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ARTICLE

Outcomes after early or midfollicular phase LH supplementation in previous inadequate responders

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Abstract Second cycle outcomes of 75 patients who had previous inadequate ovarian response with recombinant FSH (rFSH)-only ovarian stimulation during gonadotrophin-releasing hormone analogue (GnRHa) down-regulated cycles were evaluated retrospectively. In these second cycles, both rFSH and human menopausal gonadotrophin (HMG) in GnRHa long down-regulation were given to all patients, HMG initiated either on day 1 (group A, $n = 37$) or day 5–6 of the ovarian stimulation (group B, $n = 38$). Total HMG dose was higher (1198 ± 514 IU versus 726 ± 469 IU; $P < 0.001$), cumulative rFSH consumption was lower (1823 ± 804 IU versus 2863 ± 1393 IU; $P = 0.001$) and duration of stimulation was shorter (8.94 ± 1.15 days versus 10.37 ± 1.80 days; $P < 0.001$) in group A than in group B. No significant differences were found regarding fertilization, implantation or pregnancy rates and embryo quality between the groups. Further analysis by supplementary HMG dose (75 IU versus 150 IU) revealed that total gonadotrophin and HMG consumption was lower in 75 IU-supplemented subgroups. Notably, pregnancy rate was higher in patients where 75 IU HMG was supplemented on day 5–6 of ovarian stimulation, which deserves further evaluation.

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KEYWORDS: HMG, ICSI, luteal GnRH agonist protocol, rFSH, suboptimal ovarian response

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Introduction

According to the two-cell two-gonadotrophin theory, both FSH and LH are crucial for the regulation of ovarian follicular development and maturation, as well as the production of ovarian steroids (Fevold, 1941; Greep et al., 1942). The concept that threshold concentrations for FSH and LH are needed to achieve folliculogenesis and steroidogenesis and the effects by which inappropriately timed and/or abundant secretion of LH leads follicles into atresia have now been clinically documented (Hillier, 1994; McNatty et al., 1975).

It is well accepted that, in patients with hypogonadotrophic hypogonadism who have no endogenous FSH and LH activity, FSH-only ovarian stimulation does not result in a sufficient follicle growth and production of good-quality oocytes. Although a large number of studies are available, the issue of both LH supplementation and endogenous LH concentrations in the gonadotrophin-releasing hormone analogue (GnRHa) long protocol in normogonadotrophic women still remains controversial (Balasch et al., 2001; Esposito et al., 2001; Fleming et al., 1998; Humaidan et al., 2002; Westergaard et al., 2000). There is not an unequivocal LH cut-off that is able to identify the subgroup of women requiring exogenous LH supplementation. As the concentration of immunoreactive LH seems not to be related with the effect of bioactive LH, no consensus has been reached regarding the definition of an optimal LH range during ovarian stimulation (Huhtaniemi et al., 1999; Jiang et al., 1999; Ropelato et al., 1999). However, recent studies indicate that some subgroups of normogonadotrophic patients indeed seem to gain benefit from the addition of LH activity, such as patients over 35 years of age and those with an initial low or inadequate response to rFSH (De Placido et al., 2005; Humaidan et al., 2004; Marrs et al., 2004). The current study aimed to investigate the clinical effect of initiation day of human menopausal gonadotrophin (HMG) supplementation to rFSH on cycle outcome in patients with inadequate response to previous rFSH-only ovarian stimulation in GnRHa down-regulated intracytoplasmic sperm injection (ICSI) cycles.

Materials and methods

Patient population

In total, 75 patients treated at the IVF Unit of the Ankara University between October 2006 and April 2008 were enrolled in this study. The study population was comprised of a subset of normogonadotrophic women who had inadequate ovarian response to previous rFSH-only ovarian stimulation after a standard luteal-phase GnRHa down-regulation. In this retrospectively designed controlled study, allocation was made from patients who underwent ovarian stimulation during the study period according to the inclusion and exclusion criteria (**Figure 1**). Mainly two groups were allocated according to HMG-supplementation initiation day; group A was comprised of 37 patients who received rFSH plus HMG from day 1 of the ovarian stimulation until human chorionic gonadotrophin (HCG) administration, group B was comprised of 38 patients who received rFSH from day 1 of the stimulation, then HMG added on day 5–6 of stimulation until HCG administration. Thereafter, to assess whether daily dose of HMG supplementation has any effect on cycle and stimulation outcomes, both groups A and B were further analysed by two different fixed HMG supplementation doses: 75 IU/day (groups A1 and B1) and 150 IU/day (groups A2 and B2).

