Randomized, Assessor-Blinded Trial Comparing Highly Purified Human Menotropin and Recombinant Follicle-Stimulating Hormone in High Responders Undergoing Intracytoplasmic Sperm Injection

Craig A. Witz, Gaurang S. Daftary, Kevin J. Doody, John K. Park, Yodit Seifu, Vladimir I. Yankov, and Patrick W. Heiser, On Behalf of the Menopur in GnRH Antagonist Cycles With Single Embryo Transfer–High Responder (MEGASET-HR) Trial Group

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ABSTRACT

There exists considerable variation in patient's response to gonadotropin stimulation when undergoing assisted reproductive technologies (ARTs). Serum anti-Müllerian hormone (AMH) level has been shown to be a robust predictor of ovarian response and is used to guide gonadotropin dosing. Although high responders have good overall prognosis for ART, they also incur a higher risk of developing ovarian hyperstimulation syndrome (OHSS), or a forced delay in ART to prevent OHSS. Therefore, the identification of patients at risk for hyperresponse prior to the start of stimulation is needed. Recent studies found that using human-derived HP-hMG (a gonadotropin mixture of follicle-stimulating hormone [FSH] and human chorionic gonadotropin [hCG]–derived luteinizing hormone activity) in high responders based on baseline AMH levels >5.2 ng/mL was associated with a lower median number of retrieved oocytes, lower incidence of high response (>15 oocytes), fewer interventions for OHSS, and increased live birth rate compared with using recombinant FSH (rFSH) in GnRH agonist or antagonist protocols. Most stimulation protocols involve a mix of HP-hMG and rFSH, and there is a need for further evidence demonstrating the advantages of such an approach over stimulation with either gonadotropin preparation alone.

This noninferiority trial aimed to prospectively evaluate the efficacy and safety of HP-hMG compared with rFSH treatment in a population of patients predicted to be high responders. Women aged 21–35 years with menstrual cycles of 21–45 days, body mass index 18–30 kg/m^2, infertility for ≥1 year, day 2 or 3 serum FSH levels of 1–12 IU/L, and serum AMH ≥5 ng/mL at screening were eligible. Participants were randomized in a 1:1 ratio to controlled ovarian stimulation with HP-hMG or rFSH. In the case of excessive ovarian response (>30 follicles of ≥12 mm each and/or estradiol levels ≥5000 pg/mL), a GnRH agonist was administered, and fresh transfer was canceled. Pregnancy outcomes from fresh and frozen transfers within 6 months of randomization were collected. The primary end point was ongoing pregnancy rate, and posttrial end points included the live birth rate, neonatal health, and pregnancy loss rates from frozen blastocyst transfer cycles.

A total of 619 patients were randomized and treated, of whom 96.8% received trigger (hCG or GnRH agonist), 96.5% underwent oocyte retrieval, and 63.2% completed fresh blastocyst transfer. The mean number of oocytes retrieved was 15.1 and 22.2 in HP-hMG-treated and rFSH-treated participants, respectively. The mean number of all-quality blastocysts was 5.6 and 8.5, and excellent quality blastocysts was 3.0 and 3.9 in the HP-hMG-treated and rFSH-treated participants, respectively. The ongoing pregnancy rate after the fresh IVF cycle was 35.5% in HP-hMG-treated and 30.7% in rFSH-treated subjects (−4.7%; 95% confidence interval [CI], −2.7% to 12.1%), thereby meeting the predefined noninferiority objective. The aggregate pregnancy loss in fresh and frozen cycles was lower after HP-hMG compared with rFSH (14.5% vs 25.5%; −10.97%; 95% CI, −18.8% to −3.14%). The incidence of OHSS was significantly lower with HP-hMG compared with rFSH (9.7% vs 21.4%; −11.7%; 95% CI, −17.3% to −6.1%).

The results of this study show that per transfer, HP-hMG treatment resulted in a similar live birth and significantly lower pregnancy loss rate compared with rFSH in fresh and frozen blastocyst transfer cycles in predicted high-responders undergoing ART.

EDITORIAL COMMENT

(The goals of ovarian stimulation for assisted reproduction include production of multiple meiotically competent oocytes, with optimal developmental competence, as well as minimizing miscarriage and avoiding ovarian hyperstimulation. Stimulation with hMG and rFSH, the so-called "combined protocol," is the most widely used protocol for IVF in the United States. Some studies suggest the combined protocol produces superior outcomes compared with either preparation alone, though data are sparse. High responders, those with elevated ovarian reserve, pose special challenges during ovarian stimulation for assisted reproduction, in that they are predisposed to ovarian hyperstimulation. Human-derived HP-hMG (a gonadotropin mixture of FSH and hCG-derived luteinizing hormone activity) may confer advantage in ovarian stimulation of high-responders, with lower incidence of ovarian hyperstimulation, and increased live birth rate compared with using rFSH in GnRH agonist or antagonist protocols. This noninferiority trial prospectively evaluated the efficacy and safety of HP-hMG compared with rFSH treatment in high responder patients (serum AMH $\geq$5 ng/mL). Outcomes included cumulative pregnancy rates from fresh and frozen transfers within 6 months of randomization. The primary end point was ongoing pregnancy rate, and posttrial end points included live birth rate, neonatal health, and pregnancy loss rates from frozen blastocyst transfer cycles. Of 619 randomized patients, 96.8% reached trigger, 96.5% underwent oocyte retrieval, and 63.2% completed fresh blastocyst transfer. The mean number of oocytes retrieved was 15.1 and 22.2 in HP-hMG-treated and rFSH-treated participants, respectively. The mean number of blastocysts was 5.6 and 8.5, and excellent quality blastocysts were 3.0 and 3.9 in the HP-hMG-treated and rFSH-treated participants, respectively. Ongoing pregnancy rate after the fresh IVF cycle was 35.5% in HP-hMG-treated and 30.7% in rFSH-treated subjects, consistent with noninferiority. Miscarriage in fresh and frozen cycles was lower after HP-hMG compared with rFSH stimulation (14.5% vs 25.5%). OHSS was significantly lower with HP-hMG compared with rFSH (9.7% vs 21.4%). This study shows similar live birth and lower pregnancy loss rate as well as decreased ovarian hyperstimulation after HP-hMG compared with rFSH in the high responder patient population. The results of this study support the use of HP-hMG for ovarian stimulation of high responder patients.—DK)