Original Article

Clinical outcomes following long GnRHa ovarian stimulation with highly purified human menopausal gonadotropin plus rFSH or rFSH in patients undergoing *in vitro* fertilization-embryo transfer: a multi-center randomized controlled trial

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Background: This clinical trial aimed to compare the clinical efficacy of highly purified human menopausal gonadotropin (HP-HMG) plus recombinant human follicle-stimulating hormone (rFSH) versus rFSH alone on controlled ovarian stimulation (COS) *in vitro* fertilization-embryo transfer (IVF-ET).

Methods: A total of 610 women underwent long gonadotropin-releasing hormone (GnRH) agonist protocol for IVF treatment. The subjects were randomized into 2 groups: HP-HMG + rFSH group (n=305) and rFSH group (n=305). The main outcome was the progesterone (P) level on the day of HCG injection.

Results: There was no significant difference in terms of the demographic and baseline characters between the two groups. In rFSH group, the P level on the day of HCG trigger were significantly higher than that of HP-HMG+rFSH group (4.3±2.2 *vs.* 3.8±1.7 nmol/L, P<0.001). The fertilization rate in rFSH group was significantly lower than that of HP-HMG + rFSH group (69.2% *vs.* 73.9%, P<0.001). Simultaneously, the percentage of cycles with fresh embryo transfer in rFSH group was also significantly lower than that of HP-HMG + rFSH group (49.6% *vs.* 57.5%, P=0.007). However, there was no difference in terms of cleavage rate, implantation rate, clinical pregnancy rate and ovarian hyperstimulation syndrome (OHSS) rate between two groups.

Conclusions: The use of combined HP-HMG with FSH may be superior to rFSH alone in stimulating the ovary in normal responders undergoing IVF treatment. Furthermore, the further prospective studies with large sample are still needed to confirm the study.

Keywords: *In vitro* fertilization (IVF); recombinant human follicle-stimulating hormone (rFSH); highly purified human menopausal gonadotropin (HP-HMG); progesterone; pregnancy

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Introduction

Highly purified human menopausal gonadotropin (HP-HMG) and recombinant human follicle-stimulating hormone (rFSH) have been widely used for ovarian stimulation in infertile women undergoing assisted reproductive technology (ART) (1). However, the impact of different gonadotropin preparations on women, who underwent controlled ovarian stimulation (COS) in *in vitro* fertilization-embryo transfer (IVF-ET), is still controversial. Two meta-analyses reported slightly higher live birth rate when using HMG for COS in comparison with rFSH in low-dose GnRH agonist long protocols (2,3).

Luteinizing hormone (LH) plays a role in follicular development and periovulatory, and it involves in ovulation induction, completion of meiosis I, early luteinization and progesterone production. Ovarian steroidogenesis can be driven by activation of a low number (around 1%) of LH receptors (4-6). In a meta-analysis, that including 40 randomized controlled trials, it found significantly more oocytes were retrieved and higher clinical pregnancy rates were observed with rFSH+rLH versus rFSH alone in poor responders (4). In a recent survey (7), the most common form of LH supplementation used in poor ovarian response (POR) was HMG+rFSH, followed by HMG alone, rLH+rFSH and low-dose HCG+rFSH. However, the use of LH supplementation during ovarian stimulation has long been a controversy, and there was study have reported the conflicting evidence (6). The objective of this study was to compare outcomes of HP-HMG+rFSH versus rFSH alone in patients undergoing IVF-ET treatment with antagonist protocol.

Methods

Study population

In this clinical trial, patients, who underwent IVF-ET treatment from 6 reproductive centers of China between May 2014 and December 2015, were recruited. This study complied with the Declaration of Helsinki and Good Clinical Practices (GCP) and was approved by the ethics committees of all participating centers. The study was registered at the Chinese Clinical Trial Registry on 21 April 2014 (http://www.chictr.org.cn/, Unique Identifier: ChiCTR-TRC-14004552).

