Higher birth rate after recombinant hCG triggering compared with urinary-derived hCG in single-blastocyst IVF antagonist cycles: a randomized controlled trial

In a prospective randomized controlled trial, 119 patients were randomized to receive either recombinant hCG (250 μg) or urinary-derived hCG (10,000 IU) for final oocyte maturation in an antagonist protocol with a fixed dose of recombinant FSH (187.5 IU) and predefined single blastocyst transfer. The delivery rate was improved in the recombinant hCG group compared with the urinary-derived hCG group (44.1 vs. 25.7, respectively); however, adequately powered randomized controlled trials are justified to ascertain whether this difference is true. (Fertil Steril® 2010;94:2902–4. ©2010 by American Society for Reproductive Medicine.)

Key Words: Ovulation triggering, urinary hCG, recombinant hCG, delivery rate, GnRH-antagonists

Historically, urinary-derived hCG (u-hCG) has been used as an alternative to LH to induce final oocyte maturation in women undergoing ovarian stimulation for IVF or intracytoplasmic sperm injection (1). U-hCG has certain limitations such as batch to batch inconsistency, urinary protein contamination, and scarcity of the available biosource. In contrast, recombinant hCG is manufactured with a high degree of purity and high specificity, and it is practically free from fetal bovine serum proteins, nucleic acids, or other contaminants (2, 3).

A recent Cochrane review and metaanalysis reported no significant differences between recombinant hCG vs. u-hCG regarding the ongoing pregnancy rate (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.69–1.39), miscarriage rate and the incidence of ovarian hyperstimulation syndrome (OHSS) in GnRH agonist protocols (4). Interestingly, the authors, apart from three IVF studies, also included an intrauterine insemination study. Previously, ovulation triggering studies were not performed in GnRH-antagonist protocols and specifically not during the developmental stage of the embryos. Recent evidence has suggested that urinary hCG preparations contain contaminants, such as epidermal growth factor (EGF), which negatively affect the trophoblast invasion (5).

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The ovarian stimulation was performed using a recombinant FSH/GnRH-antagonist protocol (6). The initial gonadotropin dose was predefined at 187.5 IU (Gonal-F; Merck-Serono, Geneva, Switzerland) for all patients and remained fixed for 5 days; from this day onward, a GnRH antagonist was co-administered (Cetrotide; Merck-Serono). Final oocyte maturation was induced with either 10,000 IU u-hCG (Pregnyl; NV Organon, Oss, The Netherlands), or 250 μg recombinant hCG (Ovitrelle; Merck-Serono) when at least three follicles of 17 mm were present at the ultrasound examination. Luteal support was administered in the form of 600 mg micronized progesterone vaginally. A clinical pregnancy was defined as the presence of a heart beat at 7 weeks’ gestation. Data were collected during pregnancy until delivery. Sperm preparation, IVF, intracytoplasmic sperm injection procedures, and embryo culture were performed as described elsewhere (7). Group sample sizes of 56 and 56 achieve 80% power to detect a difference of 0.15 between the null hypothesis that the mean blastulation rate in both groups is 0.45, and the alternative hypothesis that the mean of group 2 is 0.60 with estimated group SDs of 0.28 and 0.28 and with a significance level (α) of 0.05000, using a two-sided two-sample t test. The preceding scenario was based on preliminary findings from the use of recombinant hCG and compared with the baseline 40–45% blastulation rate in our laboratory. Statistical analysis was performed using SPSS version 15 software (SPSS, Inc., Chicago, IL). Fisher’s exact test, t test and Mann-Whitney test were used accordingly. All tests were two tailed with a confidence level of 95% (P=0.05). Values are expressed as mean ± SEM.

