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Early versus late hCG administration to trigger ovulation in mild stimulated IUI cycles: a randomized clinical trial

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ABSTRACT

Objectives: To verify non-inferiority of the clinical pregnancy rate of Early hCG administration (leading follicle sizes within 16.0–16.9 mm in diameter) compared to Late hCG administration (leading follicle sizes within 18.0–18.9 mm in diameter).
Study design: Prospective randomized trial. Six hundred and twelve infertile women candidates for intrauterine insemination (IUI) received HP-hMG 75 IU/day SC from cycle days 4 to 8 and then as per ovarian response. Ovulation was randomly triggered (hCG 5000 IU, IM) when the leading follicle diameter ranged between either 16.0 and 16.9 mm (Early hCG group, $n = 227$) or 18.0 and 18.9 mm (Late hCG group, $n = 207$) and IUI was performed approximately 36 h later.
Results: Whereas population and sperm characteristics were comparable in both groups, the number of follicles $\geq$14 mm in diameter ($P < 0.007$) and serum estradiol levels ($P < 0.001$) on the day of hCG were lower in the Early versus the Late hCG groups. Clinical (11.9% versus 12.1%) and ongoing (11.0% versus 8.6%) pregnancy rates per randomized women were similar in the two groups and statistical non-inferiority of clinical and ongoing pregnancy rates was demonstrated.
Conclusion: These results suggest that hCG administered when the largest follicle size reaches 16.0–16.9 mm leads to similar clinical and ongoing pregnancy rates as when it reaches 18.0–18.9 mm in IUI cycles.

1. Introduction

The adequate appraisal of follicle preparedness for the release of a mature, reproductively competent oocyte constitutes the foremost objective of the monitoring of follicle growth and health, a standard prerequisite of assisted reproductive technologies (ART). Yet, in contrast with the multiple refinements made in both the reliability and the flexibility of drugs used to control final follicle maturation and ovulation during recent years, the ultrasonographic criteria used to determine follicle/oocyte readiness for ovulation triggering remain imprecise.

Over the last two decades, clinical studies aimed at examining the possible relationship between follicle size, maturation, and oocyte readiness for ovulation led to remarkably conflicting results [1–7]. All of them were focused on the fate of oocytes and/or embryos originated from individual follicles at different sizes in patients undergoing in vitro fertilization-embryo transfer (IVF-ET). Although this methodology is contributive, it does not allow definite conclusions to be drawn on the appropriate timing for administering hCG when multiple ovarian follicles are concomitantly developing, especially in non-IVF-ET cycles. Indeed, during controlled ovarian stimulation (COS), numerous follicles at different maturation stages are able to release an oocyte in response to hCG and, therefore, potentially influence the likelihood of pregnancy. Moreover, only scarce and fragmentary data [8–11] are available on the practical consequences of advancing or postponing hCG administration according to the size of the leading follicle, an issue that may contribute to improving the cost-effectiveness and simplicity of these treatments.

Hence, to address this issue, we conducted a prospective randomized study to investigate the possible influence of early versus late hCG administration on pregnancy rates in patients undergoing mild COS for intrauterine insemination (IUI). Our primary objective was to verify the non-inferiority of the clinical pregnancy rate if hCG is administered when the leading follicle

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sizes are within 16.0–16.9 mm or when they are within 18.0–18.9 mm in diameter.

2. Materials and methods

From March 2004 to April 2007 we prospectively investigated infertile women candidates for mild COS and IUI. The study was approved by the pertinent Institutional Review Boards (CPP, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France and AFSSAPS, Saint-Denis, France), and all participants signed an informed consent before inclusion. All patients conformed to the following inclusion criteria: women aged 20–40 years; regular menstrual cycles (28–32 days); infertility from 2 to 5 years; ≤3 previous IUI cycles; normal uterine cavity confirmed by hysterosalpingography and/or hysteroscopy; bilateral tubal patency confirmed by hysterosalpingography or laparoscopy; normal serum FSH and estradiol levels on cycle day 3 ± 1 within 1 year before inclusion; sperm selection test showing at least 10^6 spermatozoa, grade A/B sperm motility >30%, >30% of normal forms, and/or >30% of sperm survival after 24 h or adequate donor sperm. Exclusion criteria were as follows: unilateral or bilateral tubal obstruction; endometriosis grade III or IV; metrorrhagia of unknown origin; present or past malignant, metabolic, or endocrine diseases; cervical infection; positive serology for hepatitis B or C, HIV or syphilis; anti-spermatozoa antibodies; positive sperm culture; ejaculation disorders; alcohol or drug addiction; participation in another clinical trial in the previous month. Finally, after enrolment, exclusion criteria were: presence of a serious adverse effect, possibly due to the treatment; serum estradiol levels >1500 pg/mL; and occurrence of a spontaneous LH surge during COS before the day of hCG administration.

