Original Article

Comparison of the efficacy of letrozole and low-dose gonadotropin combination with clomiphene and low-dose gonadotropin combination as a controlled ovarian stimulation regime prior to intrauterine insemination in patients with unexplained infertility

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ABSTRACT

Objective: To evaluate and compare the effects of letrozole and low-dose gonadotropin combination with clomiphene citrate (CC) and low-dose gonadotropin combination prior to intrauterine insemination (IUI) in patients with unexplained infertility. **Design:** Prospective, randomized, clinical study. **Setting:** Academic tertiary institute. **Patient(s):** A total of 94 patients in the age group of 21-37 years with unexplained infertility were randomized using computer-generated random number table to receive follicle-stimulating hormone (FSH) injection and human menopausal gonadotropin (hMG) injection, along with either letrozole or CC. **Intervention(s):** All the patients received 150 IU of purified urinary FSH on day 2 of the cycle and from day 3 to day 7 of the cycle 5.0 mg/d of letrozole or 100 mg/d of CC were administered; this was followed by administration of 150 IU of hMG on day 9. Ovulation was triggered with human chorionic gonadotropin (hCG) injection (5,000 IU) when the dominant follicle(s) reached 18 mm in diameter. A single IUI was performed 36 h later. The luteal phase was supplemented with micronized progesterone vaginally. **Main Outcome Measure(s):** Pregnancy rates and the incidence of multiple pregnancies were our primary outcome. The secondary outcome included the number of dominant follicles, grade of perifollicular blood flow, endometrial thickness, endometrial blood flow pattern, side effects, and complications. **Result(s):** There were no differences in demographic characteristics between the two groups. Pregnancy occurred in four out of 47 patients (120 cycles) in the letrozole group (pregnancy rate: 8.5% per patient and 3.3% per cycle) and eight out of 47 patients (121 cycles) (pregnancy rate: 17% per patient and 6.6% per cycle) in the CC group; the differences were not statistically significant. None of the regimes resulted in a multiple gestation gestation. The number of follicles per cycle was significantly higher in the CC + gonadotropin group as compared to the letrozole + gonadotropin group (1.77 ± 0.99 vs. 1.39 ± 0.617, $P < 0.001$). There was no statistically significant difference in perifollicular blood flow, endometrial thickness, and endometrial blood flow pattern between the two groups. No side effects were observed in either group. There was one case of ectopic gestation in the CC group.

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Conclusion(s): The use of lower dose of gonadotropins and oral agents together resulted in decreased medication costs, lesser monitoring [ultrasound (USG) visits], and good primary and secondary outcomes. However, more randomized controlled trials are needed to prove the efficacy of one regime over the other.

Keywords: Aromatase inhibitor (AI), clomiphene citrate (CC), controlled ovarian stimulation, follicle-stimulating hormone (FSH), human menopausal gonadotropin (hMG), letrozole, intrauterine insemination (IUI)

INTRODUCTION

Out of all infertility cases, 30% are unexplained.[1] The therapy for unexplained infertility due to the absence of a correctable abnormality is usually empiric.

The proposed treatment regimens include intrauterine insemination (IUI), ovarian stimulation with oral or injectable medications, combination of IUI with ovarian stimulation, and assisted reproductive technologies (ARTs).

The underlying principle for ovarian stimulation in women with unexplained infertility is to augment the probability of pregnancy by increasing the number of oocytes available for fertilization. When used in conjunction with IUI, the likelihood of pregnancy may be further increased by raising the density of motile sperms available to these oocytes. Compared with the natural cycle of IUI, ovarian stimulation may improve the treatment outcome for couples with unexplained infertility.[2] However, there is still a dispute about which regime should be the first choice for ovarian stimulation.

Clomiphene citrate (CC) continues to be the frontline drug for ovarian stimulation. In cases not responding to CC, the traditional option is to administer gonadotropins. Several research groups have observed a higher pregnancy rate with gonadotropin therapy as compared to oral ovarian stimulation agents. The drawbacks of this approach are its high cost (both for the medication and for the extensive monitoring required), risk of potentially life-threatening ovarian hyperstimulation syndrome (OHSS), and most importantly the significant risk of high-order multiple gestation. Therefore, an alternate ovarian stimulation regime that is more economical and is as efficacious as CC would be ideal. Letrozole, a highly selective aromatase inhibitor (AI), has been found to be quite successful in patients with unexplained infertility who do not respond to CC therapy.[3] Both CC and letrozole can be used in combination with gonadotropin for ovarian stimulation.

