Clinical efficacy of highly purified urinary FSH versus recombinant FSH in volunteers undergoing controlled ovarian stimulation for in vitro fertilization: a randomized, multicenter, investigator-blind trial

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Objective: To compare the efficacy of highly purified human urinary follicle stimulating hormone (HP-hFSH) versus human recombinant follitropin-alpha (rFSH) in volunteers undergoing controlled ovarian stimulation for IVF.
Design: A randomized, controlled, investigator-blind trial.
Setting: Four assisted reproductive technology centers.
Patient(s): One hundred fifty-two IVF patients.
Intervention(s): Volunteers, aged 18–39, were randomized to HP-hFSH (n = 76) versus rFSH (n = 76) at a starting dose of 300 IU in down-regulated cycles.
Main Outcome Measure(s): Number of oocytes, clinical pregnancy rate, and live birth rate with HP-hFSH versus rFSH.
Result(s): The total IU of gonadotropin used did not differ between the two groups. There was no difference in number of oocytes retrieved with HP-hFSH (mean = 16.3) compared with rFSH (mean = 17.1), confidence interval (CI) of difference = −3.79 to +2.18. Clinical pregnancy rate, as defined by the presence of a gestational sac, was 48.7% (CI = 37.0%–60.4%) with HP-hFSH versus 44.7% (CI = 33.3%–56.6%) with rFSH (CI of difference = −11.9% to +19.8%). Live birth rate was 38.2% (29 of 76) in both groups (CI = 27.2%–50.0%), for a difference between groups of 0.0% (CI of the difference = −15.4% to +15.4%).
Conclusion(s): There were no statistically significant differences in mean oocyte number, clinical pregnancy rate, or live birth rate between HP-hFSH versus rFSH. (Fertil Steril® 2009;91:1005–11. ©2009 by American Society for Reproductive Medicine.)

Key Words: IVF, clinical outcome, highly purified urinary FSH, recombinant FSH, pregnancy

Ovarian stimulation has been a key part of assisted reproductive technology since the early days of IVF (1). Numerous trials have compared the effectiveness of urinary and recombinant gonadotropins in controlled ovarian stimulation for IVF. The most inclusive and recent meta-analysis of 20 trials published in 2003 showed no significant difference in pregnancy rate per cycle start between urinary and recombinant gonadotropins in long-agonist cycles (2). Yet questions continue to be raised regarding whether or not urinary and recombinant gonadotropins are equivalent in efficacy, because not all studies have been consistent.

Some investigators have suggested that there could be a difference in efficacy because the methods used to produce urinary and recombinant products and the final content of the products differ. Recombinant human FSH is produced by inserting the DNA encoding the α and β subunits of FSH into a Chinese hamster ovary cell line (3). Recombinant FSH has no detectable LH activity. In contrast, highly purified human urinary gonadotropin products are extracted

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from postmenopausal urine using a manufacturing process that excludes extraneous proteins. For each 75 IU of FSH, the LH content varies from <1 IU (urofollitropin) to 75 IU (human menopausal gonadotropin).

Fostimon (IBSA, Institut Biochimique SA, Switzerland) is a highly purified urinary FSH product (USP 6,162,905) with <1 IU of LH activity per 75 IU of FSH. It has been available in several European and non-European countries since 1997. The purpose of this study was to compare the efficacy of Fostimon to that of recombinant follitropin-α (Gonal-F, EMD Serono, Switzerland) in volunteers undergoing controlled ovarian stimulation for IVF.

METHODS

Study Population

Volunteers were recruited from the practices of four fertility centers (one academic practice and three private practices) to participate in the study, which was conducted from February 2005 until May 2006. Institutional review board approval was obtained by each center and informed consent obtained from each volunteer before screening for the study. The study was funded by Institut Biochimique SA (IBSA), Switzerland.

