

# Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection

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**Objective:** To evaluate the efficacy and safety of highly purified human menotropin (HP-hMG) and recombinant follicle-stimulating hormone (rFSH) for controlled ovarian stimulation in a population of patients predicted to be high responders.

**Design:** Randomized, open-label, assessor-blinded, parallel-group, noninferiority trial.

**Setting:** Fertility centers.

**Patient(s):** A total of 620 women with serum antimüllerian hormone (AMH)  $\geq 5$  ng/mL.

**Intervention(s):** Controlled ovarian stimulation with HP-hMG or rFSH in a GnRH antagonist assisted reproductive technology (ART) cycle. Fresh transfer of a single blastocyst was performed unless ovarian response was excessive, in which all embryos were cryopreserved. Subjects could undergo subsequent frozen blastocyst transfer within 6 months of randomization.

**Main Outcome Measure(s):** Ongoing pregnancy rate (OPR) after fresh transfer (primary endpoint), as well as cumulative live birth, ovarian hyperstimulation syndrome (OHSS), and pregnancy loss rates.

**Results:** OPR/cycle start after fresh transfer was 35.5% with HP-hMG and 30.7% with rFSH (difference: 4.7%, 95% CI  $-2.7\%$ ,  $12.1\%$ ); noninferiority was established. Compared to rFSH, HP-hMG was associated with significantly lower OHSS (21.4% vs. 9.7% respectively; difference:  $-11.7\%$ , 95% CI  $-17.3\%$ ,  $-6.1\%$ ) and cumulative early pregnancy loss rates (25.5% vs. 14.5% respectively; difference:  $-11.0\%$ , 95% CI  $-18.8\%$ ,  $-3.14\%$ ). Despite 43 more transfers in the rFSH group, cumulative live birth rates were similar with HP-hMG and rFSH at 50.6% and 51.5% respectively (difference:  $-0.8\%$ , 95% CI  $-8.7\%$ ,  $7.1\%$ ).

**Conclusion(s):** In high responders, HP-hMG provided comparable efficacy to rFSH with fewer adverse events, including pregnancy loss, suggesting its optimized risk/benefit profile in this population.

**Clinical Trial Registration Number:** NCT02554279 ([clinicaltrials.gov](http://clinicaltrials.gov)). (Fertil Steril® 2020;114:321–30. ©2020 by American Society for Reproductive Medicine.)

**El resumen está disponible en Español al final del artículo.**

**Key Words:** Highly purified menotropin, Menopur, recombinant FSH, high responders, GnRH antagonist

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**P**atients undergoing assisted reproductive technologies (ART) are heterogeneous in their response to gonadotropin stimulation. Further improvement in efficacy, safety, and cycle efficiency requires greater personalization of gonadotropin treatment. Newer technologies have provided an opportunity to achieve such personalization by tailoring gonadotropin dose to ovarian potential. Serum anti-müllerian hormone (AMH) levels and ultrasound-derived antral follicle count (AFC) have both been shown to be robust predictors of ovarian response. However, AFC lacks methodological standardization and is dependent on ultrasound-operator skill, making AMH the preferred biomarker, particularly in the context of multicenter clinical trials (1, 2). AMH levels have successfully guided gonadotropin dosing in ART, and therefore can be used to more accurately define and select specific study populations (3).

High responders exhibit good overall prognosis with robust follicular response, serum estradiol (E<sub>2</sub>) levels, and oocyte yields (>15) (4, 5). However, these gains are tempered by a high risk of developing ovarian hyperstimulation syndrome (OHSS) and/or cancellation of fresh embryo transfer to prevent it, causing an undesirable delay to pregnancy and the possibility of increased cost. Current strategies for such patients are reactive, delay time to pregnancy, and focus on mitigation of complications instead of proactive benefit (6–8). Thus, there is an unmet need to proactively identify patients at risk for hyper response prior to the start of stimulation, and to develop new treatment approaches to improve care in this patient population.

Serum AMH measurements have been successfully used to predict likely high responders (2, 3, 9). Moreover, a recent retrospective study indicated that there is an opportunity to personalize treatment of this cohort based not just on dose but also upon the type of gonadotropin used to drive controlled ovarian stimulation. Baseline serum AMH testing of samples collected in a post hoc analysis of two phase 3 randomized controlled trials were used to define patient quartiles. Both trials compared outcomes in patients treated with either human-derived HP-hMG (a gonadotropin mixture of follicle-stimulating hormone [FSH] and human chorionic gonadotropin [hCG]–derived luteinizing hormone [LH] activity) or recombinant follicle stimulating hormone (rFSH) produced in Chinese hamster ovarian cells. In addition to these constituent differences in the gonadotropin preparations, there is also species-related diversity in tertiary protein structure that informs their biological activity and clearance (10–12). The analysis found that HP-hMG treatment of potential high responders, defined as patients with baseline AMH levels in the highest quartile (>5.2 ng/mL), was associated with a lower median number of retrieved oocytes, significantly lower incidence of high response (>15 oocytes), fewer interventions for OHSS, and increased live birth rate compared with rFSH in GnRH agonist or antagonist protocols (13–15).