Gonadotropins used in combination with CC or letrozole decrease the dose required for optimum stimulation and make it more cost-effective. It has been found that ovulation induction with sequential CC — gonadotropins results in a fecundity double that of CC alone and equal to gonadotropins alone or concurrent with clomiphene. This, therefore, reduces the requirement for gonadotropins.[4] Similarly, combining AIs with gonadotropins for controlled ovarian stimulation not only reduces the dose of gonadotropin required for optimal follicle development but also improves the ovarian response to the same in poor respondents. The results of a prospective pilot study have shown that letrozole has a significantly higher pregnancy rate than CC in gonadotropin-combined IUI cycles. These researchers believed that their favorable outcomes could be attributed to a thicker endometrium and a lower level of estradiol (E2).[5]

In controlled ovarian stimulation, gonadotropins are usually used in higher doses and for longer durations.

A prospective study was carried out in our institute in which only a single injection of gonadotropin was used in addition to CC and it showed that minimal stimulation appears to be an effective protocol in cases of unexplained infertility undergoing IUI.[6]

Such stimulation regimes can be of great benefit in our set of population where resources are limited and cost constraints limit the management options.

The present study was undertaken to evaluate the comparative effect of letrozole and low-dose gonadotropin combination with clomiphene and low-dose gonadotropin combination prior to IUI in women with unexplained infertility.

MATERIALS AND METHODS

The cases for the study were recruited from the infertility clinic of the Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. The infertile couples were worked up according to the World Health Organization (WHO) protocol[7] and were thoroughly investigated for the etiological factor for infertility that included semen analysis, hormonal evaluation [serum thyroid-stimulating hormone (TSH) and day 2 serum prolactin], baseline ultrasound (USG) of the pelvis, hysterosalpingogram, and if indicated, tests for ovarian reserve and laparoscopy. A total of 94 women in the age group 21-37 years with unexplained infertility were recruited in the study.

These women were then randomized into two groups according to computer-generated random number table. They, then, received either of the two controlled ovarian stimulation regimes. The medication for ovarian stimulation was started from day 2 of the spontaneous menstrual cycle. In group A, injection of purified urinary follicle-stimulating hormone (FSH) of 150 IU was administered intramuscularly on day 2 and one tablet of 5 mg of letrozole was given daily for 5 days (day 3 to day 7) followed by intramuscular administration of human menopausal gonadotropin (hMG) injection of 150 IU on day 9. In group B, injection of purified urinary FSH of 150 IU was administered intramuscularly on day 2 and one tablet of 100 mg of CC was given daily for 5 days (day 3 to 7) followed by intramuscular administration of hMG of 150 IU on day 9.

In both the groups, follicle monitoring was started using transvaginal ultrasound (TVS) from day 11 till the dominant follicle was 18-20 mm. Then, ovulation was triggered by human chorionic gonadotropin (hCG) injection of 5,000 IU dosage; IUI was done 36 h afterward. Luteal phase support was given in the form of vaginal micronized progesterone. A maximum of three cycles were tried. Those who failed to conceive after three cycles were considered as failures.

Perifollicular blood flow was noted on the day of administration of hCG injection in the first cycle of controlled ovarian stimulation. The dominant follicles (≥18 mm) were taken for the perifollicular blood flow study. The perifollicular blood flow was graded using the modified grading system given by Chui *et al*.[8]

Endometrial thickness and blood flow were assessed on the same day when hCG injection was to be administered in the first cycle of controlled ovarian stimulation. Blood flow was assessed according to the criteria given by Chien *et al*.[9]

The primary outcome was the pregnancy rates and the secondary outcome was the number of dominant follicles, grade of perifollicular blood flow, endometrial thickness, endometrial blood flow patterns, side effects, and complications of either regime observed in their respective groups.

Statistical analysis

Sample size was calculated before the start of the study. The data were analyzed using the statistical package SPSS for windows 16.0 (SPSS, Chicago, Il, USA). Means, standard deviations, medians, and ranges were calculated for descriptive purposes. Comparison of patient characteristics, response to stimulation regime in terms of follicle size, perifollicular blood flow, endometrial thickness, and endometrial blood flow as well as the comparison of parameters in patients who conceived and those who did not were done using chi-square test and Student's *t*-test, as the appropriate tests. *P* values less than 0.05 were considered statistically significant [Tables 1 and 2]. Primary objective, i.e., pregnancy rates in the two groups was compared using chi-square test while the secondary objective that included all the continuous variables were compared using Student's *t*-test and Wilcoxon rank-sum test.