The inclusion criteria were: (I) aged 20–37 years, BMI 18–24 kg/m^2 and weight 40–80 kg, with regular menstrual cycle (21–35 days); (II) infertility (more than 1 year of free intercourses) with no history of IVF treatment; (III) basal FSH <10 U/L and LH <10 U/L; (IV) normal uterine anatomy confirmed by transvaginal ultrasound examination and in some cases hysterosalpingography and hysteroscopy; (V) no evidence of hydrosalpinx or ovarian cyst or endometrioma; (VI) antral follicle count (AFC) >6; and (VII) signed written informed consent. The exclusion criteria were: (I) had polycystic ovary syndrome, endometriosis of stage III/IV, hyperprolactinemia or other significant systemic disease (endocrine or metabolic abnormalities); (II) use of the following drugs within 1 month prior to randomization: clomiphene citrate, metformin, gonadotropin or GnRH analogues; (III) smokes >10 cigarettes per day within 3 months of recruitment; (IV) history of chemotherapy, radiotherapy, or ovarian surgery.

Study design

This study was a non-blinded, multi-center randomized clinical trial, it was designed to compare the therapeutic efficacy between HP-HMG (Menopur®, Ferring Pharmaceutical, Ltd., Copenhagen, Denmark) plus rFSH (Gonal-F®, Merck Serono, Geneva, Switzerland) and rFSH alone in GnRH agonist long protocols. An independent statistician provided sealed envelopes, containing two randomized groups (1:1 ratio) with a block size 4. The baseline serum estradiol (E2), FSH and LH levels, endometrial thickness and antral follicle diameter were confirmed strong down regulation after treatment with Triptorelin acetate (Decapeptyl®, Ferring Pharmaceutical, Ltd., Copenhagen, Denmark) for 14–20 days, then the randomization were performed. Based on the grouping stipulated inside the envelope, the patients were randomized into HP-HMG+rFSH group and rFSH group.

Sample size calculation

In this study, the P level on the day of HCG administration was as the primary objectives. Calculation of the sample size was based on two binomial proportions (logarithm of odds ratio); the significance level of the two-sided test was set at α=0.05, the power was 80%. Assuming a difference in P level between the 2 therapeutic regimens to be 0.5 nmol/L; the number of subjects needed in each group was 304 patients.

Treatment and monitor

Down regulation was achieved by using Triptorelin acetate

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(0.05 mg/day) 5–7 days before the onset of the next menstrual cycle. The initial dose of gonadotrophin used in HP-HMG+rFSH group was 75 IU HP-HMG + 75 IUrFSH for those weighted ≥60 kg and 75 IU HP-HMG + 150 IU rFSH for those weighted >60 kg, whereas the dose in rFSH group was 150 IU rFSH for those weighted ≤60 kg and 225 IU rFSH for those weighted >60 kg. After 5 days of continuous subcutaneous injection, the P and E2 levels in blood samples were detected. Then, according to the size of the follicle and the result of ovulation stimulation (7–15 follicles available for retrieval) (8), the dosage of rFSH was determined. If there were more than 4 follicles with diameter ≥16 mm or 3 follicles with diameter ≥18 mm (9), then 6500 IU HCG (Ovidrel®, MerckSerono, Geneva, Switzerland) was subcutaneously injected within 1 day to induce final follicular maturation, meanwhile the content of LH, E2 and P levels were measured by the central laboratory method. Oocytes were collected 36 h (±2 h) after administration of HCG. Endometrial thickness was measured on both days of initiation of gonadotrophin therapy and the HCG trigger day.