Briefly, inclusion criteria for study enrolment were as follows: patient age $\leq$38 years, having a normal menstrual cycle ranging between 21 and 35 days, normal basal serum concentrations of FSH and oestradiol and a normal basal ultrasonographic evaluation. Patients with polycystic ovarian syndrome, known poor responders and those having any endocrine abnormality including hyperprolactinaemia were excluded. Institutional review board approval was provided for the study (IRB approval 132-3783).

Ovarian stimulation

All enrolled patients underwent a standard GnRHa down-regulation protocol with leuprolide acetate 1 mg/daily (Lucrin, Abbott, Turkey), and used a combination of rFSH (Gonal-F, Merck Serono, Germany or Puregon, Organon, Turkey) and HMG (Menogon, Ferring, Italy). Following pituitary down-regulation, leuprolide acetate dose was decreased to 0.5 mg/day and maintained until the day of HCG (Pregnyl, Organon) administration. The starting dose of rFSH was between 225 and 300 IU/day, which was individually adjusted according to body mass index, previous response to ovarian stimulation and basal evaluation including hormone measurement and antral follicle counts. In both groups HMG supplementation remained constant throughout ovarian stimulation where daily dose was either 75 IU/day (in subgroups A1 and B1) or 150 IU/day (in subgroups A2 and B2) according to the treating physician's preference. Ovulation was induced by 10,000 IU of HCG i.m. when at least three follicles with a mean diameter of $>$17 mm were observed. Oocyte retrieval was performed under transvaginal ultrasound guidance at 35.5 h after HCG injection. Embryo transfer was performed on day 2 or 3 using a Swemed catheter (Vitrolife, Kungsbacka, Sweden) by experienced physicians (MS, CA). All patients received luteal-phase progesterone supplementation in the form of vaginal gel once daily (Crinone 8%, Merck Serono). Following serum βHCG assessment on day 12 after embryo transfer, clinical pregnancy was determined by demonstration of fetal cardiac activity at week 6 of gestation.

Statistical analysis

All statistical analyses were performed with Statistical Package for Social Sciences version 11.5 (SPSS, USA). Whether the continuous variables were normally distributed or not was determined by using Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), where applicable. Categorical data were presented as number of cases and as percentages. The differences between groups (group A and B) and subgroups allocated according to daily HMG-supplementation dose in both groups (subgroup A1, A2, B1 and B2), regarding the normally distributed data were tested by

