A prospective, randomized, controlled trial comparing three different gonadotropin regimens in oocyte donors: ovarian response, in vitro fertilization outcome, and analysis of cost minimization

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Objective: To compare the efficacy of three different gonadotropin regimens in an oocyte donation program. The analysis of cost minimization also was evaluated.
Design: Prospective, randomized, controlled study.
Setting: Instituto Universitario–IVI, Valencia, Spain.
Patient(s): One thousand twenty-eight donors undergoing a GnRH agonist protocol were assigned randomly to one of three groups: group 1 (n = 346), only recombinant FSH (rFSH); group 2 (n = 333), only highly purified menotropin (HP-hMG); and group 3 (n = 349), rFSH plus HP-hMG. One thousand seventy-nine oocyte recipients.
Intervention(s): Controlled ovarian stimulation.
Main Outcome Measure(s): Controlled ovarian stimulation parameters, IVF outcome, and cost analysis.
Result(s): No differences were found among the groups with respect to days of stimulation, gonadotropin dose, final E_2 and P levels, number of oocytes retrieved, and cancellation rate. Similarly, there were no differences among the groups in terms of embryo development parameters. Moreover, implantation, pregnancy, and miscarriage rates with the three regimens were similar. However, the cost of rFSH was greater than that of the other protocols.
Conclusion(s): This study suggests that in the GnRH agonist protocol the three different gonadotropin regimens evaluated herein are equally effective. Protocols using HP-hMG would appear to be the best in terms of cost-effectiveness in an oocyte donation program. (Fertil Steril® 2010;94:958–64. ©2010 by American Society for Reproductive Medicine.)

Key Words: Cost minimization, embryo quality, IVF outcome, menotropin, recombinant FSH, oocyte donation, oocyte quality, ovarian stimulation

The impact on IVF outcome of the different gonadotropin preparations, such as urinary hMG, highly purified menotropin (HP-hMG), and recombinant FSH (rFSH), has been widely debated (1–12). A PubMed search of the field yields approximately 690 publications, of which 56 are reviews, 11 are meta-analyses, and 7 are randomized controlled trials.

In an oocyte donation program, the primary objective is to obtain oocytes that can generate good embryos with a high potential for implanting and developing into a pregnancy. Discrepancies in the literature make it difficult to decide what kind of gonadotropin to administer to women undergoing the long protocol. In addition, the cost-effectiveness of the chosen regimen must be taken into account, as ovarian stimulation represents approximately 28% of the total cost of the treatment.

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Bearing in mind the controversial results, we decided to carry out a trial that would clarify the matter. The primary objective was to evaluate the implantation, pregnancy, and miscarriage rates associated with three different protocols of ovarian stimulation. The secondary objective was to compare the parameters of controlled ovarian stimulation, embryo development, and the cost observed with these regimens.

MATERIALS AND METHODS

The project was approved by the Institutional Review Board on the Use of Human Subjects in Research of the Instituto Universitario–IVI, Valencia, Spain, and complied with the Spanish Law of Assisted Reproductive Technologies (14/2006). The ClinicalTrials.gov identifier is NCT00829075. This was a prospective, randomized, controlled, parallel-groups study conducted in a private infertility clinic (Instituto Valenciano de Infertilidad, Valencia, Spain) between January 2005 and December 2007.

Inclusion and Exclusion Criteria

Donors were healthy women of 18 to 34 years of age, with regular menstrual cycles, no family history of hereditary or

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chromosomal diseases, normal karyotype, and body mass index (BMI) 18 to 29 kg/m^2 and showing negative screening for sexually transmitted diseases. Written informed consent was obtained. Women with polycystic ovary syndrome were excluded from this study (13, 14).

Recipients were healthy women of 18 to 49 years of age, with BMI 18 to 29 kg/m^2, and whose male partner did not present severe male factor (fresh spermatozoa $<5 \times 10^6$/mm^3, <5% normal forms, and/or nonobstructive azoospermia). The recipient couple gave their written informed consent. Cases with uterine pathology (submucous or more than 2 cm intramural fibroids, polyps, adhesions, adenomyosis, or müllerian defects), implantation failure, and recurrent miscarriage were excluded (13).