Participants were randomly allocated to receive hCG injection when the mean diameter of the leading follicle ranged from 16.0 to 16.9 mm (Early hCG group) or from 18.0 to 18.9 mm (Late hCG group). Groups of randomization were automatically generated using a centralized telephonic system (Interactive Voice Response System). The study was coordinated by the Reproductive Medicine Unit, Hôpital Antoine Béclère, Clamart, France and conducted by independent clinicians in their own medical office (a hundred of clinicians participated). All participants received precise and standardized instructions and the follicle measurement technique was standardized. Follicle diameters were assessed using transvaginal ultrasound scans by determining the two orthogonal diameters (d1 and d2) at the largest follicle plane with calipers placed at the inner follicle borders. Mean follicle diameter corresponded to (d1 + d2)/2 and results were expressed in millimeters (mm).

For mild COS, women received highly purified human menopausal gonadotropin (HP-hMG, Menopur®, Ferring Pharmaceuticals, Gentilly, France), SC, 75 UI/day from cycle days 4 to 8. Thereafter, dose adjustments were made according to ovarian response until the criteria for hCG administration were met. The daily HP-hMG dose never exceeded 300 IU. Transvaginal ultrasounds were performed at least on cycle days 4 and 9 for follicle measurement and also serum levels of estradiol, progesterone, and LH were verified. For ovulation induction, 5000 IU of hCG, IM, was administered in both groups (Gonadotrophine Chorionique Endo®, Organon SA, Puteaux, France). Approximately 36 h latter, IUI was performed. Sperm was collected on site by masturbation, then evaluated and prepared within 1 h by double centrifugation using standardized protocols. Luteal phase support was obtained with natural micronized progesterone (Estima Gé®, Effik, Bièvres, France), 600 mg/day, by the vaginal route until the pregnancy test (serum ß-hCG measurement), 14 days later. Compliance was assessed by comparing the amount of medication delivered by and returned to investigators.

The primary outcome was the clinical pregnancy rate, defined as the presence of an intrauterine gestational sac with fetal cardiac activity 4 weeks after IUI. Secondary outcomes were ongoing intrauterine pregnancy rate at 10 weeks after IUI and incidence of a premature LH surge before hCG administration (serum LH >10 mIU/mL).

All statistics were performed by an independent group (ICTA-PM, Fontaine-les-Dijon, France), using SAS software (version 8.2, SAS Institute Inc., NC, USA). To assess the equivalence of both methods, a non-inferiority analysis was conducted. Considering estimated clinical pregnancy rate at 12%, a type I error of 0.05, a statistical power of 80%, and a maximum inter-group difference in clinical pregnancy rates of 2.7% with a lower limit of the 95% confidence interval of −8%, 260 patients in each group would be necessary according to the bilateral Dunnett and Gent method. Assuming a likelihood of 30% non-analyzable patients, it would be necessary to include 338 patients in each group. Data are presented as means and standard deviations whenever the normal distribution is confirmed. Qualitative data are described as percentages, and differences between both groups were assessed by Pearson's Chi Square test.

3. Results

A patient flow-chart is depicted in Fig. 1. As shown, 635 patients were randomized to one of the two study groups (Early hCG group, $n = 317$; Late hCG group, $n = 318$). From these, 309 patients from the Early hCG group and 303 from the Late hCG effectively started the ovarian stimulation protocol and were defined as the intention to treat (ITT) population. Finally, 434 patients received hCG according to protocol requirements (Early hCG group, $n = 227$; Late hCG group, $n = 207$), thereby constituting the per-protocol (PP) population. Four patients had cycle cancellation due to excessive follicular growth.

Population characteristics in the Early and Late hCG groups in the PP population are detailed in Table 1. Patients from both groups were similar with regard to baseline characteristics and sperm characteristics. Homogeneity analysis showed that ITT and PP populations were strictly comparable (data not shown).