RESULTS

The study comprised 94 women with unexplained infertility who underwent 241 cycles of controlled ovarian stimulation and IUI. In group A (letrozole + gonadotropins), 47 women were recruited who underwent 120 cycles of controlled ovarian stimulation followed by IUI. Out of these women, 35 underwent three cycles, three underwent two cycles, and the remaining nine underwent one cycle. In group B (CC + gonadotropin) also, 47 women were recruited, of whom 35 underwent three cycles, four underwent two cycles, and eight underwent only one cycle. The cause of noncompletion of three cycles of ovarian stimulation was either conception, refusal by the patient, or lost to follow-up.

Pregnancy rate per patient in group A (letrozole + gonadotropin) was 8.5% while in group B (CC + gonadotropin), it was 17.0%. Though the pregnancy rate in group B was double than that seen in group A, the *P* value with respect to the number of pregnancies in the two groups was 0.216 that is statistically not significant. The pregnancy rates per cycle were 3.3% and 6.6% in group A and group B, respectively, (*P* value > 0.05).

The number of follicles per cycle was significantly higher in the CC + gonadotropin group as compared to the letrozole + gonadotropins group. The average number of follicles per cycle in group A was 1.39 ± 0.617 while in group B it was 1.77 ± 0.99 (*P* value < 0.001). In both group A and group B, grade 4 perifollicular blood flow was observed in 22 patients (46.81%). The difference with respect to the grades of perifollicular blood flow was statistically insignificant (*P* value > 0.05).

The mean endometrial thickness in group A (letrozole + gonadotropins) was 8.22 ± 1.28 mm (5.7-13.0 mm) and in group B (CC + gonadotropins), it was 8.15 ± 1.56 mm (5.2-13.0 mm) (*P* value > 0.05). The most common pattern of endometrial blood flow was pattern C. It was observed in 29 (61.7%) and 30 (63.83%) patients in group A and group B, respectively.

There was no significant difference in the number of follicles observed per cycle among the patients who conceived and who did not conceive (1.75 ± 1.05 vs. 1.58 ± 0.845) (*P* value > 0.05). Most of the patients had grade 3 or grade 4 perifollicular blood flow irrespective of the outcome of the cycles. There was no significant difference in the endometrial thickness in the patients who got pregnant and those who did not. Most of the patients had pattern C endometrial blood flow irrespective of whether the cycle resulted in conception or not (*P* value > 0.05). None of the regimes resulted in a higher order gestation or ovarian hyperstimulation. No side effects were observed in either group. There was one case of ectopic gestation in the CC group.

Table 1: Characteristics of the patients

	Demographic characteristics	Group A (*n* = 47)	Group B (*n* = 47)	*P* value
1	Age (years)	29.21±3.23	29.81±3.98	0.42
2	Duration of infertility (years)	4.94±3.01	5.29±3.54	0.62
3	Height (cm)	157.27±6.08	157.09±5.52	0.88
4	Weight (kg)	55.51±11.3	55.04±7.7	0.81
5	Body mass index (kg/m^2)	22.40±4.60	22.33±3.21	0.93

None of the differences were statistically significant (*P* < 0.05)

Table 2: Comparison of the results

	Outcomes (primary and secondary)	Group A (letrozole + gonadotropins)	Group B (CC + gonadotropins)	*P* value
1	Pregnancy rate per cycle	3.3%	6.6%	
2	Pregnancy rate per patient	8.5%	17%	
3	Mean endometrial thickness (mm)	8.22±1.28	8.15±1.56	0.473
4	Average number of follicles per cycle	1.39±0.617	1.78±0.99	0.000*
5	Average follicle size (mm)	18.91±3.5	18.26±2.6	0.060

DISCUSSION

Irrespective of the definition used, the inability to bear a child seriously impacts the psychosocial and emotional lives of couples affected by infertility. A vast proportion of the world's population has no access to medical treatment for infertility and in developing countries, there are great inequalities in the diagnosis and treatment due to limited resources.

