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Clinical utility of newly developed highly purified human menopausal gonadotrophins: a randomized controlled trial

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KEY MESSAGE
The newly developed HP-HMG, IVF-M HP, was not inferior to Menopur in number of retrieved oocytes when used for ovarian stimulation after GnRH antagonist protocol in women undergoing IVF. Additionally, IVF-M HP had a comparable clinical efficacy and safety profile to those of Menopur, without significant safety concerns.

A B S T R A C T

The aim of this study was to evaluate the safety and efficacy of IVF-M HP, a newly developed highly purified human menopausal gonadotrophin preparation, for ovarian stimulation in women with infertility undergoing IVF, intracytoplasmic sperm injection (IVF–ICSI) and embryo transfer using a GnRH antagonist protocol. This was a multicentre, randomized, active-controlled, parallel design, open-label, non-inferiority clinical study. Of the 112 patients randomized for treatment using the GnRH antagonist protocol, 111 were treated. No significant difference was found in the number of oocytes retrieved from the IVF-M HP and Menopur groups (13.1 ± 7.6 versus 10.3 ± 6.7, respectively). The lower limit of the one-sided 97.5% confidence interval for the difference between the groups was –0.25, i.e., greater than the pre-defined non-inferiority margin (–5). Therefore, the IVF-M HP treatment was considered non-inferior to Menopur. Furthermore, no significant difference was observed between the groups in the number of good-quality oocytes, leading follicles, good-quality embryos, or in fertilization, implantation, positive beta-HCG and clinical pregnancy rates. The safety analysis revealed that 40.4% and 35.2% in the IVF-M HP and Menopur groups, respectively, reported adverse events. In conclusion, IVF-M HP had comparable clinical efficacy and safety profiles to Menopur.

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Introduction

In modern medicine, IVF is a method that is actively used to treat couples with infertility. This process requires ovarian stimulation, and various medicines have been developed to achieve this. The gonadotrophin preparations for ovarian stimulation are classified as FSH-only products and combinations, which possess FSH and LH activity. Among them, the menotrophin preparation is a gonadotrophin extracted from the urine of postmenopausal women, and contains FSH, LH and HCG, unlike the recombinant FSH preparations, and shows biological activity of FSH and LH in a 1:1 ratio. The advantages of LH activity have already emerged in ovarian stimulation (De Placido et al., 2001). It is known that LH plays an important role in the follicular development process by acting on the theca cells to synthesize androgen in the early follicular phase. In addition, it plays an important role in oestradiol synthesis, follicular growth and final maturation of oocytes in the mid-late follicular phase (Raju et al., 2013).

During ovarian stimlation for IVF, the granulosa cells, which are hyperstimulated by FSH, produce a large amount of progesterone. Furthermore, insufficient enhancement of LH activity results in the non-activation of theca cells, which consequently causes some of the progesterone produced by the granulosa cells to enter the blood circulation and, thereby, increase the blood progesterone level. This may cause endometrial prematurity, which in turn may affect pregnancy and implantation. In such cases, the exogenous stimulation of LH activity further activates the theca cells and directs progesterone to the androgen synthesis pathway, which prevents progesterone absorption into the blood. As a result, the progesterone level is decreased while the oestrogen level is increased in the body circulation, which would increase the endometrial receptivity and improve the quality of oocytes and embryos (Fleming and Jenkins, 2010; Leao Rde and Esteves, 2014).

Preparations with LH activity can be classified into HMG menotrophins and highly purified HP-HMG based on the manufacturing process. The advantage of HP-HMG is that it is available as a subcutaneous injection based on its improved purity. The enhanced purity is achieved by subjecting the HMG to two or three additional purification steps, which reduces the local reactions on injection sites. In addition, the LH activity in HP-HMG is mainly derived from HCG, which is concentrated during purification steps (van de Weijer et al., 2003; Practice Committee of the ASRM, 2008; Leao Rde and Esteves, 2014).