Randomization Method and Sample Size Calculation

One thousand twenty-eight donors were recruited and randomly assigned to groups fulfilling our inclusion criteria. The randomization visit took place on the first day of controlled ovarian stimulation (after pituitary down-regulation). Donors were assigned randomly to three groups by a study nurse, using computer-generated random numbers: group 1 (n = 284), 225 IU of rFSH (Gonal; Serono, Madrid, Spain); group 2 (n = 280), 225 IU of HP-hMG (Menopur; Ferring Pharmaceuticals, Madrid, Spain); group 3 (n = 290), 150 IU of rFSH (Gonal; Serono) plus 75 IU HP-hMG (Menopur; Ferring).

The study nurse coordinated the randomization process and distribution of medication throughout the controlled ovarian stimulation cycles. All embryologists, laboratory personnel, and sponsor staff, including the statistician responsible for the statistical analysis, were blinded to the treatment allocation. The sample size had been calculated previously assuming a pregnancy rate of 55% per cycle, alpha risk of 0.05, and beta risk of 0.20, thereby making it possible to detect differences >10% in a bilateral test.

Oocyte Donors

For controlled ovarian stimulation, only GnRH agonist protocols were used as previously described (15). In short, administration of 0.5 mg of leuprolide acetate (Procrin; Abbott, Madrid, Spain) began in the midluteal phase of the previous cycle and continued until negative vaginal ultrasound defined ovarian quiescence. The dose of GnRH agonist then was decreased to 0.25 mg until the day of hCG administration. The fixed starting dose of 225 IU gonadotropins per day was initiated on day 3 of menstruation and sustained for the first 5 days of controlled ovarian stimulation, during which serum E_2 was assessed. The gonadotropin dose was adjusted if necessary. Serial transvaginal ultrasound examinations were initiated on day 5 of controlled ovarian stimulation and were performed every 48 hours to monitor the follicular growth.

Human chorionic gonadotropin (Ovitrelle, 250 μg; Serono) was administered when three or more follicles reached 18 mm in diameter, and oocyte retrieval was scheduled 36 hours later. Serum E_2 and P levels were measured on the morning of hCG administration. Samples were tested with a microparticle enzyme immunoassay Axsym System (Abbott Cientifico S.A., Madrid, Spain). The serum E_2 kit had a sensitivity of 28 pg/mL and intraobserver and interobserver variation coefficients of 6.6% and 7.7%, respectively. The serum P kit had a sensitivity of 0.2 ng/mL, with intraobserver and interobserver variation coefficients of 9.6% and 3.9%, respectively. Groups were compared regarding controlled ovarian stimulation parameters, number of oocytes and proportion of mature oocytes retrieved (number of metaphase II oocytes/total oocytes retrieved—calculated for patients having intracytoplasmic sperm injection only), ovarian hyperstimulation syndrome (OHSS) incidence (16), and cost of treatment.

Oocyte Recipients

The protocol for hormonal replacement therapy has been described previously (17). In brief, down-regulation was achieved with use of an IM dose of 3.75 mg of triptorelin (Decapeptyl; Ipsen Pharma, Barcelona, Spain) beginning in the midluteal phase. Hormonal replacement therapy was initiated on day 1 to 3 of the following cycle, and doses of E_2 valerate (Progynova; Schering, Madrid, Spain) were increased as follows: 2 mg/d for the first 8 days of treatment, 4 mg/d for the following 3 days, and at least 6 mg/d until a pregnancy test was performed. On day 15, a scan was performed to evaluate endometrial growth. On the day after donation, 800 mg/d of micronized intravaginal P (Progeffik; Effik Laboratories, Madrid, Spain) were added. Embryo transfer was performed under ultrasound guidance on day 3 of development.

Oocyte and Embryo Evaluation—IVF Outcome

An oocyte was considered to be normally fertilized when two pronuclei were visible. Fertilization rate was defined as the proportion of oocytes resulting in the formation of two pronuclei. Cleavage rate was calculated as the number of cleaving embryos divided by the total number of normally fertilized oocytes.

Embryos were classified according to cell number, symmetry, and degree of fragmentation (18). The number of top-quality embryos was calculated by adding the number of cryopreserved embryos to the number of transferred embryos. Serum β-hCG was measured in recipients 16 days after oocyte donation. Implantation rate was obtained by dividing the number of gestational sacs revealed by the scan by the number of replaced embryos. Clinical pregnancy was confirmed 2 weeks later if a heartbeat was confirmed by transvaginal scan. Ectopic pregnancy was defined as a pregnancy sited out of the endometrium, detected by ultrasound or laparoscopy, or highly suspected because of symptoms and/or the β-hCG serum curve of the patient. Miscarriage rate was defined as the percentage of pregnancies not