Data on ovarian response to stimulation in both groups in the PP population are summarized in Table 2. Despite the fact that, in the Early hCG group, follicle size criteria to administer hCG should have been met earlier than in the Late hCG group, both the total HP-hMG dose administered and the cycle day in which hCG was administered were comparable in both groups. However, the number of follicles ≥14 mm in diameter on the day of hCG administration was lower in the Early hCG group as well as the prevalence of ≥3 follicles ≥14 mm. Serum estradiol ($P < 0.001$) but not progesterone ($P = 0.513$) levels were lower on the day of hCG administration in the Early hCG group. Moreover, serum LH levels on the day of hCG administration were lower ($P < 0.03$) in this group.

Clinical outcomes in both ITT and PP populations are presented in Table 3. Clinical pregnancy rates were comparable in the Early and Late hCG groups in both ITT (11.7% and 9.6%, respectively) and PP (11.9% and 12.1%, respectively) populations. Non-inferiority of the clinical pregnancy rate in the Early hCG group as compared to the Late hCG group was demonstrated in both populations ($P < 0.001$ and $P < 0.007$ for ITT and PP populations). Also, in both ITT and PP populations, ongoing pregnancy rates in the Early (11.0% and 11.5%, respectively) and Late hCG groups (8.6% and 10.7%, respectively) were comparable and non-inferiority of the Early hCG group was demonstrated. Finally, the multiple pregnancy rate was not statistically different between groups.

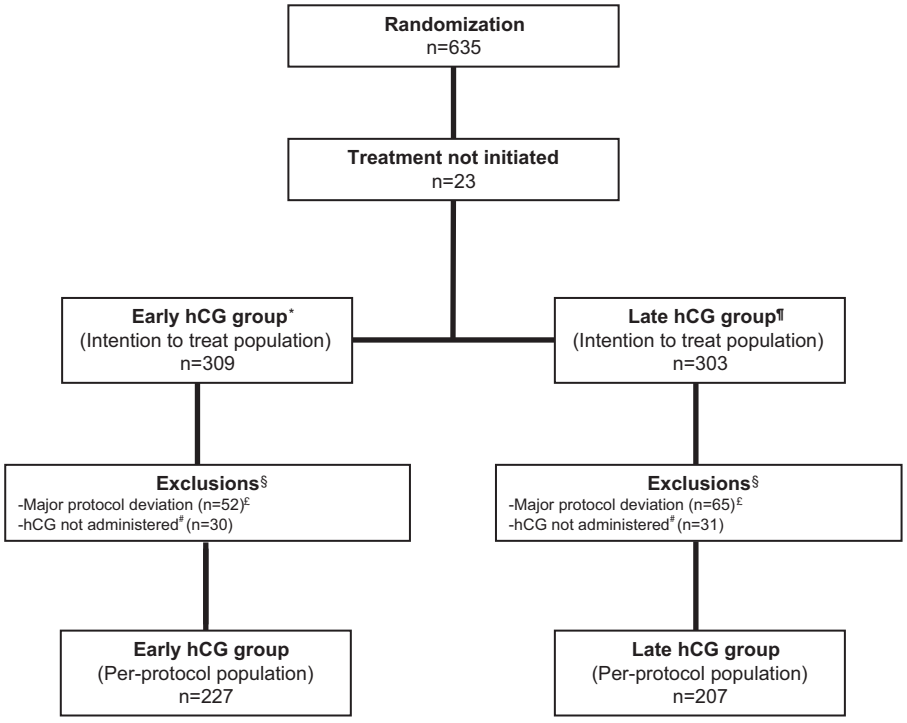

Fig. 1. Patients' flow-chart. *hCG administration when leading follicle reached 16.0–16.9 mm in diameter; ¶hCG administration when leading follicle reached 18.0–18.9 mm in diameter; §each patient could be excluded for more than one reason; £major protocol deviation at inclusion were tubal permeability not assessed (1 patient in the Early hCG group and 2 in the Late hCG group), tubal obstruction (1 patient in the Early hCG group and 2 in the Late hCG group), endometriosis stage III/IV (1 patient in the Late hCG group). Major protocol deviation during COS were another hormonal treatment during COS (2 patients in the Early hCG group and 4 in the Late hCG group), leading follicle size on the hCG day not corresponding to randomization groups (51 patients in the Early hCG group and 60 in the Late hCG group). #Due to insufficient follicular growth, serum estradiol levels >1500 pg/mL, or premature LH peak (serum LH levels ≥10 mUI/mL) before the criteria for hCG administration were met.