In the United States, most clinicians use both HP-hMG and rFSH concurrently as mixed stimulation protocols. However, there is an absence of high-quality evidence demonstrating the advantages of such an approach over stimulation with either gonadotropin preparation alone. Furthermore, there is tremendous heterogeneity in the ratios of HP-hMG:rFSH as applied in current clinical practice, which makes it difficult to select meaningful consensus ratios for evaluation in a trial. Finally, any difference attributable to specific gonadotropin preparations can be determined only when their use as single agents is compared.

Therefore, the aims of the current noninferiority trial were as follows: to prospectively evaluate the efficacy and safety of HP-hMG vs. rFSH treatment, aligned with previous studies, as a proof-of-concept in a predefined population of patients predicted to be high responders; to characterize differences first observed in the earlier analysis; and to offer a novel strategy for therapeutic personalization.

## MATERIALS AND METHODS

### Trial Design

MEGASET-HR was an open-label, parallel-group trial conducted in 31 U.S. centers between August 2015 and February 2018 in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable regulatory requirements. The first subject was randomized and enrolled on October 15, 2015. The trial was assessor blinded to individuals performing the ultrasound monitoring, embryologists, and central laboratory personnel.

### Trial Population

Eligible subjects included women aged 21–35 years with menstrual cycles of 21–45 days, body mass index (BMI) 18–30 kg/m<sup>2</sup>, infertility for ≥ 1 year, day 2 or 3 serum FSH levels of 1–12 IU/L, total testosterone, prolactin, and thyroid stimulating hormone within normal limits, and serum AMH ≥ 5 ng/mL at screening. All AMH measurements were determined at a single reference laboratory (ReproSource, Inc.), using materials and reagents from Beckman Coulter-DSL. As an additional step to ensure assay consistency, this laboratory used a reference serum sample to normalize AMH measurements. Women with stage III–IV endometriosis; history of recurrent miscarriage; previous ART failure from poor response; AFC (diameter 2–10 mm) <10 for both ovaries combined and/or use of hormonal birth control <3 months prior to screening were excluded. Full inclusion and exclusion criteria are listed in [Supplemental Table 1](#).

## Trial Procedures

Randomization lists were generated by the study statistician prior to the first subject's initial visit. Subjects were randomized 1:1 to controlled ovarian stimulation with HP-hMG (Menopur, Ferring Pharmaceuticals) or rFSH (Gonal-f; EMD-Serono) immediately prior to administration of trial drug. Randomization numbers were allocated sequentially to the subjects in the order in which they were randomized. Treatment was initiated on day 2 or 3 of the menstrual cycle at a dose of 150 IU HP-hMG or rFSH for the first 5 days (Supplemental Fig. 1). Starting at day 6, the dose could be adjusted daily by 75 IU. The maximum daily dose was 300 IU/d and the maximum treatment duration was 20 days. Coasting was not permitted. Once the lead follicle measured  $\geq 14$  mm and/or serum  $E_2$  levels were  $\geq 300$  pg/mL, 0.25 mg/d GnRH antagonist (Ganirelix acetate injection; Ganirelix; Merck) was administered. When three follicles of  $\geq 17$  mm were observed by transvaginal ultrasound, oocyte maturation was induced by 250  $\mu$ g hCG (Ovidrel; EMD-Serono). Oocytes were retrieved  $\sim 36$  hours after hCG administration and inseminated by intracytoplasmic sperm injection (ICSI) 4  $\pm$  1 hours after retrieval. DNA was prepared from trophectoderm biopsy samples of all blastocysts in the trial. Preimplantation genetic testing for aneuploidy (PGT-A) was used as an independent, objective indicator of embryo quality. At the time of trial design, the clinical utility of PGT-A in different patient cohorts based on age was less understood. Biopsied cells were designated euploid (46, XX or 46, XY) or aneuploid by real-time polymerase chain reaction analysis as previously described (16). During the trial, the assay displayed a higher error rate than previously reported due to a reagent issue, with no reason to believe that assay variances differed for either trial arm.

Patients receiving an hCG trigger underwent fresh transfer of a single blastocyst of best quality by morphology on day 5, following ICSI. All remaining blastocysts were frozen using vitrification. Genetics results were not available to inform blastocyst selection for fresh transfer. Starting on the evening of the day after retrieval, 100 mg two times per day of vaginal progesterone ( $P_4$ ) (Endometrin; Ferring Pharmaceuticals) was administered until the serum hCG test (10–14 days after transfer). Vaginal  $P_4$  was continued for a maximum of 10 weeks with confirmed pregnancy.

In cases of excessive ovarian response ( $>30$  follicles of  $\geq 12$  mm each and/or estradiol [ $E_2$ ] levels  $\geq 5,000$  pg/mL), a GnRH agonist (4 mg leuprolide acetate) was administered  $\geq 12$  hours after the last GnRH antagonist dose, fresh transfer was canceled, and all blastocysts were biopsied; viable blastocysts were frozen for use in a subsequent transfer cycle.

Pregnancy outcomes from fresh transfer were collected in a post-trial follow-up. In addition, for subjects with no ongoing pregnancy in the fresh cycle, single frozen blastocyst transfers could be initiated within 6 months of the date of randomization, in which genetic results could be used to select a euploid blastocyst for transfer; there was no trial limitation to the number of transfers that could be performed during this period. Pregnancy outcomes for these frozen blastocyst transfers were also collected in the post-trial follow-up.