IVF-M HP is a newly developed HP-HMG preparation by LG Life Sciences, Ltd, and this is the first clinical study using this new preparation. Therefore, the primary objective of this study was to demonstrate the non-inferiority of IVF-M HP to comparator product (Menopur) in the number of oocytes retrieved, and to evaluate further clinical utility, including efficacy and safety of IVF-M HP for ovarian stimulatoin in women undergoing IVF–ICSI and embryo transfer using the GnRH antagonist protocol.

Material and methods

Study approval and ethics

This was a multicentre, randomized, active-controlled, parallel design, open-label clinical study conducted in three institutions in Korea from July 2013 to November 2014, and was registered at clinicaltrials.gov (NCT02458768). It was designed as a non-inferiority study. The study, which was approved by the Institutional Review Boards (IRBs) of the respective sites (Cheil General Hospital and Women's Healthcare Center (IRB Approval No. CGH-IRB-2013-6, 4 April, 2013); CHA Fertility Center of Bundang CHA General Hospital (BD2013-039, 16 April, 2013); Samsung Medical Center (SMC2013-03-012-001, 12 April, 2013), was conducted in accordance with Good Clinical Practice, Declaration of Helsinki, and the International Conference on Harmonization guidelines for Good Clinical Practice, and local regulatory requirements and laws. The aims, methods, anticipated benefits and potential hazards of the study were explained to all participants, and written informed consent was subsequently obtained from each participant.

Study population

The study was conducted in women with infertility aged 20–39 years, with a mean menstrual cycle length of 25–35 days, and who were undergoing IVF procedures using assisted reproduction techniques. The infertility of the enrolled participants was caused by at least one of the following: tubal, male, unknown causes or combined factors. Among the paraticipants, those that met any of the following criteria were excluded from the study: FSH level exceeding the upper limit of normal at each study institution, a body mass index over 30 kg/m^2, ovarian hyperstimulation syndrome (OHSS), poor ovarian responders based on the Bologna criteria (Ferraretti et al., 2011), and more than three experiences of IVF procedures. In addition, those who were ineligible for the clinical study (with at least a borderline ovarian tumour; history of breast malignant tumour; severe diseases such as heart, renal, or hepatic failures, or a history of thromboembolism in the vein or artery) were excluded from the study. Eligible participants were randomized to either of the test or active comparator groups in a 1:1 ratio at menstrual cycle day 2 or 3 (**Table 1**).

Study design

A total 124 participants were screened, out of which 112 were randomized for treatment with the GnRH antagonist protocol. The block randomization by a computerized random allocation was conducted on menstrual cycle day 2 or 3. One patient randomized to the Menopur group withdrew before receiving treatment. The investigational product was initiated for 57 and 54 participants in IVF-M HP (LG Life Sciences, Ltd. Korea) and the active comparator (Menopur, Ferring) groups, respectively, at the initial recommended dose of 225 IU, and the same dose was administered by the next visit. After 5 days of investigational product administration, the dose could be adjusted based on follicular growth and serum oestradiol concentration to avoid poor ovarian response or OHSS, and the administration time point of the GnRH antagonist (Orgalutran injection [Inj.], 0.25 mg/0.5 ml, Organon Korea) was determined. Once at least three follicles reached a diameter of 17 mm or more, HCG (Ovidrel, Merck Serono, 250 μg or Pregnyl, MSD, 5000–10000 IU) was administered to induce final oocyte maturation and ovulation. The oocytes were retrieved 36–38 h after HCG administration, and fertilization was carried out using IVF, ICSI, or IVF–ICSI based on the investigator's decision. For the luteal phase enhancement, progesterone (Utrogestan, Besins Healthcare; Taiyu progesterone Inj., Taiyu C&P) was administered intravaginally or intramuscularly up to 8 weeks after oocyte retrieval. Embryo transfer was carried out 2–5 days after oocyte retrieval, and the blood test (beta-HCG) was conducted about 2 weeks after oocyte retrieval to confirm pregnancy. The gestational sac was monitored using a transvaginal

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