4. Comment

The present trial compared the efficacy of two strategies of hCG administration for ovulation triggering in HP-hMG stimulated IUI cycles according to leading follicle sizes. It examined the hypothesis that, in this modality of treatment, preovulatory follicles can release a reproductively competent oocyte at a diameter as small as 16 mm and that prolonging ovarian stimulation further to achieve larger follicle sizes would not improve treatment effectiveness. To reduce the risk of overlapping between follicle size groups and misinterpretation of results, we considered only follicles included into two distinct and specific diameter frames. Non-inferiority analysis demonstrated similar clinical and ongoing pregnancy rates irrespective of whether hCG was administered when the leading follicle was 16.0–16.9 mm or 18.0–18.9 mm in diameter. We also observed that, although the number of follicles > 13 mm was significantly larger in the Late as compared to the Early hCG group, multiple pregnancy rate remained similar in both groups. As the present study was not powered to detect differences in multiple pregnancies rate, it does not allow a conclusion on the possible increase in the prevalence of this complication when hCG injection is postponed.

Another potential inconvenience often associated with the prolonging of COS is the risk of a premature LH surge. Despite the fact that median serum LH levels on the day of hCG administration were slightly increased in the Late hCG group, we failed to observe a significant difference in the incidence of premature LH surges between the two strategies. Besides the clear difference in leading follicle sizes, dissimilarities in the intensity of ovarian response to stimulation, after the 5-day 75 IU/day course, may constitute a possible additional explanation for this phenomenon.

The present study did not aim at specifically assessing the reproductive potential of 16.0–16.9 mm follicles as compared to 18.0–18.9 mm follicles. Given that the coexistence of 18.0–18.9 mm follicles with smaller follicles in the Late hCG group could not be excluded, it is not possible to assert that 18.0–18.9 mm follicles are as healthy as 16.0–16.9 mm follicles, despite the lack of difference observed in pregnancy rates between both groups. Our data simply indicate that cycles with leading follicles measuring 18.0–18.9 mm in diameter are not associated with an increased chance of obtaining a clinical or an ongoing pregnancy as compared to those in which the leading follicles measured 16.0–16.9 mm. In contrast with this, Richmond et al. [11] observed that whereas ≥17 mm follicles are

Table 1
Population characteristics in the Early (16.0–16.9 mm) and Late (18.0–18.9 mm) hCG groups in the PP population.

	Early hCG group (n = 227)	Late hCG group (n = 207)	P
Age (years)	30.9 ± 3.8	31.0 ± 3.8	0.823
Body mass index (Kg/m^2)	22.7 ± 4.2	22.3 ± 3.5	0.846
Duration of infertility (months)	38.3 ± 22.2	38.3 ± 20.0	0.484
Type of infertility (%)			
Primary	68.2	68.5	0.945
Secondary	31.8	31.5	
Etiology of infertility (%)			
Female	26.4	22.2	0.545
Male	21.2	25.2	
Mixte	24.2	27.0	
Unexplained	28.2	25.6	
Endometriosis (stages I or II) (%)	12.3	8.6	0.334
No. of previous IUI (%)			
0	77.0	69.1	0.198
1	10.2	15.9	
2	12.4	13.0	
≥3	0.4	2.0	
Past history of pregnancy after ART (%)	7.5	9.2	0.348

Table 2
Clinical parameters, ovarian response to stimulation and sperm characteristics in the Early (16.0–16.9 mm) and Late (18.0–18.9 mm) hCG groups in the PP population.

	Early hCG group ($n=227$)	Late hCG group ($n=207$)	P
Total HP-hMG dose (IU)	639 ± 282	648 ± 250	0.183
Daily HP-hMG dose (IU)	80.7 ± 14.2	80.4 ± 11.9	0.607
Day of hCG administration (cycle day)	11.7 ± 2.2	11.6 ± 1.9	0.416
No. of follicles ≥14 mm[a,b]	1.56 ± 0.14	1.69 ± 0.07	0.025
Prevalence of follicles ≥14 mm[a]			
1 or 2 (%)	94.7	86.0	0.007
≥3 (%)	5.3	14.0	
Endometrium thickness (mm)[a]	8.7 ± 1.6	9.0 ± 1.6	0.056
Serum estradiol level (pg/mL)[a,b]	338.4 ± 15.22	403.9 ± 14.67	0.001
Serum progesterone level (ng/mL)[a,b]	0.85 ± 0.1	0.68 ± 0.038	0.513
Serum LH level (IU/L)[a,b]	6.10 ± 0.44	6.93 ± 0.48	0.022
Incidence of premature LH surge (%)[c]	13.4	18.1	0.177
Sperm characteristics at IUI			
Volume of inseminate (mL)	0.25 ± 0.11	0.27 ± 0.11	0.346
Inseminated motile sperm count ($\times 10^6$)[d]	8.1 [5.7–10.5]	10.8 [5.0–16.7]	0.830