## Trial Endpoints and Assessments

In the core trial, the primary endpoint was ongoing pregnancy rate, defined as the presence of one or more intrauterine pregnancies with a fetal heartbeat at 10–11 weeks' gestation (8–9 weeks after fresh blastocyst transfer). Secondary endpoints included the following: cumulative ongoing pregnancy, early pregnancy loss (two positive  $\beta$ -hCG tests but no ongoing pregnancy at 10–11 weeks' gestation), OHSS frequency, follicular development, endocrine profile, endometrial development, number of oocytes retrieved, and blastocyst quality. Endocrine parameters were centrally assessed on blood samples throughout the stimulation period; a description of assay platforms and their associated limits of quantitation is provided in Supplemental Table 2. Day 5 blastocyst quality was locally assessed by the Gardner and Schoolcraft scale (17).

Safety was assessed based on vital signs, laboratory results, and reports of treatment-emergent adverse events (TEAEs) that occurred from the time of first administration of trial drug to the last end-of-treatment visit. OHSS was classified using the Golan classification system (18).

Post-trial endpoints included the live birth rate after fresh or frozen transfer and cumulatively, neonatal health, and pregnancy loss rates from frozen blastocyst transfer cycles.

## Sample Size and Statistical Analysis

The trial was powered to demonstrate noninferiority in ongoing pregnancy rate for fresh cycles treated with HP-hMG vs. rFSH based on a prespecified margin of  $-12\%$  for the lower limit of the two-sided 95% confidence interval (CI) for the difference in ongoing pregnancy rates consistent with the exploratory objectives of the trial. An estimated 275 randomized subjects per treatment group were needed to achieve  $\geq 80\%$  power, assuming an ongoing pregnancy rate of 50% for both groups and a one-sided significance level of 0.025 (19).

The 95% CIs for the difference between HP-hMG and rFSH in ongoing pregnancy, positive  $\beta$ -hCG, clinical pregnancy, and live birth rates as well as other binary outcomes were established based on an asymptotic normal distribution. Treatment group differences in continuous outcomes were calculated by the Hodges–Lehmann estimates with 95% CIs calculated by the Moses method. Categorical data were summarized using numbers and percentages, with percentages based on the total number of subjects within the given analysis set. Continuous data were summarized with descriptive statistics. All statistical tests were performed using a two-sided test at a 5% significance level. No adjustments were made for multiple tests. Comparability of baseline and clinical characteristics between treatment groups was assessed by the Wilcoxon–Mann–Whitney test using  $\chi^2$  statistic (degrees of freedom = 1) for continuous variables and the two-sided Fisher's exact test for categorical variables.

## RESULTS

### Trial Subjects

Of 1,258 screened patients, 620 were randomized and 619 were treated (modified intent to treat [mITT]). One subject

randomized to HP-hMG spontaneously became pregnant prior to the start of ovarian stimulation and was the sole mITT population exclusion. A total of 99.5% completed stimulation day 6, 96.8% received trigger (hCG or GnRH agonist), 96.5% underwent oocyte retrieval, and 63.2% completed fresh blastocyst transfer (Supplemental Fig. 2). Overall, 91 (14.7%) subjects (37 [11.9%] HP-hMG subjects and 54 [17.5%] rFSH subjects) had the hCG trigger replaced with GnRH agonist. Baseline characteristics did not significantly differ between groups. Mean subject age was 30.2 years, body mass index was 24.3 kg/m<sup>2</sup>, AMH was 7.7 ng/mL, and AFC was 30.7 (Table 1).

### Stimulation Response

The mean number of oocytes retrieved was 15.1 and 22.2 in HP-hMG-treated and rFSH-treated subjects respectively. This difference of approximately seven fewer retrieved oocytes per HP-hMG-treated subject culminated in three fewer all-quality (5.6 vs. 8.5) and similar numbers of morphologically excellent quality blastocysts (3.0 vs. 3.9). The percentage of blastocysts subdivided by either morphological or genetic (euploidy) quality parameters was similar between groups; HP-hMG was associated with a longer treatment duration (10.9 vs. 9.3 days) and greater total administered dose (2114.5 vs. 1498.9 IU) (Table 2). Additional stimulation and blastocyst transfer parameters are summarized in Supplemental Table 3.

### Efficacy and Safety Outcomes

The primary endpoint, ongoing pregnancy rate/cycle start after the fresh IVF cycle, was 35.5% in HP-hMG-treated compared to 30.7% in rFSH-treated subjects (difference: 4.7%; 95% CI, -2.7%, 12.1%) (Fig. 1A), thereby meeting the predefined noninferiority objective. Live birth rates were 52.2% and 48.7% respectively in HP-hMG-treated and rFSH-treated subjects after fresh blastocyst transfer. The live birth rates were 63.4% and 50.8% in HP-hMG-treated and rFSH-treated subjects respectively, after frozen blastocyst transfer within 6 months of randomization (Fig. 1B, C).

Cumulative live birth rates per cycle start were 50.6% and 51.5% in HP-hMG-treated and rFSH-treated patients (difference: -0.8%, 95% CI -8.7%, 7.1%) (Fig. 1D). However, subjects treated with rFSH underwent more transfers (334 vs. 291) (Fig. 1E) with greater numbers of transfers involving multiple embryos (39 vs. 17: considered protocol deviations; no subject received a transfer of more than two blastocysts) compared to those treated with HP-hMG (Fig. 1F). Of the 56 cycles in which more than one embryo was transferred, 53 occurred in frozen cycles. A complete summary of the number of blastocysts transferred per cycle and treatment group is provided in Supplemental Table 4.