The morphology of cumulus oocyte was observed during oocyte retrieval operation, then after oocyte retrieved 3 h (±1 h) the assisted fertilization was carried out. After oocyte retrieved 20 h (±1 h), 44 h (±1 h) and 68 h (±1 h), the fertilization and embryo quality were evaluated by an experienced embryologist using an inverted microscope. Fresh embryo transfer was performed on 3 days after fertilization. It was worth noting that patients with ovarian hyper-stimulation syndrome (OHSS) risk or elevation of progesterone on the day of HCG trigger (>8 nmol/L) should be freeze the embryo for transfer in a subsequent cycle. Luteal support was started on the day of oocyte retrieval and performed through intramuscularly administering P (60 mg/day). After embryo transfer 14 days, the blood samples were obtained for HCG measurement to confirm whether pregnancy. If the pregnancy test was positive, ultrasound examination could be offered 2 weeks later to confirm the ability and location of pregnancy.

Outcome

Clinical pregnancy was defined as the presence of one or more gestational sacs detected through ultrasound scan 4–5 weeks after embryo transfer. Biochemical pregnancy was defined as plasma HCG of >10 IU/L 14 days after embryo transfer, with no subsequent evidence of any intrauterine gestational sac on ultrasonography. The primary outcomes were the P levels on the day of HCG injection. The secondary outcomes include the levels of E2, LH; follicle number and endometrial thickness on the day of HCG injection; the number of oocytes retrieved per cycle initiated; fertilization rate; cleavage rate; implantation rate; rate of moderate/severe OHSS; cycles with fresh embryo transfer and clinical pregnancy.

Statistical analysis

SPSS17.0 software was used for statistical analysis of data obtained in this study; the results were expressed as mean ± standard deviation (SD) or proportion; *t*-test and chi-square test were used for comparison between groups. P<0.05 was considered statistically significant.

Results

Baseline characteristics

In this study, a total of 955 women were assessed for eligibility. Finally, after administration of Triptorelin (0.05 mg/day) for down-regulation therapy, 610 patients were randomized into two groups: HP-HMG+rFSH group (n=305) received HP-HMG+rFSH and rFSH group (n=305) received rFSH (*Figure 1*). Baseline demographic characteristics and hormone level at the beginning of ovulation induction therapy were presented in *Table 1*, there was no statistically significant differences between two groups (all P>0.05).

Treatment outcome

The clinical outcomes of the two groups were compared in *Table 2*. In the rFSH group, the P level on the day of HCG trigger was significantly higher than HP-hMG+rFSH group (4.3±2.2 *vs.* 3.8±1.7 nmol/L, P<0.001). The percentage of patients who with progesterone at the end of stimulation >7 nmol/L was also higher in the rFSH group, compared with HP-hMG+rFSH group (11.1% *vs.* 5.6%, P=0.013). The number of oocytes retrieved in rFSH group was significantly higher than HP-hMG+rFSH group (12.9±5.6 *vs.* 11.9±6.0, P<0.05). On the contrary, the fertilization rate in the rFSH group was significantly lower than HP-hMG+rFSH group (69.2% *vs.* 73.9%, P<0.001). Simultaneously, the percentage of cycles with fresh embryo transfer in rFSH group was significantly lower than HP-hMG+rFSH group (49.6% *vs.* 57.5%, P=0.007).

