Low-dose human chorionic gonadotropin may improve in vitro fertilization cycle outcomes in patients with low luteinizing hormone levels after gonadotropin-releasing hormone antagonist administration

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Objective: To evaluate the effect of low levels of endogenous luteinizing hormone (LH) and low-dose human chorionic gonadotropin (hCG) supplementation on in vitro fertilization (IVF) cycle outcomes in a gonadotropin-releasing hormone (GnRH) antagonist protocol.
Design: Retrospective study.
Setting: Military medical center.
Patient(s): General in vitro fertilization/embryo transfer (IVF-ET) population.
Intervention(s): Addition of low-dose urinary hCG to IVF stimulations using a recombinant follicle-stimulating hormone (FSH) and GnRH antagonist protocol.
Main Outcome Measure(s): Implantation and live-birth rates.
Result(s): As part of a larger cohort of 239 patients, 42 patients with LH levels $\leq$0.5 mIU/mL were evaluated. In the larger cohort, there were no differences in implantation and pregnancy rates between the recombinant FSH only (n = 113) and the recombinant FSH with low-dose hCG supplementation (n = 126) groups. In the FSH-only group, patients with LH levels $\leq$0.5 mIU/mL had decreased implantation rates (19% vs. 42%) and live-birth rates (25% vs. 54%) as compared with patients with LH levels >0.5 mIU/mL. Low LH patients in the recombinant FSH with low-dose urinary hCG group had statistically significantly higher implantation rates (54% vs. 19%) and live-birth rates (64% vs. 25%) as compared with patients with similar low LH levels in the recombinant FSH-only group.
Conclusion(s): Endogenous LH levels $\leq$0.5 mIU/mL after GnRH antagonist treatment are associated with statistically significantly lower implantation and pregnancy rates in recombinant FSH-only cycles. The addition of low-dose urinary hCG results in improved implantation and live-birth rates in patients with low LH levels. (Fertil Steril® 2011;96:898–904. ©2011 by American Society for Reproductive Medicine.)

Key Words: GnRH antagonist, IVF, low-dose uhCG, luteinizing hormone

The use of gonadotropin-releasing hormone (GnRH) antagonists in place of GnRH agonists has increased in in vitro fertilization (IVF) stimulation protocols (1). Unlike GnRH agonists, which require prolonged administration for pituitary suppression, GnRH antagonists allow for immediate suppression of pituitary gonadotropins (2). Additional advantages of GnRH antagonists include reducing the amount of exogenous gonadotropins required for IVF stimulation, shortening the duration of stimulation, and avoiding a gonadotropin flare (2). Rates of ovarian hyperstimulation syndrome are also decreased with GnRH antagonists (3). However, GnRH antagonists cause a rapid and profound inhibition of endogenous luteinizing hormone (LH) secretion (4–6), and this suppression occurs at a time when the follicle is most sensitive to LH activity. As described in the two-cell two-gonadotropin theory, normal follicular growth depends on both FSH and LH, and it has been shown that low levels of LH may negatively affect pregnancy and implantation rates (7). Although the level of endogenous LH necessary for normal follicular development is unknown, the conclusions from several studies suggest that low levels of LH are associated with higher rates of early pregnancy loss (7–9).

The effect of GnRH antagonist on LH and estradiol levels before oocyte retrieval was studied in the ganirelix dose-finding study (10).

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It was shown that as the dose of ganirelix acetate increased, the serum LH and estradiol concentrations decreased in a dose-dependent manner (10). The number of good-quality embryos and the number of embryos transferred in the four different dosage groups were similar. However, the ongoing pregnancy rate was significantly lower in the groups with low levels of LH and estradiol before oocyte retrieval (10).

Donor IVF cycles using GnRH antagonists that were supplemented with recombinant LH had significantly higher fertilization and implantation rates (11). This suggests that GnRH antagonist use with recombinant FSH alone may have a negative impact on follicular growth and oocyte development. It is speculated that LH supplementation is necessary for normal granulosa cell function in GnRH antagonist cycles. These data indirectly suggest that low LH levels might lead to decreased implantation and pregnancy rates.

Recent evidence also shows that supplementation of GnRH antagonist cycles with human chorionic gonadotropin (hCG), a mimic of endogenous LH, provides comparable pregnancy rates to cycles using standard ovulation-induction protocols (12, 13). The administration of hCG promotes follicular growth and oocyte maturation, thereby decreasing the amount of FSH needed for ovarian stimulation (12, 14, 15). We previously published a study that showed that hCG supplementation results in lower medication costs and similar pregnancy rates compared with FSH-only stimulation for GnRH-antagonist IVF cycles (14). This retrospective study determines the effects of profound LH suppression after GnRH antagonist administration and determines whether low-dose hCG administration was beneficial in this patient population.

MATERIALS AND METHODS

This retrospective analysis examined 239 IVF or ICSI cycles in patients aged 23 to 40 years during the period May 2002 to October 2005. Institutional review board approval was obtained from Wilford Hall Medical Center. Inclusion criteria included all women who underwent ovarian hyperstimulation with recombinant FSH and ganirelix acetate (Merck) during this time period. Ovarian stimulation with recombinant FSH alone occurred until May 2004. After that all, patients were supplemented with low-dose hCG. An LH threshold of $\leq$0.5 mIU/mL was chosen to further group patients for analysis. The LH threshold of $\leq$0.5 mIU/mL was chosen based on data demonstrating that normogonadotropic patients with suppressed LH levels below this threshold have a higher rate of abortion and lower chance of live birth (8). Due to the retrospective nature of the study, a power analysis was not performed. The specific time frame for analysis was chosen, and data were not analyzed from other time periods so as not to introduce bias by choosing a time period that showed results in a specific direction.