Early pregnancy loss rates were lower in HP-hMG-treated compared to rFSH-treated cohorts in both fresh and frozen cycles (Fig. 1G). Cumulatively, the aggregate pregnancy loss in fresh and frozen cycles was significantly lower at 14.5% after HP-hMG compared to

**TABLE 1**

#### Baseline demographic and clinical characteristics (mITT).

Parameter	HP-hMG (n = 310)	rFSH (n = 309)	Total (n = 619)	P value <sup>a</sup>
Age, y	30.0 ± 3.08	30.4 ± 3.02	30.2 ± 3.05	.0894
Weight, kg	66.1 ± 10.12	65.8 ± 10.96	65.9 ± 10.54	.5888
BMI, kg/m <sup>2</sup>	24.4 ± 3.29	24.3 ± 3.39	24.3 ± 3.34	.5167
Duration of infertility, mo	36.7 ± 25.79	37.1 ± 28.38	36.9 ± 27.09	.6614
Cause of infertility, n (%) <sup>b</sup>				
Oligo-ovulation	50 (16.1)	56 (18.1)	106 (17.1)	.5238
Endometriosis	20 (6.5)	25 (8.1)	45 (7.3)	.4439
Male factor	136 (43.9)	129 (41.7)	265 (42.8)	.6262
Tubal factor	44 (14.2)	43 (13.9)	87 (14.1)	1.0000
Idiopathic	105 (33.9)	112 (36.2)	217 (35.1)	.5561
Other	28 (9.0)	29 (9.4)	57 (9.2)	.8904
AFC	30.5 ± 15.47	31.0 ± 12.24	30.7 ± 13.94	.2130
AMH, pmol/L (ng/mL)	56.1 ± 25.96 (7.8 ± 3.61)	53.9 ± 17.47 (7.5 ± 2.43)	55.4 ± 22.15 (7.7 ± 3.08)	.7988
≥ 35.7 (≥ 5.0)	310 (100)	309 (100)	619 (100)	
≥ 42.9 (≥ 6.0)	217 (70.0)	216 (69.9)	433 (70.0)	
≥ 50.0 (≥ 7.0)	143 (46.1)	141 (45.6)	284 (45.9)	
≥ 57.1 (≥ 8.0)	92 (29.7)	96 (31.1)	188 (30.4)	
LH, U/L	6.9 ± 4.04	6.4 ± 3.49	6.6 ± 3.78	.0543
FSH, U/L	6.4 ± 1.55	6.2 ± 1.55	6.3 ± 1.55	.2750
E <sub>2</sub> , pmol/L (pg/mL)	136.95 ± 70.00 (37.3 ± 19.1)	144.59 ± 84.02 (39.4 ± 22.9)	140.7 ± 77.2 (38.3 ± 21.0)	.0671
P <sub>4</sub> , nmol/L (ng/mL)	0.6 ± 1.82 (0.2 ± 0.6)	0.7 ± 2.46 (0.2 ± 0.8)	0.6 ± 2.16 (0.2 ± 0.7)	.4218
Total testosterone, nmol/L (ng/dL)	1.0 ± 0.52 (28.8 ± 15.0)	1.0 ± 0.42 (28.8 ± 12.1)	1.0 ± 0.47 (28.8 ± 13.6)	.7734

Note: Unless otherwise noted, data are presented as mean ± standard deviation or n (%). AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; df = degrees of freedom; E<sub>2</sub> = estradiol; FSH = follicle-stimulating hormone; HP-hMG = highly purified human menopausal gonadotropin; LH = luteinizing hormone; mITT = modified intent-to-treat; P<sub>4</sub> = progesterone; rFSH = recombinant follicle-stimulating hormone.

<sup>a</sup> P values were calculated from the Wilcoxon-Mann-Whitney test using chi-square statistic (df = 1) for continuous variables and from the two-sided Fisher exact test for categorical variables.

<sup>b</sup> Subjects may have had more than one cause of infertility.

Witz. HP-hMG vs. rFSH in high responders. *Fertil Steril* 2020.