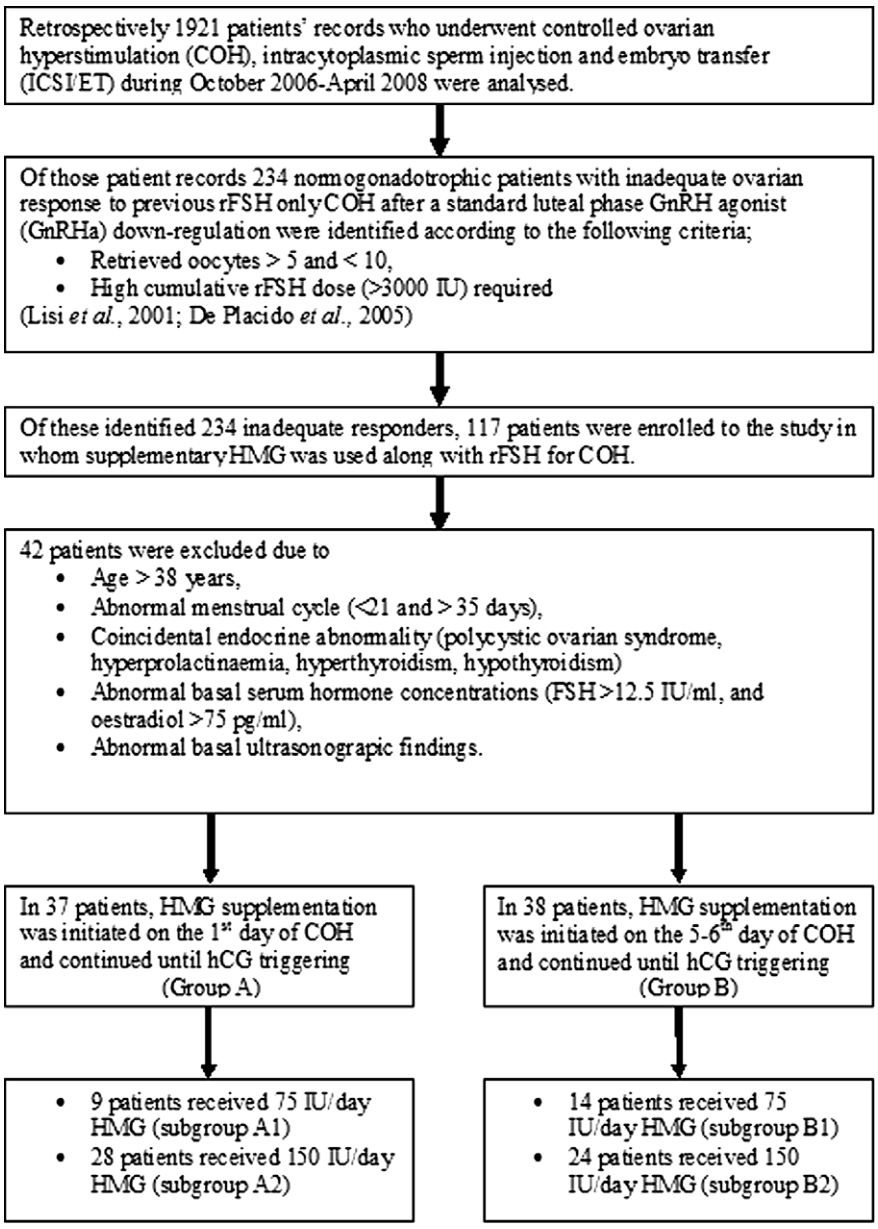


Figure 1 Consort diagram of the patients enrolled in the study.

Student's *t*-test and non-normally distributed data were evaluated by Mann–Whitney *U*-test. Fisher's exact test and Pearson chi-squared test was applied for statistical contingency analysis and categorical comparisons. A *P*-value less than 0.05 was considered as statistically significant.

Results

There were no statistically significant differences between group A and B with regard to patient characteristics (Table 1). When demographic data and patient characteristics were further analysed according to allocated subgroups, the subgroups were found unmatched with respect to difference in mean age, duration of infertility and day-3 serum FSH concentrations. In both subgroups A1 and B1 (75 IU/day HMG), the mean age was younger and the mean duration of infertility was shorter compared with subgroups A2 and B2 (150 IU/day HMG) (data not shown, $P < 0.05$). However, there was not any difference in mean age and duration of infertility between subgroup A1 and B1, as well as between subgroup A2 and B2 (data not shown). With respect to basal evaluation, only mean day-3 serum FSH concentration was found to be statistically lower in subgroup A1 (75 IU/day HMG) than all other subgroups (data not shown, $P < 0.05$). The previous ICSI/embryo transfer cycle outcome and embryology data of the enrolled patients are given in Table 2.

Comparison of the previous and HMG-supplemented cycle outcomes

The cycle outcomes of rFSH-only ovarian stimulation and HMG-supplemented cycles are shown in Table 2. The mean days of ovarian stimulation in the rFSH-only cycle was longer

Table 1 Demographic characteristics of the study groups including basal assessment.

Parameter	*Group A (n = 37)*	*Group B (n = 38)*
Age (years)	32.94 ± 3.56	32.13 ± 4.51
BMI (kg/m^2)	25.15 ± 5.04	26.17 ± 5.06
Duration of infertility (years)	8.81 ± 4.37	8.08 ± 5.33
Antral follicle count	6.8 ± 1.9	7.1 ± 1.1
Day-3 FSH (IU/ml)	7.14 ± 2.57	7.50 ± 1.95
Day-3 oestradiol (pg/ml)	52.35 ± 26.90	46.98 ± 21.13
Infertility cause		
Male factor	22 (59.5)	23 (60.5)
Unexplained	15 (40.5)	15 (39.5)

Group A = HMG initiated on day 1; Group B = HMG initiated on day 5–6.
Values given as mean ± SD or number (%).
There were no statistically significant differences between the groups.
BMI = body mass index.