Overall, 119 patients were randomized: 59 received 250 μg recombinant hCG triggering, and 60 received the standard 10,000 IU u-hCG. All patients were analyzed according to an intention to treat analysis. There was no difference between the two groups regarding age, stimulation days, and total gonadotrophin consumption; however, serum hCG was significantly higher in the u-hCG group on the day of the oocyte retrieval (246 vs. 120, respectively; P=0.01) and on day 5 after oocyte retrieval (21 vs. 8, respectively; P=0.01; Table 1). The mean number of fertilized oocytes was 8.3 in the recombinant hCG group (13.2 cumulus oocyte complexes [COCs] retrieved) compared with 6.9 in the standard group (12 COCs retrieved; P=0.08). Two patients in the recombinant hCG group and four in the u-hCG group did not undergo embryo transfer, because none of their embryos reached the blastocyst stage. The blastulation rate was equal between the two groups (59 vs. 59%, respectively; Table 1).

Initially, similar positive hCG rates were achieved with both protocols (47.5 in the recombinant hCG group vs. 41.7% in the u-hCG group). However, because of a significantly higher early pregnancy loss rate (biochemical pregnancies) with the standard 10,000 u-hCG protocol (28.0% vs. 3.5; P=0.01), a statistically significant higher delivery rate was observed in the recombinant hCG group (44.1%) compared with the u-hCG group (25.7%; OR, 2.16; 95% CI, 1.01–4.67; P=0.04) (Table 1). Two OHSS cases, one early and one late, were recorded when recombinant hCG was used to trigger final oocyte maturation. One early OHSS case was observed in the u-hCG group.
To our knowledge, this is the first study in which possible differences between recombinant hCG and u-hCG regarding blastulation rate and reproductive outcome were studied in GnRH antagonist cycles. Several randomized trials have tested the aforementioned regimens in GnRH agonist downregulated IVF cycles, finding either equivalence (8, 9) or superiority with recombinant hCG (10–12). In all previous trials, the exact number and stage of embryos transferred were not strictly defined according to the study protocol. In contrast, the present trial was designed to focus on a single blastocyst stage embryo transfer, because single blastocyst transfer appears to be the most optimal choice in women younger than 36 years (7). This design constitutes a major strength of the study; therefore, the differences in delivery rates could be attributed solely to the different regimens used (recombinant hCG and u-hCG) for oocyte maturation. Nevertheless, the study was powered for blastulation rate and is, therefore, underpowered to detect statistical differences regarding the delivery rates.

The difference in reproductive outcome observed in the current study—in favor of recombinant hCG—could be attributed either to the use of a recombinant preparation to trigger final oocyte maturation or to the lower dose equivalent of the 250 µg of recombinant hCG (6,500 IU vs. 10,000 IU), or a combination of both. Principally, the higher delivery rates favoring recombinant hCG might be attributed to differences in endometrial advancement induced by recombinant hCG and u-hCG. A previous randomized study by our group (13) revealed a nonsignificant higher number of patients with ≥3 days of endometrial advancement when treated with the standard 10,000 IU u-hCG compared with 250 µg recombinant hCG. Moreover, it is known that when endometrial advancement exceeds 3 days, the probability of pregnancy becomes poor (14). Because we found significantly higher serum concentrations of hCG after u-hCG administration compared with the recombinant group and hCG receptors are present on the endometrium, a direct effect of the hCG preparations and the dose administered for oocyte maturation cannot be excluded.

Alternatively, an embryonic factor could also be of importance for the present outcome. Thus, the higher dose of hCG and the fact that u-hCG contains hCG degradation products (15) might play a role in the final oocyte maturation. As a result, with 10,000 IU u-hCG the produced mature oocytes might have accomplished nuclear maturation, but not an appropriate cytoplasmic maturation, resulting in defective fertilized oocytes and thus blastocysts with a high probability of miscarriage if implantation occurs. Furthermore, Saleh et al. (5) have shown that the EGF contamination of urinary hCG considerably affects the function of the trophoblast. Using EGF-free hCG preparations, as is the case in the recombinant form, the authors demonstrated an increased trophoblast invasion and syncytialization that suggests appropriate implantation (5).

This randomized trial shows that in GnRH-antagonist IVF or intracytoplasmic sperm injection cycles, triggering of final oocyte maturation with recombinant hCG (250 µg) seems to improve the reproductive outcome, compared with u-hCG. However, to draw firm conclusions, an adequately powered randomized controlled trial is needed.

REFERENCES