Inclusion criteria were as follows: female, aged 18–39 years, body mass index (BMI) 18–30 kg/m^2, fewer than three prior oocyte retrievals, basal FSH <10 IU/L and estradiol <80 pg/mL, ≥10 antral follicles 2–10 mm in size, uterine cavity consistent with normal expected function as assessed through hysterosalpingogram, sonohysterogram, or hysteroscopy within 12 months of beginning the study, normal or clinically insignificant hematology and blood chemistry values, normal thyroid stimulating hormone (TSH) level or euthyroid as determined by the investigator (TSH could be low if secondary to exogenous thyroid medication as long as the volunteer was euthyroid by normal free thyroxine level). There were no other restrictions with respect to infertility diagnoses. Each volunteer was permitted to cycle once under the study protocol.

Exclusion criteria included the following: primary ovarian failure or women known to be poor responders (previous treatment cycles requiring >300 IU of FSH as a starting dose of having fewer than three oocytes retrieved or having a peak estradiol concentration of <500 pg/mL or 1,800 pmol/L), prior ovarian hyperstimulation syndrome, polycystic ovarian syndrome if the starting dose for that volunteer would normally be lower than that required by the study (i.e., likely intolerance to even 2 days of FSH 300 IU daily dose), one or both ovaries inaccessible for oocyte retrieval, persistent ovarian cysts >20 mm, hydrosalpinx if it had not been surgically removed or ligated, stage III or stage IV endometriosis, oocyte donation, any contraindication to pregnancy, abnormal bleeding of undetermined origin, uncontrolled thyroid or adrenal dysfunction, neoplasia, severe impairment of renal or hepatic function, and use of concomitant mediations that might interfere with study evaluations (e.g., nonstudy hormonal medications, prostaglandin inhibitors, psychotropic agents).

Study Design

This was a randomized, controlled, open-label, investigator-blind, multicenter study comparing highly purified human urinary FSH (HP-hFSH, Fostimon, IBSA, Switzerland, n = 76) versus recombinant follitropin-α (rFSH, Gonal-F, EMD Serono, Switzerland, n = 76).

After enrollment but before randomization, pituitary down-regulation was achieved with oral contraceptive pills and daily leuprolide acetate in the cycle before treatment. After 21 ± 7 days of oral contraceptive pills, volunteers began taking daily leuprolide acetate. Down-regulation was confirmed if endometrial thickness was ≤5 mm and there were no cysts >10 mm in diameter. If a cyst was present that was >10 mm but ≤20 mm, the patient was considered to be down-regulated if the estradiol level was <50 pg/mL. If criteria for down-regulation were not met on the initial baseline visit, daily leuprolide was continued for 6–24 days. If down-regulation was still not achieved, the volunteer was discontinued from the study.

After down-regulation was confirmed, volunteers were randomized to HP-hFSH or rFSH. Both products were supplied in vials each containing 75 IU. Randomization was performed according to a computer-generated randomization list in which volunteers were assigned to treatment at each center in blocks of four for the first 36 volunteers and then a block of two for the 37th and 38th volunteers. Randomization numbers were assigned chronologically from the list before the start of treatment. Sealed envelopes containing the randomization number on the exterior and treatment assignment in the interior were provided for all volunteers at each site to be opened by the investigator, requiring knowledge of the stimulatory agent, in case of an emergency. Study coordinators and volunteers were aware of which product was assigned to which volunteer, but both were strictly instructed to not discuss the treatment assignment with the physicians or embryologists. Study medication was handled only by study coordinators (not physician investigators), and was kept in a locked cupboard not accessible to the physician investigators.

All volunteers received a starting dose 300 IU. The dose could be adjusted up or down as early as stimulation day 3, up to a maximum dose of 450 IU/day. Measurements were made of all follicles ≥10 mm in diameter in two perpendicular diameters including the greatest diameter visualized. Estradiol levels were measured at each site using commercially available immunoassays. Daily gonadotropin and leuprolide acetate were continued until at least two follicles were >16 mm in average diameter. Human chorionic gonadotropin (hCG) dosage could be individualized per investigator preference.

Transvaginal oocyte retrieval was performed 34–36 hours after administration of hCG. Oocytes were fertilized either