Table 2 Ovarian stimulation and cycle outcomes of the enrolled patients in previous and supplemented ICSI/embryo transfer cycles.

Parameter	*Previous cycles*	*HMG-supplemented cycles*	
	Groups A and B (n = 75)	*Group A (n = 37)*	*Group B (n = 38)*
Duration of stimulation (days)	9.64 ± 1.69[a,b]	8.94 ± 1.15[a,c]	10.37 ± 1.80[b,c]
Total rFSH dose (IU)	3930 ± 1776[d,e]	1823 ± 804[d,c]	2863 ± 1393[e,c]
Total HMG dose (IU)	–	1198 ± 514[c]	726 ± 469[c]
Total gonadotrophin dose (IU)	3930 ± 1776[d]	3020 ± 1112[d]	3573 ± 1503
Oestradiol concentration on HCG day (pg/ml)	2119 ± 1022[d]	2726 ± 1063[d,c]	2002 ± 1119[c]
Endometrial thickness on HCG day (mm)	10.5 ± 1.9	11.15 ± 2.63	10.87 ± 2.35
Follicles ≥14 mm on HCG day (*n*)	9.7 ± 3.5	9.75 ± 4.19	8.92 ± 4.14
Diameter of leading follicle (mm)	18.7 ± 1.6	18.96 ± 2.13	19.07 ± 1.86
Oocytes retrieved (*n*)	7.8 ± 2.2[d]	12.27 ± 7.41[d]	9.78 ± 5.96
Mature (MII) oocytes (*n*)	6.2 ± 2.1[a,b]	9.59 ± 6.76[a]	8.10 ± 4.71[b]
2PN embryos (*n*)	4.3 ± 2	5.66 ± 4.91	4.63 ± 3.69
Cleavage-stage embryos (*n*)	3.8 ± 1.8[a]	5.33 ± 3.83[a]	4.52 ± 3.49
Embryos transferred (*n*)	3.1 ± 1.1	3.23 ± 1.04	3.15 ± 1.17
Grade A embryos%	73.5	75.3	83.3
Fertilization rate%	66.12	66.5	55.6

Group A = HMG initiated on day 1; Group B = HMG initiated on day 5–6.
Values given as mean ± SD or number (%).
HCG = human chorionic gonadotrophin; MII = metaphase II; PN = pronucleate; rFSH = recombinant FSH.
[a] $P < 0.05$ between the previous cycle outcomes and the HMG-supplemented cycle outcomes of group A.
[b] $P < 0.05$ between the previous cycle outcomes and the HMG-supplemented cycle outcomes of group B.
[c] $P < 0.001$ between the HMG-supplemented cycle outcomes of group A and group B.
[d] $P < 0.001$ between the previous cycle outcomes and the HMG-supplemented cycle outcomes of group A.
[e] $P < 0.001$ between the previous cycle outcomes and the HMG-supplemented cycle outcomes of group B.

than mean duration of ovarian stimulation in the HMG-supplemented cycle of group A patients, whereas it was shorter than in the HMG-supplemented cycle of group B patients (**Table 2**, $P < 0.05$). The total gonadotrophin consumption in the preceding cycle was significantly higher than that in HMG-supplemented cycles in group A (**Table 2**, $P < 0.05$), whereas it was similar in the preceding and HMG-supplemented cycles in group B. With respect to stimulation outcome, only the mean peak serum oestradiol concentration was significantly lower in the preceding cycle than in HMG-supplemented cycle of group A (**Table 2**, $P < 0.001$). Regarding embryology data, only the mean number of retrieved oocytes, metaphase II oocytes and cleavage-stage embryos were favourable in HMG-supplemented cycle in group A (**Table 2**; retrieved oocytes $P < 0.05$, cleavage-stage embryos and MII oocytes $P < 0.001$).