In this study, out of 94 women, 12 conceived, eight out of 47 patients (121 cycles) in the CC + gonadotropins group (pregnancy rate in group A: 17% per patient and 6.6% per cycle) and four out of 47 patients in the letrozole + gonadotropins group (pregnancy rate in group B: 8.5% per patient and 3.3% per cycle), the difference being statistically insignificant. This is consistent with the observations of Badawy *et al*. who reported a pregnancy rate of 23.7% with the letrozole + gonadotropin group and 26.2% with the clomiphene + gonadotropin group. However, in their study the gonadotropins were used in a sequential manner in the letrozole group while in the CC group they were used as an overlapping regime.[10] Jee *et al*. also reported comparable pregnancy rates for letrozole (18.2%) and CC (25.9%) in combination with gonadotropins in their prospective pilot study. The study was, however, nonrandomized, with the groups being assigned as per the couple's preferences; also, the couples who were recruited did not exclusively have unexplained infertility.[11] The pregnancy rates observed in both the abovementioned studies were higher than those observed in our study. This may be attributed to the higher dose of gonadotropin used in these studies. The pregnancy rates observed in our study were, however, comparable to those seen in a study by Dhaliwal *et al*. In their study, they compared minimal stimulation with the standard conventional stimulation protocol, along with IUI in patients with unexplained infertility and CC failures. The pregnancy rate observed by them with the minimal stimulation and conventional protocol was 14.63% and 18.75%, respectively.[6] Barroso *et al*. carried out a prospective, randomized, clinical trial in couples with unexplained infertility in which the establishment of pregnancy was a secondary end point owing to the relatively low sample size and statistical power for assessing such outcome. Nevertheless, there were no differences in the clinical pregnancy rates among the groups (23.8% in the letrozole group vs. 20% in the CC group).[12] Mitwally *et al*. also did not find any statistically significant difference in the pregnancy rates achieved with letrozole and CC in combination with gonadotropins (19.6% vs. 16.1%). Their study, however, comprised couples with all kinds of infertility factors.[13] Another study conducted by the same author, however, is in contrast to the findings of the present study. This study was carried out in couples with unexplained infertility to test the hypothesis that the use of the AI letrozole in conjunction with FSH for controlled ovarian stimulation would decrease the dose of gonadotrophins required for controlled ovarian stimulation similar to CC with FSH. They found a higher pregnancy rate with the letrozole + gonadotropins group (22.2%) as compared to the CC + gonadotropins group (11.1%), the difference being statistically significant.[5]

In our study, the average follicular size in group A was 18.91 ± 3.5 mm while in group B, it was 18.26 ± 2.6 mm, the difference between the two groups being statistically insignificant. However, the average number of follicles per cycle was higher in group B (1.78 ± 0.99) as compared to group A (1.39 ± 0.617), the difference between the two being highly significant statistically (P value < 0.001). This is in agreement with the observations made by Badawy *et al*., the follicle number being 4.1 ± 0.46 in the CC group and 2.6± 0.43 in the letrozole group in their study.[10] Jee *et al*. also reported similar findings in their study with significantly lesser number of follicles observed in the letrozole group (3.2 ± 1.7 vs. 5.6 ± 2.4).[11] This is also in agreement with the results of Sh Tehrani *et al*.[14] Their study, which was a prospective randomized trial, recruited 140 patients with unexplained infertility who then received either letrozole or CC + gonadotropin as per randomization. The number of mature follicles (1.8 ± 0.7 vs. 2.46 ± 2.3; P = 0.042) were significantly lower in the letrozole group. This incongruity between the high ovulation rates after CC treatment and a relatively low pregnancy rate may be attributed to the antiestrogenic properties of CC. Barroso *et al*.; however, they reported no significant difference in the mean number of follicles per cycle in their study (2.1 ± 0.9 in letrozole vs. 1.9 ± 0.5 in CC).[12]

We also compared the perifollicular blood flow assessed in the first cycle of controlled ovarian stimulation in each group and it was found that there was no significant difference in perifollicular blood flow in the two groups. Experimental data have demonstrated that perifollicular blood flow assessment is a good marker of oocyte competence.[15,16] However, most of the studies in which perifolicular blood flow assessment has been done are in *in vitro* fertilization IVF-ET cycles. Literature comparing perifollicular blood flow prior to IUI in controlled ovarian stimulation cycles is scarce.