TABLE 2

Stimulation, oocyte retrieval, and embryo development (mITT).			
Parameter	HP-hMG (n = 310)	rFSH (n = 309)	Difference (95% CI) <sup>a</sup>
Stimulation			
Total dose of gonadotropin, IU	2,114.5 ± 798.85	1,498.9 ± 417.36	525.00 (450.00, 600.00)
Dose increase (%)	181 (58.4)	71 (23.0)	
Dose maintained (%)	114 (36.8)	209 (67.6)	
Dose decreased (%)	13 (4.2)	29 (9.4)	
Duration of stimulation, days	10.9 ± 2.40	9.3 ± 1.42	1.00 (1.00, 2.00)
Day of hCG trigger			
Estradiol, pmol/L (pg/mL)	10,311.00 ± 6,543.75 (2,808.8 ± 1,782.6)	11,750.46 ± 7,353.34 (3,200.9 ± 2,003.1)	-1211.46 (-2276.08, -146.85)
Progesterone, nmol/L (ng/mL)	2.2 ± 2.75 (0.7 ± 0.9)	3.3 ± 3.02 (1.0 ± 0.9)	-0.89 (-1.14, -0.63)
Oocyte retrieval			
No. of oocytes retrieved/subject	15.1 ± 10.12	22.2 ± 11.54	-7.00 (-8.00, -5.00)
No. of MII oocytes/subject	10.1 ± 7.18	15.9 ± 9.01	-5.00 (-7.00, -4.00)
No. of 2PN oocytes/subject	8.2 ± 5.90	12.9 ± 7.38	-4.00 (-5.00, -3.00)
Fertilization rate <sup>b</sup>	55.09 ± 21.73	59.07 ± 18.73	-3.57 (-6.76, 0.00)
Embryo development (day 5)			
No. of blastocysts/subject	5.6 ± 4.31	8.5 ± 5.68	-3.00 (-3.00, -2.00)
No. of excellent blasts/subject	3.0 ± 2.77	3.9 ± 3.73	0.00 (-1.00, 0.00)
Blastocyst morphology			
Excellent <sup>c</sup>	28.3%	30.7%	
Good <sup>d</sup>	26.5%	22.5%	
Neither <sup>e</sup>	45.1%	45.8%	
Missing	0.1%	1.0%	
Blastocyst karyotype			
Aneuploidy rate <sup>f</sup>	24.5% ± 25.14	27.4% ± 26.25	
No. of subjects with fresh transfer (%)	201 (64.8)	191 (61.8)	3.03 (-4.56, 10.62)
No. of subjects with frozen transfer (%)	82 (26.5)	130 (42.1)	-15.62 (-23.00, -8.24)
Ongoing pregnancy/cycle start (%)	35.5	30.7	4.7 (-2.7, 12.1)
Live birth rate (fresh transfer)	52.2	48.7	3.6 (-6.4, 13.4)
Live birth rate (frozen transfer)	63.4	50.8	12.7 (-0.9, 26.2)

Note: Unless otherwise noted, data are presented as mean ± standard deviation. CI = confidence interval; HP-hMG = highly purified human menopausal gonadotropin; MII = metaphase II; mITT = modified intent-to-treat; PN = pronuclei; rFSH = recombinant follicle-stimulating hormone.

<sup>a</sup> Differences between HP-hMG and rFSH were calculated by the Hodges-Lehmann estimates with 95% CIs calculated by the Moses method for continuous outcomes; the 95% CIs for binary outcomes were based on asymptotic normal distribution.

<sup>b</sup> Calculated as the number of 2PN oocytes divided by the number of oocytes retrieved.

<sup>c</sup> Defined as those with blastocyst expansion and hatching status 4–6, inner cell mass grade A, and trophectoderm grade A or B.

<sup>d</sup> Defined as those with blastocyst expansion and hatching status 3–6, inner cell mass grade B, and trophectoderm grade A or B.

<sup>e</sup> All other blastocysts.

<sup>f</sup> Calculated as number of aneuploid blastocysts per number of blastocysts with known ploidy.

Witz. HP-hMG vs. rFSH in high responders. *Fertil Steril* 2020.

25.5% after rFSH treatment (difference: -10.97%, 95% CI -18.8%, -3.14%).

The overall incidence of treatment-emergent adverse events (TEAEs) was 57.7% with HP-hMG and 70.6% with rFSH. The incidence of OHSS was significantly lower with HP-hMG compared with rFSH treatment (9.7% vs. 21.4%; difference: -11.7%, 95% CI -17.3%, -6.1%); (Table 3). Most OHSS cases were mild or moderate in intensity in both groups. Cycle cancellations due to excessive response were reported for three subjects treated with HP-hMG and for six subjects treated with rFSH. Early OHSS rates were significantly lower in those treated with HP-hMG compared with rFSH (6.1% vs. 17.5%: difference: -11.3%, 95% CI -16.4%, -6.3%) (Table 3). Severe early OHSS was reported in 3 (1.0%) subjects in the HP-hMG group and 7 (2.3%) subjects in the rFSH group.