Comparison of groups A versus B

When stimulation and cycle outcomes in the HMG-supplemented cycles are compared, except for higher mean oest-

radiol concentrations in group A, all other stimulation parameters were similar in group A and group B (Table 2). The total dose of HMG was significantly higher, however, the total rFSH dose was lower in group A than in group B (Table 2; $P < 0.001$). Although cumulative gonadotrophin consumption was similar, duration of stimulation was shorter in group A than in group B (Table 2; $P < 0.001$). Although the clinical pregnancy rate per embryo transfer was higher in group B patients, the difference was not statistically significant (21.6% [8/37] and 28.9% [11/38] in groups A and B, respectively).

Comparison of subgroups according to supplementary daily dose of HMG

This study further analysed the impact of different doses of HMG, 75 IU (A1 and B1) and 150 IU (A2 and B2), on both stimulation outcome and IVF success. The stimulation duration was longer in subgroup B2 compared with subgroups A1 and A2 (Table 3; both $P < 0.001$). In both group A and B, total gonadotrophin and HMG consumption were higher in patients receiving 150 IU/day HMG than in those receiving 75 IU/day HMG (Table 3; $P < 0.05$ and $P < 0.001$). When 150 IU/day HMG-supplemented subgroups were compared, mean total rFSH ($P < 0.001$) was higher and mean total HMG was lower in subgroup B2 than in subgroup A2 (Table 3). Total rFSH and cumulative gonadotrophin consumption were lower, whereas total HMG consumption was higher in subgroup A1 than in subgroup B1 (Table 3; $P < 0.001$ and $P < 0.05$). With respect to ovarian stimulation outcome parameters, except for peak serum oestradiol that was only found lower in group B2 compared with group A2 (Table 3, $P < 0.05$), all other parameters were similar between the subgroups.

No difference was found in embryology data between the groups and subgroups (Table 4). The clinical pregnancy rate per embryo transfer was statistically higher in subgroup B1 compared with subgroups A2 and B2 (Table 4; both $P < 0.05$). The implantation and pregnancy rates were reanalysed after redistribution of the data according to treating physician, and no difference was observed. No cases of ovarian hyperstimulation syndrome were observed in any of the groups.

Discussion

The current study showed that duration of stimulation and total dose of rFSH can be reduced with early-phase LH supplementation compared with mid-phase supplementation, without any beneficial effect on IVF success in GnRHa down-regulated patients with previous inadequate ovarian response. Moreover, with regards to the daily dose of LH supplementation, 75 IU/day LH supplementation seemed to be favourable than 150 IU/day LH supplementation in respect of total HMG and total gonadotrophin consumption regardless of early or mid-phase supplementation.

Table 3 Outcome of ovarian stimulation in the groups and subgroups.

Parameter	*Group A* (n = 37)		*Group B* (n = 38)	
	Group A1 (75 IU, n = 9)	*Group A2 (150 IU,* n = 28)	*Group B1 (75 IU,* n = 14)	*Group B2 (150 IU,* n = 24)
Duration of stimulation (days)	8.8 ± 0.78[a]	8.9 ± 1.26[b]	9.7 ± 1.72	10.78 ± 1.75[a,b]
Total rFSH dose (IU)	1462 ± 405[a,c,d]	1943 ± 872[b,c]	2435 ± 1015[d]	3104 ± 1535[a,b]
Total HMG dose (IU)	558 ± 246[e,f,g]	1403 ± 392[e,h,i]	321 ± 198[f,h,j]	962 ± 417[g,i,j]
Total gonadotrophin dose (IU)	2020 ± 439[a,e,f]	3354 ± 1070[e]	2758 ± 1000[f,j]	4034 ± 1561[a,j]
Oestradiol concentration on HCG day (pg/ml)	2543 ± 1154	2787 ± 1067[i]	2415 ± 1217	1726 ± 1026[i]
Endometrial thickness on HCG day (mm)	10.85 ± 2.66	11.25 ± 2.66	11.05 ± 2.41	10.75 ± 2.36
Follicles ≥14 mm on HCG day (*n*)	10 ± 4.33	9.67 ± 4.22	8.5 ± 4	9.16 ± 4.3
Diameter of leading follicle (mm)	19.2 ± 2	18.64 ± 2.1	19 ± 1.6	18.8 ± 2
Oocytes retrieved (*n*)	11.6 ± 6.2	12.46 ± 7.85	8.7 ± 4.98	10.41 ± 6.48
Mature (MII) oocytes (*n*)	9.1 ± 5.4	9.7 ± 7.2	7.2 ± 3.79	8.6 ± 5.1