[a] On the day of hCG administration.
[b] Mean ± standard deviation.
[c] Defined as serum LH levels ≥10 mIU/mL.
[d] Mean [95% CI].

Table 3
IUI clinical outcome in both ITT and PP populations.

	Early hCG group	Late hCG group	Δ (95% CIs)[a]	$P^{\dagger}$	$P^{\ddagger}$
ITT population					
n	309	303	–	–	–
Clinical pregnancies, n (%)[b]	36 (11.7)	29 (9.6)	2.1 (−3.1–7.3)	0.001	0.404
Ongoing pregnancies, n (%)[c]	34 (11.0)	26 (8.6)	2.4 (−2.6–7.4)	0.001	0.314
PP population					
n	227	207	–	–	–
Clinical pregnancies, n (%)[b]	27 (11.9)	25 (12.1)	−0.2 (−6.8–6.4)	0.007	0.953
Ongoing pregnancies, n (%)[c]	26 (11.4)	22 (10.6)	0.8 (−5.5–7.2)	0.002	0.784
No. of multiple pregnancies[d]	2	0	–	–	0.223

[a] Difference in clinical and ongoing pregnancy rates between both groups with 95% continuity-corrected Wald confidence intervals.
[b] Defined as the presence of an intrauterine gestational sac with fetal cardiac activity at 4 weeks after IUI.
[c] Defined as the presence of an ongoing intrauterine pregnancy at 10 weeks after IUI.
[d] Only twin pregnancies were observed.
[†] Non inferiority between both groups demonstrated when $P<0.025$; unilateral χ^2 of Dunnett and Gent.
[‡] Difference between both groups demonstrated when $P<0.05$; bilateral χ^2 of Pearson.

associated with 74% of attributable fetal hearts obtained after IUI, 16 mm or 15 mm follicles are associated only with respectively 31% ($P<0.0001$) and 8.1% ($P<0.0009$) of them, suggesting an improved reproductive potential of ≥17 mm follicles. The inherent difficulties for establishing an accurate link between the follicle diameter and the respective gestational sac in IUI cycles may explain, at least in part, the discrepancy between their results and ours. Some other few, retrospective trials, studying different follicle sizes than those elected in the present investigation and including several thousands of stimulated IUI cycles, alternately showed that pregnancy rates are reduced when follicle diameter is either ≥20 mm or < 15 mm [8], similar when follicle diameters are 15–19 mm or ≥ 20 mm [9], or influenced by the number of ≥12 mm follicles on the day of hCG administration [10].

The possible relationship between follicle size and in vitro fate of the ensuing oocyte in IVF-ET cycles has been addressed in different studies [1–7]. Most of them considered the size of follicles on the day of oocyte retrieval instead of the day of hCG administration. Haines and Emes failed to associate either fertilization rates or embryo morphology with the diameter of the originating follicle [1]. In contrast, Dubey et al. showed higher fertilization rates when the oocyte came from follicles with a mean diameter ≥16 mm than when it came from those ≤14 mm [2]. Similarly, Arnot et al. identified a significant improvement of fertilization and ensuing embryo grading with the progressive increase in the follicle volumes [3]. These results were partially confirmed by Ectors et al., who observed decreased fertilization rates but not embryo morphology when oocytes were originated from <2 mL follicles [4]. In a recent study, both fertilization and embryo morphology were observed to be affected by small follicle size on the day of oocyte retrieval [7]. Others observed a reduction in the ability of an oocyte to generate a pregnancy when it came from <2 mL follicles after conventional IVF-ET, but not IVF-ET with ICSI, as if ICSI could overcome possible insufficiencies of oocytes originated from small follicles [5]. Another extensive analysis of a total of 9 933 oocytes concluded that follicle size and developmental capacity of the oocyte are not closely related and IVF-ET outcome of oocytes/embryos from ≤1 or >1 mL follicles [6]. Together, these data suggest that very small follicle sizes are possibly associated with a decrease in oocyte/embryo functions but the ability of these oocytes to generate a pregnancy remains controversial.