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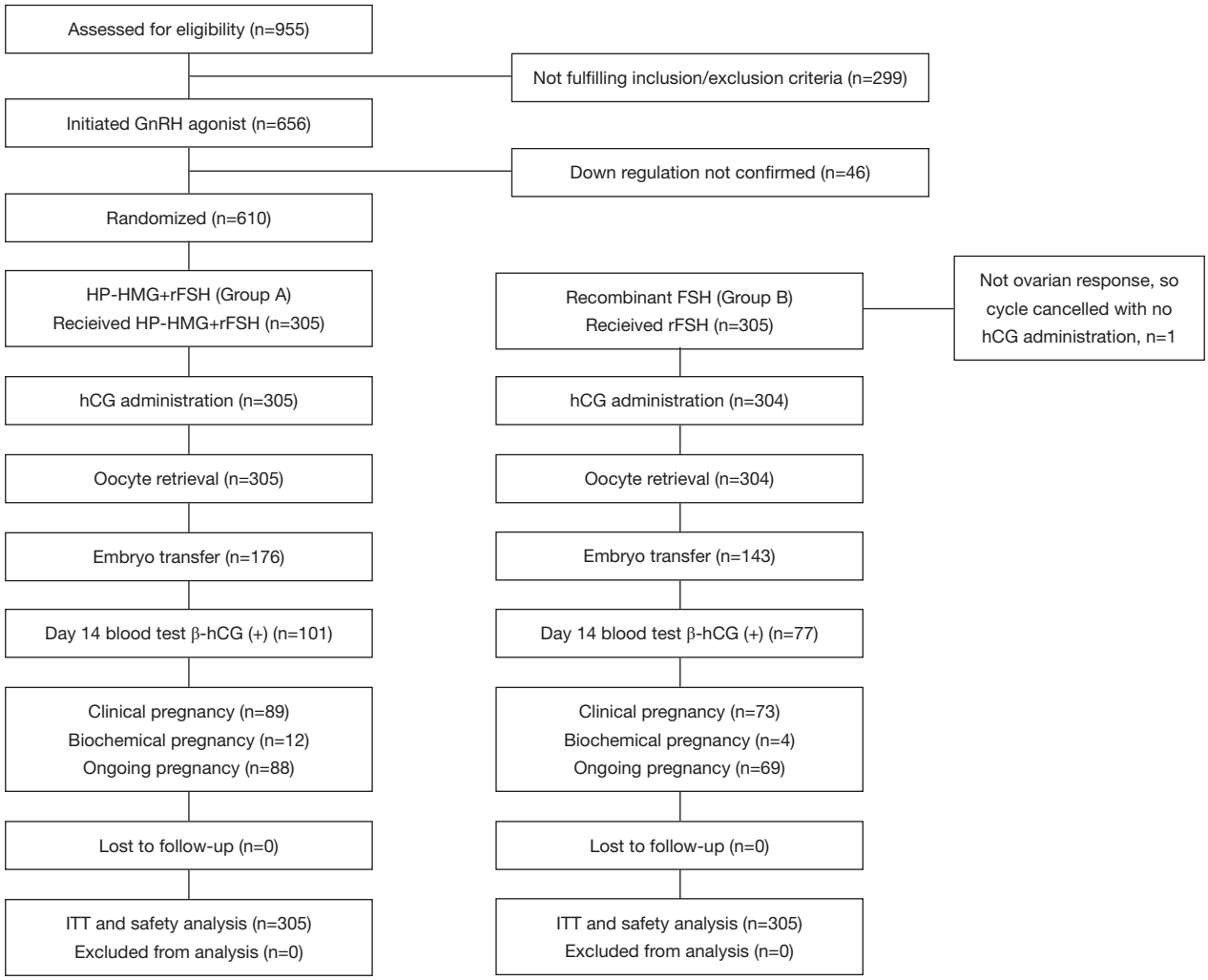

Figure 1 Study flow chart and disposition of patients by study visit. ITT, intention-to-treat population.

Table 1 Demographic and baseline characteristics between two groups

Characteristics	HP-HMG + rFSH (n=305)	rFSH (n=305)	P value
Age (years)	28.7±3.6	28.3±3.5	0.090
Weight (kg)	54.6±5.6	54.5±5.6	0.982
BMI (kg/m^2)	21.1±2.1	21.1±1.8	0.981
Primary infertility (n, %)	179 (58.7)	188 (61.6)	0.457
Duration of infertility (years)	3.4±2.6	3.4±2.3	0.910
Duration of GnRH agonist before start of stimulation (days)	14.3±1.2	14.4±1.6	0.209
Antral follicles count on day 1	15.1±4.8	14.9±5.0	0.635
FSH on day 1 (IU/L)	3.9±1.1	3.9±1.1	0.925
LH on day 1 (IU/L)	2.1±1.0	2.2±0.9	0.802
E2 on day 1 (pmol/L)	89.7±54.8	91.2±50.3	0.573
Progesterone on day 1 (nmol/L)	1.7±1.3	1.8±1.4	NS

Day 1 refers to day 1 of stimulation. NS, no significant.