The mean endometrial thickness was comparable in both groups (8.12 ± 1.2 mm in group A vs. 8.15 ± 1.5 mm in group B), the difference being statistically insignificant (P value = 0.765) This finding was consistent with the observation of Badawy *et al*. who concluded the same from their study in which they compared the combination of letrozole and gonadotropins to that of CC and gonadotropins combination. Endometrial thickness, in their study, was 9.1 ± 0.42 mm in the letrozole group while in the CC group, it was 8.9 ± 0.62 mm.[10] One possible explanation is that the combinaton of CC with gonadotropins and the resulting high estrogen and progesterone level neutralize the antiestrogenic action of CC on endometrium. This, however, is in contrast to the results of a prospective study conducted by Barroso *et al*. who reported a significantly higher endometrial thickness with letrozole and gonadotropin combination (9.5 ± 1.5 mm) as compared to CC and gonadotropin combination (7.3 ± 1.1 mm).[12] Similar results were also reported by Sh Tehrani *et al*. who found a statistically significant difference between the endometrial thickness of the two groups; it was higher in the letrozole group as compared to CC and gonadotropin combination (9.7 ± 1.6 mm vs. 7.8 ± 2 mm; P < 0.001).[14] This was in agreement with the previous literature that attributed lower endometrial thickness to the antiestrogenic action of CC and seemed to negate our possible explanation to similar endometrial thickness observed in the two groups observed in our study.

There was no statistically significant difference in the endometrial blood flow pattern observed in the two groups, with majority of the patients (61.7% in group A and 63.8% in group B) having

pattern C blood flow. The importance of endometrial blood flow cannot be overemphasized as it is well known that patients with detected endometrial blood flow have a higher pregnancy and implantation rate. In a study conducted by Wang *et al*., the pregnancy rate and implantation rate of the patients with detected endometrial and subendometrial blood flow were significantly higher than those with only subendometrial blood flow detection or those without detected blood flow, while the miscarriage rate in the patients with detected endometrial and subendometrial blood flow was significantly lower.[17] Akihito *et al*. found that cycles stimulated with CC had reduced endometrial blood flow as compared to natural cycles. Their possible explanation to this was the antiestrogenic action of estrogen that compromises both endometrial thickness and blood flow.[18] There is, however, limited literature on endometrial blood flow in controlled ovarian stimulation cycles. A recent retrospective analysis found that the multiple pregnancy rates were significantly lower in the letrozole + FSH than in the CC + FSH cycles.[13] In our study, however, no multiple gestation was observed. This may be attributed to the low-dose gonadotropins used in spite of the conventional regime where the gonadotropins are administered as guided by the USG findings. This is in agreement to a previous study conducted in our institute by Dhaliwal *et al*. In their study, there was no incidence of multiple gestation in the patients recruited in the minimal stimulation group as compared to two cases (5.16%) observed in patients recruited in the conventional stimulation group. In addition, a single USG visit sufficed for the minimal stimulation group while patients in the conventional group required an average of 3.16 ± 1.50 visits per cycle. The total number of ampoules of hMG required in a cycle differed significantly (2.0 for minimal stimulation vs. 12 ± 5.4 for conventional stimulation). The cost of minimal protocol was even less than one-third of that of the conventional protocol in their study.[6] For majority of the patients in our study too, a single USG visit sufficed and the cost was significantly less as only four ampoules of gonadotropins were required in a cycle.

In the present study, there was one case of ectopic gestation (1.06%). The incidence of ectopic pregnancy, however, is high with controlled ovarian hyperstimulation (COH) + IUI, and varies from 4% to 8%.[19,20]

In our study, the various parameters observed in patients who conceived and in patients who did not conceive were also compared. Average follicle size in the pregnant subjects was 18.54 ± 2.48 mm while in the nonpregnant subjects it was 18.57 ± 3.14, the difference between the two being statistically insignificant (*P* value: 0.75). The mean endometrial thickness in the pregnant subjects was 7.75 ± 1.22 mm and in the nonpregnant subjects it was 8.2 ± 1.42 mm, with no statistically significant difference between the two (*P* value: 0.245). Also, there was no statistically significant difference in the two groups as far as perifollicular blood flow and endometrial blood flow were concerned.