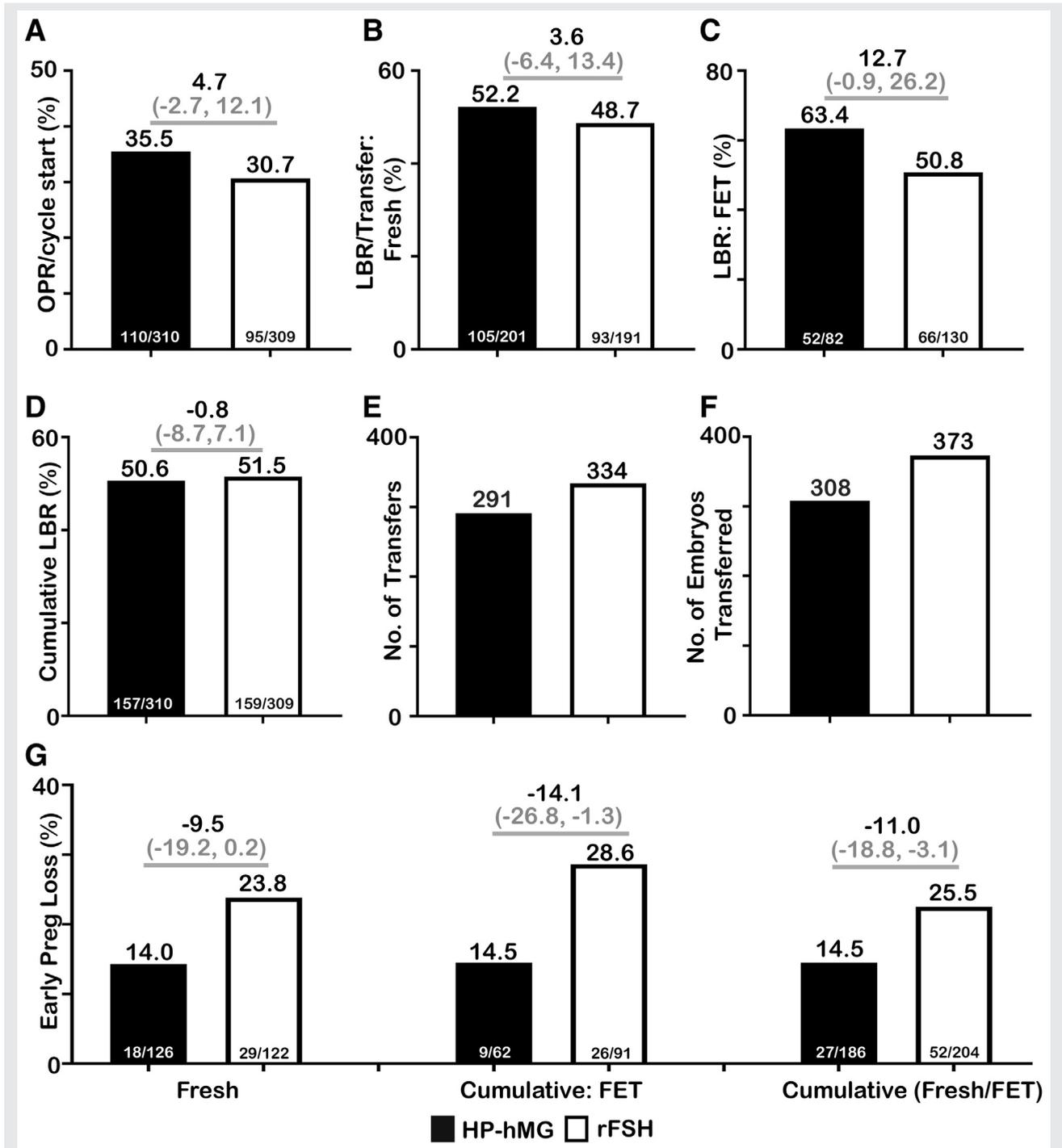
## DISCUSSION

In this randomized, open-label, assessor-blinded, parallel-group, multicenter noninferiority U.S. trial, we have estab-

lished that per transfer, HP-hMG treatment was associated with similar live birth and significantly lower pregnancy loss rates in fresh and frozen blastocyst transfer cycles in predicted high-responder subjects undergoing ART. Consequently, 43 more transfer cycles and 65 more transferred embryos were required in the rFSH arm to achieve similar cumulative live birth rates.

This is the first comparator trial to show that HP-hMG was associated with lower pregnancy loss rates after both fresh and frozen transfers. HP-hMG-treated subjects also had lower peak estradiol levels, lower trigger-day progesterone levels, and a significantly diminished incidence of OHSS, an iatrogenic complication. It is possible that these differences in response to gonadotropin stimulation could have affected the endometrium, altering the likelihood of achieving an ongoing pregnancy after fresh transfer. However, this is unlikely to be the primary cause of the difference in pregnancy loss rate observed between treatment groups. Trial criteria mandated leuprolide trigger and freeze-all for extreme hyper response. Importantly, the differential pregnancy loss

**FIGURE 1**



MEGASET-HR: efficacy outcomes. (A) Ongoing pregnancy rate per cycle start defined as the presence of one or more intrauterine pregnancies with a fetal heartbeat at 10–11 weeks’ gestation or 8–9 weeks after fresh blastocyst transfer. (B) Live birth rate in subjects with fresh blastocyst transfer. (C) Live birth rate in subjects with frozen blastocyst transfer. (D) Cumulative live birth rate. (E) Total number of blastocyst transfers (fresh and frozen). (F) Total number of blastocysts transferred. (G) Pregnancy loss occurring in fresh cycles, any frozen cycle, and cumulative (defined as the ratio of all patients with early pregnancy loss in fresh and frozen cycles, i.e., before 11 weeks’ gestation) to outcomes of all patients with two consecutive serum  $\beta$ -hCG tests. HP-hMG = highly purified human menotropin; rFSH = recombinant follicle-stimulating hormone; OPR = ongoing pregnancy rate; LBR = live birth rate; FET = frozen embryo transfer.

Witz. HP-hMG vs. rFSH in high responders. *Fertil Steril* 2020.