Pituitary down-regulation was achieved with combined oral contraceptives (OCPs), which were started on day 5 of the cycle before ovarian stimulation. In the group using FSH alone, recombinant FSH (Gonal F, EMDSerono; or Follistim, Merck) was started at a dose of 150–600 IU per day (divided between a morning and evening dose) 5 days after discontinuation of combined OCP. In the group that was supplemented with low-dose hCG, recombinant FSH was started at a morning dose of 150 or 225 IU. Low-dose hCG (Pregnyl; Merck) was started concomitantly with recombinant FSH and was given in a daily evening dose of either 50 or 100 IU. The hCG dose was chosen to replace the evening FSH dose, and patients were given 50 IU of hCG if the FSH dose was less than 225 IU or 100 IU of hCG if the FSH dose was 225 IU or more. Transvaginal ultrasound was performed after 4 days of stimulation, and the dose of recombinant FSH and hCG was adjusted based on the number and size of follicles and the estradiol level.

A daily morning dose of 250 μg of ganirelix acetate was started when lead follicles were 13 to 14 mm in mean diameter. When there were at least two follicles with a mean diameter of $\geq$18 mm, with at least two additional follicles sized $\geq$10 mm, hCG was administered (5,000–10,000 IU). Oocyte retrieval was performed 36 hours later, and the embryos were transferred either 3 or 5 days after retrieval, depending on embryo number and quality. Luteal phase support was maintained with 50 mg of progesterone intramuscular injections daily beginning the evening after the oocyte retrieval and continuing until 7 to 8 weeks' estimated gestational age.

Serum LH and estradiol levels were measured before stimulation with FSH, before the start of the GnRH antagonist, at several intervals after the start of GnRH antagonist, and on the day of hCG administration for final oocyte maturation. All serum tests were drawn in the morning before the morning doses of gonadotropins or ganirelix acetate were administered. Luteinizing hormone and estradiol were measured by using an electrochemiluminescence immunoassay (Modular Analytics E170 module; Roche). The detection limits for LH and estradiol were 0.10 mIU/mL and 5.0 pg/mL, respectively. The intra-assay and interassay coefficients of variation were 1.2% and 2.0%, respectively, at the lowest mean dose of LH. The intra-assay and interassay coefficients of variation were 2.0% and 2.2%, respectively, at a mean level of 3,715 pg/mol. The LH assay used shows no cross-reactivity with FSH, thyroid-stimulating hormone (TSH), or hCG. Serum hCG levels were not measured in this study, including in the patients in the recombinant FSH + hCG group.

Statistical Methods

All analyses were performed using SPSS 13 for Windows (SPSS, Inc.). Exploratory data analysis was initially performed to determine normality of the data. The parametric continuous variables were analyzed by using Student's *t*-test, and the results are expressed as mean $\pm$ standard deviation. The nonparametric continuous or ordinal data were analyzed with the Mann-Whitney *U* test. Percentages or rates were compared by using either chi-square or Fisher's exact test, as indicated.

RESULTS

A total of 239 IVF-ICSI cycles were analyzed. Forty-two cycles where patients had an LH level $\leq$0.5 mIU/mL were analyzed as part of this larger cohort. Seven cycles were canceled before embryo transfer, and two after oocyte retrieval had occurred. All of the canceled cycles were in the LH >0.5 IU/mL group. Patients were grouped based on stimulation with or without low-dose hCG and based on the lowest value of LH obtained at any point after the initiation of GnRH antagonist before the administration of hCG for final oocyte maturation using a threshold of LH $\leq$0.5 mIU/mL or greater. Any LH value $\leq$0.5 mIU/mL at any time after the start of the GnRH antagonist qualified a patient to be placed in the low LH group. There were 113 cycles in the FSH-only group and 126 cycles in the FSH with low-dose hCG group. In the FSH-only group, 20 patients had LH levels $\leq$0.5 mIU/mL. In the FSH with low-dose hCG group, 22 patients had LH levels $\leq$0.5 mIU/mL.

Estradiol and LH levels were measured at baseline and at each ultrasound visit through the administration of the hCG trigger shot (Table 1). The baseline LH levels of the FSH-only and FSH with low-dose hCG groups were similar (2.5 $\pm$ 2.4 vs. 2.5 $\pm$ 2.4 mIU/mL, P=.98). Patients in the low LH group who received FSH only had lower baseline LH levels than did the patients in the normal LH group who received FSH only (0.5 $\pm$ 0.6 vs. 2.9 $\pm$ 2.5 mIU/mL, P<.01). Similarly, patients in the low LH group who received low-dose hCG had lower baseline LH levels than did the patients in the normal LH group who received low-dose hCG (1.1 $\pm$ 2.2 vs. 2.5 $\pm$ 2.4 mIU/mL, P<.01). The baseline LH levels were not different between the FSH-only and FSH with low-dose hCG groups (0.33). The women in the FSH with low-dose hCG group were on average 1 year older (P=.04).

There were no differences in implantation, spontaneous abortion, or live-birth rates between the groups receiving FSH only and FSH with low-dose hCG (see Table 1). The FSH with low-dose hCG group used less total FSH (1,868 vs. 2,899 IU, P<.01) and had