Another interesting issue observed was that, although hCG was deliberately administered earlier in the Early hCG group, both the total HP-hMG dose administered and the duration of stimulation remained similar in both groups. These unexpected results possibly reflect patient-to-patient differences in terms of gonadotropin requirements for COS. Indeed, specific modulation of HP-hMG doses from cycle day 9 onwards could have either slowed or hastened the pace of follicle growth irrespective of the randomization group. This methodological contingency prevented us from

drawing definite conclusions on the presumable cost-effectiveness advantages of early hCG administration.

In conclusion, our results failed to demonstrate a clear benefit in targeting larger leading follicle sizes for hCG administration in mild-stimulated cycles for IUI. By extrapolation, they also suggest that prolonging COS to obtain leading follicles $\geq$18 mm is cost-ineffective and potentially more complex. From a practical standpoint, our present data are reassuring with regard to the possibility of scheduling IUI to convenient days for physicians and patients. Also, they are in line with data from a previous investigation conducted in IVF-ET cycles showing the lack of outcome improvement when hCG administration was postponed for 1 or 2 days [12]. Yet, our study included a selected normo-responder population submitted to precise criteria for hCG administration. The results may be different in other clinical pictures or when different criteria for hCG administration are considered. Further studies focusing on the consequences of administering hCG at different follicle size ranges than those chosen by the present study and in different COS protocols, maybe including new technological refinements for assessing follicle volumes at ultrasound scans, are needed to define the proper ultrasonographic criteria for triggering final follicle maturation and ovulation with hCG in mild stimulated IUI cycles.

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References

[1] Haines CJ, Emes AL. The relationship between follicle diameter, fertilization rate, and microscopic embryo quality. Fertility and Sterility 1991;55:205–7.
[2] Dubey AK, Wang HA, Duffy P, Penzias AS. The correlation between follicular measurements, oocyte morphology, and fertilization rates in an in vitro fertilization program. Fertility and Sterility 1995;64:787–90.
[3] Arnot AM, Vandekerckhove P, DeBono MA, Rutherford AJ. Follicular volume and number during in vitro fertilization: association with oocyte developmental capacity and pregnancy rate. Human Reproduction 1995;10:256–61.
[4] Ectors FJ, Vanderzwalmen P, Van Hoeck J, Nijs M, Verhaegen G, Delvigne A, et al. Relationship of human follicular diameter with oocyte fertilization and development after in vitro fertilization or intracytoplasmic sperm injection. Human Reproduction 1997;12:2002–5.
[5] Bergh C, Broden H, Lundin K, Hamberger L. Comparison of fertilization, cleavage and pregnancy rates of oocytes from large and small follicles. Human Reproduction 1998;13:1912–5.
[6] Salha O, Nugent D, Dada T, Kaufmann S, Levett S, Jenner L, et al. The relationship between follicular fluid aspirate volume and oocyte maturity in in vitro fertilization cycles. Human Reproduction 1998;13:1901–6.
[7] Rosen MP, Shen S, Dobson AT, Rinaudo PF, McCulloch CE, Cedars MI. A quantitative assessment of follicle size on oocyte developmental competence. Fertility and Sterility 2008;90:684–90.
[8] Ghosh C, Buck G, Priore R, Wacktawski-Wende J, Severino M. Follicular response and pregnancy among infertile women undergoing ovulation induction and intrauterine insemination. Fertility and Sterility 2003;80:328–35.
[9] Ibérico G, Vioque J, Ariza N, Lozano JM, Roca M, Llácer J, et al. Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. Fertility and Sterility 2004;81:1308–13.
[10] Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Relationship of follicle numbers and estradiol levels to multiple implantation in 3608 intrauterine insemination cycles. Fertility and Sterility 2001;75:69–78.
[11] Richmond JR, Deshpande N, Lyall H, Yates RW, Fleming R. Follicular diameters in conception cycles with and without multiple pregnancy after stimulated ovulation induction. Human Reproduction 2005;20:756–60.
[12] Tan SL, Balen A, el Hussein E, et al. A prospective randomized study of the optimum timing of human chorionic gonadotropin administration after pituitary desensitization in in vitro fertilization. Fertility and Sterility 1992;57:1259–64.