Although use of low-dose gonadotropins yields significantly fewer number of oocytes compared to conventional stimulation, a higher percentage of mature oocytes are produced. Availability of better quality oocytes and more receptive endometrium can assure good outcome even with the use of low-dose gonadotropins. The controlled ovarian stimulation regime used in this study was easy to administer, required less intensive monitoring and fewer medications, with virtually no risk of OHSS and multiple gestation.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Dodson WC, Whitesides DB, Hughes CL Jr, Easley HA 3rd, Haney AF. Superovulation with intrauterine insemination in the treatment of infertility: A possible alternative to gamete intrafallopian transfer and *in vitro* fertilization. Fertil Steril 1987;48:441-5.
2. Verhulst SM, Cohlen BJ, Hughes E, Te Velde E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev 2006;CD001838.
3. Mitwally MF, Casper RF. Use of aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305-9.
4. Dickey RP, Olar TT, Taylor SN, Curole DN, Rye PH. Sequential clomiphene citrate and human menopausal gonadotrophin for ovulation induction: Comparison to clomiphene citrate alone and human menopausal gonadotrophin alone. Hum Reprod 1993;8:56-9.
5. Mitwally MF, Casper RF. Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. Hum Reprod 2003;18:1588-97.
6. Dhaliwal LK, Sialy RK, Gopalan S, Majumdar S. Minimal stimulation protocol for use with intrauterine insemination in the treatment of infertility. J Obstet Gynaecol Res 2002;28:295-9.
7. Rowe PJ, Comhaire FH, Hargreave TB, Mellows HJ. Manual for the investigation and diagnosis of the infertile couple WHO Special Programme of Research, Development and Research Training in Human Reproduction: published in year 1993: study number 78923; p. 7-38.
8. Chui DK, Pugh ND, Walker SM, Gregory L, Shaw RW. Follicular vascularity — The predictive value of transvaginal power Doppler ultrasonography in an *in-vitro* fertilization programme: A preliminary study. Hum Reprod 1997;12:191-6.
9. Chien LW, Au HK, Chen PL, Xiao J, Tzeng CR. Assessment of uterine receptivity by the endometrial-subendometrial blood flow distribution pattern in women undergoing *in vitro* fertilization-embryo transfer. Fertil Steril 2002;78:245-51.
10. Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors combined with gonadotropins for superovulation in women undergoing intrauterine insemination: A prospective randomised trial. J Obstet Gynaecol 2010;30:617-21.
11. Jee BC, Ku SY, Suh CS, Kim KC, Lee WD, Kim SH. Use of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles: A pilot study. Fertil Steril 2006;85:1774-7.
12. Barroso G, Menocal G, Felix H, Rojas-Ruiz JC, Arslan M, Oehninger S. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: A prospective, randomized, blinded clinical trial. Fertil Steril 2006;86:1428-31.
13. Mitwally MF, Biljan MM, Casper RF. Pregnancy outcome after the use of an aromatase inhibitor for ovarian stimulation. Am J Obstet Gynecol 2005;192:381-6.
14. Sh Tehrani Nejad E, Abidiasl Z, Rashidi BH, Azimi Nekoo E, Shariat M, Amirchaghmaghi E. Comparison of the efficacy of aromatase inhibitor letrozole and clomiphen citrate gonadotropins in controlled ovarian hyperstimulation: A prospective, simply randomized, clinical trial. J Assist Reprod Genet 2008;25:187-90.

15. Van Blerkom J. Can the developmental competence of early human embryos be predicted effectively in the clinical IVF laboratory? Hum Reprod 1997;12:1610-4.
16. Nargund G, Bourne T, Doyle P, Parsons J, Cheng W, Campbell S, *et al*. Associations between ultrasound indices of follicular blood flow, oocyte recovery and preimplantation embryo quality. Hum Reprod 1996;11:109-13.
17. Wang L, Qiao J, Li R, Zhen X, Liu Z. Role of endometrial blood flow assessment with color Doppler energy in predicting pregnancy outcome of IVF-ET cycles. Reprod Biol Endocrinol 2010;8:122.
18. Nakai A, Yokota A, Koshino T, Araki T. Assessment of endometrial perfusion with Doppler ultrasound in spontaneous and stimulated menstrual cycles. J Nippon Med Sch 2002;69:328-32.
19. Dodson WC, Haney AF. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of infertility. Fertil Steril 1991;55:457-67.
20. Horvath PM, Bohrer M, Shelden RM, Kemmann E. The relationship of sperm parameters to cycle fecundity in superovulated women undergoing intrauterine insemination. Fertil Steril 1989;52:288-94.