Group A = HMG initiated on day 1; Group B = HMG initiated on day 5—6.
Values are mean ± SD.
HCG = human chorionic gonadotrophin; HMG = human menopausal gonadotrophin; MII = metaphase II; rFSH = recombinant FSH.
[a] $P < 0.001$ between group A1 and group B2.
[b] $P < 0.001$ between group A2 and group B2.
[c] $P < 0.05$ between group A1 and group A2.
[d] $P < 0.001$ between group A1 and group B1.
[e] $P < 0.001$ between group A1 and group A2.
[f] $P < 0.05$ between group A1 and group B1.
[g] $P < 0.05$ between group A1 and group B2.
[h] $P < 0.001$ between group A2 and group B1.
[i] $P < 0.05$ between group A2 and group B2.
[j] $P < 0.05$ between group B1 and group B2.

Table 4 Embryology data and cycle outcome of the study groups and subgroups.

Parameter	*Group A* (n = 37)		*Group B* (n = 38)	
	Group A1 (75 IU, n = 9)	*Group A2 (150 IU,* n = 28)	*Group B1 (75 IU,* n = 14)	*Group B2 (150 IU,* n = 24)
2PN embryos (*n*)	5.62 ± 3.24	5.73 ± 5.3	4.5 ± 2.17	4.81 ± 4.39
Cleavage-stage embryos (*n*)	5.25 ± 3	5.35 ± 4	4.38 ± 2.8	4.62 ± 3.8
Embryos transferred (*n*)	3.6 ± 0.5	3.1 ± 1	3.5 ± 1	3 ± 1
Grade A embryos (%, *n*)	77 (37/48)	82 (127/154)	74 (48/65)	85 (94/111)
Fertilization rate (%, *n*)	57.7 (52/90)	55.1 (163/296)	66 (70/106)	54.7 (116/212)
Implantation rate (%, *n*)	6.2 (2/32)	8.3 (7/84)	12 (6/50)	8.3 (6/72)
By physician 1 (MS) (%, *n*)	7.54 (4/53)		10.4 (5/48)	
By physician 2 (CA) (%, *n*)	7.93 (5/63)		9.4 (7/74)	
Clinical pregnancy rate				
Total group (%, *n*)	21.6 (8/37)		28.9 (11/38)	
According to subgroups (%, *n*)	22.2 (2/9)	21.4 (6/28)[a]	42.9 (6/14)[a,b]	20.8 (5/24)[b]
By Physician 1 (MS) (%, *n*)	23.5 (4/17)		30.0 (6/20)	
By Physician 2 (CA) (%, *n*)	20.0 (4/20)		27.8 (5/18)	

Group A = HMG initiated on day 1; Group B = HMG initiated on day 5–6.
Values are mean ± SD or% (number/total).
PN = pronucleate.
[a] $P < 0.05$ between subgroup A2 and subgroup B1.
[b] $P < 0.05$ between subgroup B1 and subgroup B2.

In normogonadotrophic nonselected women, randomized trials investigating the effect of LH supplementation (in the form of HCG, HMG or recombinant LH) to rFSH/GnRHa long protocol have conflicting results (Filicori et al., 1999; Fleming et al., 1998; Laml et al., 1999; Nyboeandersen et al., 2008; Shoham, 2002). A recent meta-analysis showed no significant advantage of LH supplementation on mean numbers of retrieved and mature oocytes or on clinical pregnancy and implantation rates (Oliveira et al., 2007). Nevertheless, similar to these current findings, LH supplementation to rFSH was found to reduce the duration of stimulation and total amount of rFSH and to increase serum oestradiol concentrations on HCG day.