TABLE 3

## Summary of safety outcomes.

Parameter	HP-hMG (n = 310)	rFSH (n = 309)	Total (n = 619)
TEAE <sup>a</sup>	179 (57.7%)	218 (70.6%)	397 (64.1%)
Procedural pain	71 (22.9%)	71 (23.0%)	142 (22.9%)
Nausea	37 (11.9%)	40 (12.9%)	77 (12.4%)
Abdominal distension	25 (8.1%)	35 (11.3%)	60 (9.7%)
Constipation	22 (7.1%)	36 (11.7%)	58 (9.4%)
Headache	29 (9.4%)	22 (7.1%)	51 (8.2%)
Abdominal pain	21 (6.8%)	24 (7.8%)	45 (7.3%)
Vaginal hemorrhage	21 (6.8%)	22 (7.1%)	43 (6.9%)
OHSS <sup>b</sup>	30 (9.7%) <sup>c</sup>	66 (21.4%) <sup>c</sup>	96 (15.5%)
Mild	7 (2.3%)	18 (5.8%)	25 (4.0%)
Moderate	15 (4.8%)	39 (12.6%)	54 (8.7%)
Severe	8 (2.6%)	9 (2.9%)	17 (2.7%)
Serious TEAEs	8 (2.6%)	11 (3.6%)	19 (3.1%)
AE-related discontinuation	2 (0.6%)	4 (1.3%)	6 (1.0%)
Deaths	0	0	0

Note: Unless otherwise noted, data are presented as n (%). AE = adverse events; HP-hMG = highly purified human menotropin; OHSS = ovarian hyperstimulation syndrome (early OHSS was defined as having an onset  $\leq 9$  days after triggering final follicular maturation, before trigger, or during stimulation when trigger was not used; late OHSS was defined as onset  $>9$  days after trigger); rFSH = recombinant follicle-stimulating hormone; TEAEs, treatment-emergent adverse events.

<sup>a</sup> TEAEs with an incidence of at least 5% by MedDRA System Organ Class and Preferred Term (safety analysis set).

<sup>b</sup> Classification of grade was determined using Golan's classification system (18).

<sup>c</sup> Difference in OHSS incidence: 11.7%, (confidence interval -17.3, -6.1%).

Witz. HP-hMG vs. rFSH in high responders. *Fertil Steril* 2020.

rate was observed even in frozen embryo transfer cycles in which earlier stimulation response would presumably have had no impact on the endometrium. Instead, an improvement in embryo quality associated with use of HP-hMG could account for the early lower pregnancy loss rate observed in that trial arm. However, embryo quality as determined by conventional (morphology) and state-of-the-art (chromosome number) parameters was similar in the two groups. Therefore, HP-hMG stimulation may have had a beneficial impact on the oocyte that was not reflected by currently established embryo assessment technologies.

In contrast to two fewer retrieved oocytes observed in prior studies, HP-hMG-treated subjects in this trial, limited to predicted high-responders, had a mean of seven fewer oocytes retrieved; this difference in yield narrowed with advancing embryo development (13, 15). Differential gonadotropin response observed here could result from inclusion of patients with polycystic ovary syndrome (PCOS); 106 oligo-ovulatory subjects (17.1%) with elevated serum AMH level were likely to have PCOS pathology, which was not explicitly excluded. The inherent heterogeneity of PCOS means that in real-world clinical practice, such subjects contribute significantly to the overall pool of predicted high responders. Luteinizing hormone activity-driven atresia of small/medium follicles could have diminished oocyte numbers in HP-hMG-treated subjects (20, 21). Reduced follicular recruitment in the HP-hMG arm is likely to have been a contributor to the lower OHSS rate that was also observed in these patients, a key benefit identified in this trial.

Currently, there are no consensus criteria that identify potential high responder patients before starting therapy. Instead, hyper response is diagnosed while patients are in

treatment, and reactive measures to mitigate complications are then instituted, usually resulting in a delay in time to pregnancy. This is the first trial to use serum AMH ( $\geq 5$  IU/mL) as a marker to prospectively identify potential hyper responders and to offer a potential strategy to prevent complications while enabling efficient progression to embryo transfer and opportunity for pregnancy. Mean serum AMH levels were 7.5 IU/mL in patients treated with rFSH and 7.8 IU/mL in those treated with HP-hMG. As expected, the incidence of OHSS among trial subjects was high, which validated the prognostic significance of AMH as a marker for identification of hyper responder patients prior to treatment start. Moreover, despite clinical consequences for individual patients, OHSS is often underdiagnosed and underreported in the literature (26). A combination of including only high-risk patients, in a trial setting, with standardized application of diagnostic, monitoring, and follow-up criteria, is another reason for the high rate of OHSS in this study. However, the starting gonadotropin dose of 150 IU/d in the trial is aligned with the indicated dose of rFSH and lower than that of HP-hMG when endogenous gonadotropins are suppressed. Moreover, on average, this dose is lower than that in current stimulation protocols in the United States.

OHSS incidence was mostly mild/moderate in intensity. Nevertheless, these findings suggest that there is scope for further dosage reduction, particularly for rFSH, to diminish the incidence of freeze-all and delayed embryo transfer. Although the trial design did mandate leuprolide acetate trigger for extreme high response based on best clinical evidence at the time, the intervention could be applied to patients with more modest levels of hyper response.