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Table 2 Clinical parameters between HP-hMG+rFSH and rFSH groups

Parameters	HP-HMG + rFSH (n=305)	rFSH (n=305)	P value
Progesterone (nmol/L), day of HCG	3.8±1.7	4.3±2.2	<0.001*
Patients with progesterone at the end of stimulation >7 nmol/L	5.6% (17/305)	11.1% (34/305)	0.013*
E2 (pmol/L), day of HCG	16,962.0±7,959.6	17,146.4±6,327.3	0.752
LH (IU/L), day of HCG	2.4±1.3	2.3±1.1	0.204
Follicle number, day of HCG*, total	11.9±6.0	12.9±5.6	<0.05*
≥14 mm	11.9±4.5	12.2±5.0	0.413
≥18 mm	5.8±3.7	6.1±3.6	0.311
Endometrial thickness (mm), day of HCG	11.7±2.6	11.9±6.4	0.476
Duration of ovarian stimulation (days)	10.2±1.7	9.9±1.4	0.004*
Total dose (IU) of FSH used	1,740.8±460.0	1,593.1±367.4	<0.05*
Oocytes retrieved per cycle initiated	12.3±6.4	12.9±5.8	0.198
MII oocytes per cycle initiated	10.6±5.7	11.4±5.2	0.074
Fertilization rate (%)	73.9% (2,685/3,635)	69.2% (2,715/3,923)	<0.001*
Cleavage rate (%)	97.2% (2,611/2,685)	97.2% (2,640/2,715)	0.989
Cycles with fresh ET (%)	57.7% (176/305)	46.9% (143/305)	0.007*
Cycle without fresh ET, all cases (%)	42.3% (129/305)	53.1% (162/305)	
A. OHSS risk (E2 >18,000 pmol/L or oocytes retrieved >15, %)	34.8% (106/305)	43.2% (132/305)	0.031*
B. high P (P>8 nmol/L, %) (check)	2.0% (6/305)	4.9% (15/305)	0.046*
C. no viable embryo (%)	3.3% (10/305)	3.0% (9/305)	0.816
D. other reasons (%)	2.3% (7/305)	2.0% (6/305)	0.779
Total cleavage embryos produced per cycle initiated	8.6±5.3	8.8±4.9	0.763
Cleavage embryos transferred in fresh ET	1.8±0.4	1.8±0.3	0.580
Biochemical pregnancy/fresh embryo transfer (%)	6.8% (12/176)	2.8% (4/143)	0.102
Clinical pregnancy/fresh embryo transfer (%)	50.1% (89/176)	51.0% (73/143)	0.932
Clinical pregnancy per cycle initiated (%)	29.2% (89/305)	23.9% (73/305)	0.142
Twin pregnancy rate	43.9% (39/89)	24.7% (18/73)	0.011*
Implantation rate (%)	39.8% (128/322)	34.5% (91/264)	0.189
Embryos frozen per cycle initiated	4.1±2.6	4.7±3.4	0.104
Rate of moderate/severe OHSS (%)	3.3% (10/305)	3.6% (11/305)	0.824

*, P<0.05. OHSS, ovarian hyper-stimulation syndrome.

However, there was no significant difference in the implantation and clinical pregnancy rate between the two groups.

Discussion

Many studies have reported that the high P level on the day of HCG administration on endometrial receptivity may reduce implantation rate and pregnancy rate (10-13). In this study, we found that there was no difference of elevated P level on day of HCG on implantation rate between two groups. There were two possible explanations as following. Firstly, in our study, based on the recommendation of

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earlier reports, we have frozen all embryos for later transfer in women with high P level on the day of HCG administration. Such a policy would avoid the replacement of (fresh) embryos in cycles with a lower chance of successful consequent upon the high progesterone. Secondly, the number of fresh embryo cycles in our study was relatively small (176 *vs.* 143).