In a similar group of patients as compared with this study, De Placido et al. (2001) demonstrated favourable stimulation duration, number of retrieved oocytes, clinical pregnancy and abortion rates by supplementation with HMG (150 IU/day) on day 8 to rFSH stimulation. In contrast to this study's findings, the same group reported superior outcome with 150 IU/day recombinant LH compared with 75 IU/day recombinant LH when supplemented to rFSH-only stimulation in inadequate ovarian responders on day 8 (De Placido et al., 2004). Once again, the same group indicated that recombinant LH supplementation (150 IU/day) is more effective than increasing the dose of rFSH (plus 150 IU/day) in terms of increased number of retrieved cumulus–oocyte–complexes (De Placido et al., 2005), whereas, in patients with poor ovarian response the beneficial effect of LH supplementation initiated on day 7 of ovarian stimulation is again controversial (Barrenetxea et al., 2008; Ferrari et al., 2002). In the current study, when HMG-supplemented and rFSH-only initial cycles were compared, cycle outcome parameters and embryology data were restored by early HMG supplementation regardless of daily supplementary HMG dose (75 IU or 150 IU/day).

Another critical point was the possible favourable effect of a higher starting dose of gonadotrophins in group A since rFSH and HMG were initiated concomitantly. It has been clearly asserted by some prospective randomized double-blind studies that the number of retrieved and mature oocytes as well as number of >14 mm follicles tend to be higher even in fixed 200 IU/day compared with 100 IU/day rFSH-only stimulation (Asian Puregon Study Group, 2002; Out et al., 1999, 2001). Nevertheless, in this study's population, the required cumulative dose in the previous cycle was already >3000 IU due to inadequate response, therefore it is expected that such patients would require a higher dose of gonadotrophins than their normoresponder counterparts in subsequent cycles.

The main weakness of this preliminary retrospective study was the number of enrolled patients, which may impair the study results, wherein at least 491 patients, equally allocated to the groups, are required in order to detect a statistical significance in clinical pregnancy rates among groups A and B with alpha set at $P < 0.05$ (Z power −1.65). This study did not use pure LH; notwithstanding this, it is purported that using HMG for LH activity showed us some important findings. As has been extensively discussed, it is still unclear whether improved cycle outcome is due to LH activity or to HCG activity that exists in the purified HMG. LH concentrations might have been monitored, however measuring serum LH may not be of great significance, since it has a short life and the electric charge and the immunoreactivity of LH might not be closely linked (Niccoli et al., 1996). Besides the specificity and sensitivity of the immunoassay used may affect the value of serum LH

concentration (Costagliola et al., 1994). Moreover, it was demonstrated that measuring serum LH throughout the follicular phase does not predict ovarian response and assisted reproductive treatment outcome (Balasch et al., 2001; Humaidan, 2006; Peñarrubia et al., 2003).

A daily dose of 75 IU recombinant LH was usually found effective in promoting optimal follicular development (De Placido et al., 2001, 2004, 2005; Lisi et al., 2001). Conversely, increasing the dose of LH during the follicular phase could also reduce the number of growing follicles, which reflects the concept of 'LH ceiling' (The European Recombinant Human LH Study Group, 1998). In the current study total gonadotrophin and HMG consumption was lower in the 75 IU-supplemented subgroups (groups A1 and B1). However, the demographic data and patient characteristics were unmatched, as reflected by younger mean age and shorter duration of infertility in 75 IU/day subgroups as opposed to their 150 IU/day counterparts. Notably, pregnancy rate was found higher in patients where 75 IU supplementary HMG was given on day 5—6 of ovarian stimulation (group B1). The pregnancy rate per embryo transfer and implantation rate in this subgroup (42.9% (6/14) and 12% (6/50)) were quite similar to the rates (44% (846/1921) and 17% (915/5379)) for all IVF patients ($n = 1921$) who underwent ICSI during the study period in the study centre. Notably, both the pregnancy and implantation rates of all other groups/sub-subgroups were lower than the mean rates of all IVF patients. Due to the retrospective nature of the study, it is not know whether this improved pregnancy rate in group B1 might have been confounded by better ovarian response and this deserves further evaluation.

Currently, a prospective randomized study is being conducted with matched groups to assess whether HMG starting dose has any significant effect on IVF success in the study centre's IVF clinic. Larger prospective randomized trials are still required to assess the definitive role of LH supplementation in ovarian stimulation cycles as well as effect of initiation day and dose of HMG supplementation to rFSH, on IVF outcome in patients with inadequate previous ovarian response during GnRHa down-regulation.

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