in polyssystic ovarian syndrome. New England Jmed 338:1876,1998.
9. Y.Z. Diamant, S.evron induction of ovulation by combined clomiphene citrate and dexamethasone in clomiphene nonrespondereuropean Journal of OBST& GYN vol.11, issue 5. Page 335:340.
10. Keay SD, Jenkins JM Adjuvant use of dexamethasone in clomid resistant patients Fertilsteril 80:230,2003.
11. Danoforthdr=R: Endocrine and paracrine control of oocyte develop[ment Am J ObstetGynecol172:747,1995.
12. Thompson Cr, Hansen LM pergonal (menotropins) a summary of clinical experience in induction of ovulation and pregnancy FertilSteril 21:844,1970.
13. Vendola KA, Zhou J, Adesanya OO, Weil Sj, bondy CA: Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest 1998;101:2622-2629.
14. Sh Tehrani Nrjad E, Abediasl Z, Rashidi BH, AzimiNekoo E, Shariat M, Amirchaghmaghi E Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate gonadotropins in controlled ovarian hyperstimulation : a prospective, simply randomized, clinical trial. JassistRepord GENET. 2008 Apr 19.
15. Begum MR, Quadir E, Begum A, Begum RA, Begum M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate J obstet Gynecol Res.2006 oct;32(5):502-6.
16. Al Fadhli R; Sylvestre C; Buckett W; Tan SL; Tulandi T A randomized trial of superovulation with two different doses of letrozole fertile steril 2006 85(1):161-4(issn 1556-5653).
17. Badway A, Mosbah A, Tharwat A, Eid M Extended letrozole therapy for ovulation induction in clomiphene resistant women with polycystic ovarian syndrome: a novel protocol fertile steril 2008 Aug 13.
18. Mitwally MF, Bijian MM, Casper RF pregnancy outcome after the use of an aromatase inhibitor for ovarian stimulation Am J obstetGYnecol 2005; 192:381-6.