Recently, self-injecting pen type of rFSH has been widely used and it has been shown to improve the patient's convenience (14). In comparison with daily administration of short-acting GnRHa, a single administration of long-acting GnRHa can append these advantages by reducing the number of injections in controlled ovarian hyperstimulation (COH) (15). In the long protocol, the combination of long-acting GnRHa with self-injecting pen type rFSH can reduce the number and the cost of hospital visits to have an injection of GnRHa and gonadotrophins. Taken together, a single administration of long-acting GnRHa in combination with self-injecting pen type of rFSH can significantly improve the patient's convenience and comfort. In women receiving rFSH alone, the number of follicles retrieved was significantly higher than rFSH+HP-HMG group, which was consistent with previous studies (16). One possible explanation for the greater number of oocytes retrieved in the rFSH group was the greater potency of rFSH compared HMG. Furthermore, several previous reports have suggested that 75 units of HMG were equivalent to 56 units FSH activity (17). Nevertheless, the increasing number of oocytes in rFSH group did not translate into an increasing number of embryos produced. On the contrary, the number of embryos produced in the two groups was similar, because the higher number of oocytes retrieved in the rFSH group was offset by a lower fertilization rate. The above findings were consistent with a previous report, that the LH supplementation might reduce the number of oocyte retrieved, while improve quality of oocyte (18).

OHSS is one of the severe, occasionally lethal iatrogenic conditions of IVF in COH process (19). Besides the relationship with the individual difference, the incidence of OHSS is mainly correlated with multiple-follicle development and high E2 level (9). In our study, we found that the proportion of cases considered as high risk for development of OHSS in the rFSH group was significantly higher than that of the rFSH+HP-HMG group. Previous study reported that the addition of LH to ovarian stimulation protocol in IVF could reduce the OHSS risk (20), due to LH was able to reduce the recruitment of small follicles in early follicular phase (21), increase the development of large follicles in late follicular phase, reduce the number of oocytes retrieved, and thus decrease the incidence of OHSS. In our study, some measures including freezing all embryos for later replacement and dextran infusion were taken to reduce the occurrence of OHSS in women considered as high risk. In this study, the rate of moderate/severe OHSS in the rFSH group was similar to the rFSH + HP-HMG group.

Several controversies exist in relation to the role of LH supplementation during ovarian stimulation. Previously, some studies compared rLH+rFSH with rFSH alone (22), some compared HMG to rFSH alone (23), and some compared HCG+rFSH with rFSH alone (24), all showed inconsistent results. A systematic review and meta-analysis has demonstrated that rLH supplementation did not increase ongoing pregnancy rate, however it could reduce the amount of rFSH required and the oestradiol level was higher on the day of HCG administration in the LH supplemented group than the rFSH alone group (25). Another recent systematic review and meta-analysis found the more significant oocytes were retrieved and the higher clinical pregnancy rates were observed with rFSH plus rLH versus rFSH alone in poor responders (4), which seem to support that LH supplementation is beneficial to PORs. Furthermore, the role of LH supplementation in normal responders, who underwent long GnRHa protocol for IVF-ET, remains controversial. Some investigators reported that LH supplementation could increase the pregnancy rate and reduce OHSS rate (26), but other investigators found that the addition of LH to FSH did not improve clinical outcomes in normal responders (27). There were several reasons for the different observations. Firstly, the dose of LH used in the various studies was not standardized. Secondly, the ratio of LH to FSH appeared to have significant impact on the outcome, and some investigators have reported that the optimal ratio of LH to FSH was around 1:2 (28), which was also taken in our study.

Conclusions

In conclusion, the use of combined HP-HMG with FSH may be superior to rFSH alone in stimulating the ovary in normal responders undergoing IVF treatment. Furthermore, the further prospective studies with large sample are still needed to confirm the study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study complied with the Declaration of Helsinki and Good Clinical Practices (GCP) and was approved by the ethics committees of all participating centers.

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