Despite seven fewer oocytes per subject, the difference in the mean number of excellent-quality blastocysts was reduced to 0.9. Moreover, the supernumerary oocytes retrieved in rFSH-treated subjects did not appear to confer an appreciable clinical benefit in the trial. An open question is whether collection of live birth data from frozen transfers for longer periods of time could have revealed differences. Embryo quality generally establishes the hierarchy of transfer order. In this trial, embryos of highest morphological grade were transferred fresh, and mostly euploid embryos of highest morphological grade were transferred in up to three consecutive subsequent frozen transfers; such practice trends would argue against the possibility of significant gains in cumulative live birth rates over a longer period of time.

Current U.S. clinical practice trends favor maximizing ovarian response. Relative unfamiliarity with the inherent differences in ovarian response between the two gonadotropins may have accounted for upward revision of dosage after day 6 in the HP-hMG group in this assessor-blinded trial, resulting in higher total doses of HP-hMG administered vs. rFSH. However, there is no robust evidence that mid-cycle gonadotropin dose changes provide benefit in follicle recruitment, progression, or ultimate maturity. Health economic outcomes research is required to assess the projected financial impact of the higher drug use of HP-hMG observed in the trial relative to other efficacy and safety parameters.

Another emerging practice trend is a preference for elective frozen embryo transfer over fresh transfer. However, recent

clinical trials did not find increased live birth rates after frozen transfer in non-PCOS patients (22–25). Significant differences in the live birth rate were not observed between fresh and frozen transfer in the MEGASET-HR trial, even though PGT results informed euploid blastocyst transfer in frozen transfers. These findings are significant, as high-responder patients typically have all embryos frozen (26). A lower incidence of excessive response and accompanying OHSS suggests a reduced imperative to freeze all embryos, allowing a greater opportunity for fresh transfer. The shorter time to birth that results would likely translate to increased convenience, patient satisfaction, and lower costs, although these parameters remain to be analyzed, particularly considering the differences in the total gonadotropin dose administered and the duration of stimulation. Several studies have found evidence of worse maternal and neonatal outcomes associated with fresh vs. frozen transfer cycles, suggesting that the suprphysiological environment created by ovarian stimulation protocols may be detrimental to both embryo implantation and placentation (27–31). Response to stimulation with HP-hMG as a single agent is more moderate compared with protocols containing rFSH, which could mitigate such risks in fresh transfer cycles.

There is an increased need to provide patient-tailored care across all medical disciplines (32–34). One way to personalize controlled ovarian stimulation is through choice of gonadotropin (13, 15, 35). In high responders, HP-hMG treatment was consistently associated with a moderate stimulation profile, lower incidence of complications, lower pregnancy loss, and corresponding higher probability of ongoing pregnancy and live birth per transfer in fresh or frozen cycles. The optimized risk/benefit profile with HP-hMG presents an opportunity to individualize the treatment of high responders and suggests that choice of gonadotropin has a role in protocol personalization.

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**Ensayo aleatorizado, ciego para el evaluador, que compara la menopina humana altamente purificada y la hormona estimulante del folículo recombinante en pacientes con alta respuesta sometidas a inyección intracitoplasmática de espermatozoides.**

**Objetivo:** Evaluar la eficacia y la seguridad de la menopina humana altamente purificada (HP-hMG) y la hormona estimulante del folículo recombinante (rFSH) para la estimulación ovárica controlada en una población de pacientes con alta respuesta prevista.

**Diseño:** Ensayo aleatorizado, abierto, ciego para el evaluador, grupo paralelo, de no inferioridad.

**Entorno:** Centros de fertilidad.

**Paciente(s):** Un total de 620 mujeres con un valor sérico de hormona antimülleriana (AMH)  $\geq 5$  ng/mL.

**Intervención (es):** estimulación ovárica controlada con HP-hMG o rFSH en un ciclo de técnica de reproducción asistida (TRA) con antagonista de la GnRH. Se realizó una transferencia en fresco de un solo blastocisto a menos que la respuesta ovárica fuera excesiva, en cuyo caso todos los embriones se criopreservaron. Los sujetos pudieron someterse a una transferencia de blastocisto congelado posterior dentro de los 6 meses desde la aleatorización.

**Principales medidas de resultados:** tasa de embarazo en curso (TEC) después de una transferencia en fresco (objetivo primario), así como la tasa acumulada de nacidos vivos, síndrome de hiperestimulación ovárica (SHO) y tasas de pérdida de embarazo.

**Resultado(s):** La TEC/ciclo iniciado después de una transferencia en fresco fue de 35.5% con HP-hMG y 30.7% con rFSH (diferencia: 4.7%, IC 95% -2.7%, 12.1%); se estableció la no inferioridad. En comparación con rFSH, HP-hMG se asoció con tasas significativamente más bajas de SHO (21.4% vs. 9.7%, respectivamente; diferencia: -11.7%, IC 95% -17.3%, -6.1%) y tasas acumuladas de pérdida gestacional temprana (25.5% vs. 14.5% respectivamente; diferencia: -11.0%, IC 95% -18.8%, -3.14%). A pesar de que hubo 43 transferencias más en el grupo de rFSH, las tasas acumuladas de nacidos vivos fueron similares con HP-hMG y rFSH de 50.6% y 51.5% respectivamente (diferencia: -0.8%, IC 95% -8.7%, 7.1%).

**Conclusión(es):** En pacientes con alta respuesta, HP-hMG proporcionó una eficacia comparable a la rFSH con menos eventos adversos, incluida la pérdida del embarazo, lo que sugiere su perfil optimizado de riesgo/beneficio en esta población.