Successful Pregnancies in Patients with Estrogenic Anovulation After Low-Dose Human Chorionic Gonadotropin Therapy Alone Following hMG for Controlled Ovarian Hyperstimulation

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Objective: To demonstrate that folliculogenesis can be sustained with 200 IU human chorionic gonadotropins (hCG) after FSH-priming and result in pregnancy in women with estrogenic ovulatory dysfunction and risk factors for severe ovarian hyperstimulation syndrome (OHSS).

Design: Case report: Three women with infertility associated with estrogenic ovulatory dysfunction and hyperinsulinemia who appeared to be at high risk for severe OHSS during gonadotropin therapy.

Interventions: After 10 days of receiving either 150 IU hMG or recombinant FSH, patients were switched to 200 IU hCG/day alone for 2–3 days. 5,000 IU of hCG was then administered followed by either home intercourse, intrauterine insemination or transvaginal oocyte retrieval-embryo transfer.

Main Outcome Measures: Endovaginal ultrasound measurement of follicle number and size, serum estradiol levels, symptoms of ovarian hyperstimulation, pregnancy test, and evaluation of pregnancy by transvaginal ultrasound.

Results: After discontinuation of hMG or recombinant FSH, serum estradiol concentrations continued to rise, and follicles >14 mm continued to grow during low-dose hCG administration. All women conceived without developing symptoms of OHSS. Pregnancy outcomes achieved include a term singleton delivery, a term twin delivery, and triplets delivered at 31 weeks gestation.

Conclusion: The use of low-dose hCG alone is sufficient for supporting the late stages of folliculogenesis in women with estrogenic ovulatory dysfunction. This ovulation induction regimen appears to support the follicular growth of larger follicles while decreasing the number of smaller preovulatory follicles, thereby reducing a known risk factor for OHSS. We report on the positive pregnancy outcomes in 3 women with estrogenic ovulatory dysfunction and clinically appeared to be at high risk for developing severe OHSS who safely underwent this protocol.

KEY WORDS: Gonadotropin therapy; infertility; ovarian hyperstimulation syndrome; polycystic ovarian syndrome; pregnancy.

INTRODUCTION

Ovulation induction with exogenous gonadotropins is based on the principle that continuous dosing with FSH beginning in the early follicular phase will
recruit multiple antral follicles and subsequently lead to full maturity of the oocytes contained within these follicles. Traditionally, recombinant FSH or a purified mixture of FSH and LH has been used for ovulation induction. It has been classically taught that FSH is the major stimulatory factor needed for ovulation induction, while LH has a more accessory role in stimulating thecal androgen production and triggering ovulation. More recently, several studies in ovulatory women have focused on the use of low-dose hCG alone in the later part of the follicular phase, following a week of more traditional FSH stimulation (1–3). Successful outcomes have been reported following such an ovulation induction scheme followed by assisted reproduction technology or in association with controlled ovarian stimulation protocols. All of these studies have focused on the ovulatory infertile patient.

Polycystic ovarian syndrome (PCOS) affects an estimated 6–10% of reproductive age women and is the most common endocrinopathy affecting infertile young women. The hallmark of PCOS is estrogenic anovulation. In the last decade, it has been found that both obese and thin women with PCOS can exhibit insulin resistance, and a compensatory hyperinsulinemia. Excess insulin has been shown to indirectly stimulate ovarian androgen production by increasing LH-driven ovarian androgen synthesis (4,5). Although the use of insulin-sensitizers such as the biguanides (Metformin) in PCOS patients has been demonstrated to increase both spontaneous ovulation and ovulation in conjunction with clomiphene citrate, there is still a group of these patients who will remain refractory to this therapy and require treatment with parenteral gonadotropins. Ovarian hyperstimulation is a potential complication of gonadotropin therapy, especially among PCOS patients whose ovaries appear to be exquisitely sensitive to FSH stimulation. An exaggerated number of small preovulatory follicles has been correlated with an increased risk of developing severe ovarian hyperstimulation syndrome (OHSS) (6). As demonstrated by Fillicori (1,2), increasing the dose of hCG in the late follicular phase is associated with a decrease in the number of small (<12 mm) follicles.

This protocol utilized medications standard to ovulation induction, albeit at different dosages, and was approved by our institutional review board.

CASE REPORTS

1) S.E. is a 28-year old thin, nulligravid female (BMI 22) with 1 year of infertility, a history of irregular menses since menarche and mild insulin resistance. Her insulin level rose to 40 mIU/mL (reference 2–23 mIU/mL) 1 h after a 75 g glucose load. The diagnostic evaluation included a normal semen analysis, normal hysterosalpingogram, and a normal diagnostic laparoscopy and hysteroscopy.

Ovulation induction was initiated with parenteral gonadotropins after she failed to resume normal cycles while taking metformin 1,000 mg twice daily in conjunction with clomiphene citrate (100 mg, 3–7 days). She received 75 IU hMG (Repronex) and 75 IU recombinant FSH (Follistim) for a total of 8 days. On cycle day 8 the ultrasound examination revealed 6 follicles 10 mm in diameter, >30 follicles smaller than 8 mm, and a serum estradiol concentration of 735 pg/mL. Two days later, she had 14 follicles with a diameter of 12 mm, and >30 follicles less than 8 mm and an estradiol of 987 pg/mL. FSH and hMG therapy was discontinued and she was given 200 IU hCG/day for 3 days. On cycle day 13, she had 8 follicles greater than 15 mm, 20 follicles <10 mm, and an estradiol of 1289 pg/mL. After discussing the risks of multiple gestation and ovarian hyperstimulation, she received an ovulatory dose of hCG (5,000 IU) followed by home intercourse 36 h later. She was instructed to report any symptoms associated with OHSS, including nausea, sudden weight gain, and increased abdominal distension. In addition a telephone call was made to her to confirm the absence of OHSS symptoms.

Fourteen days after the surrogate LH surge, her serum hCG was 243 mIU/mL. An ultrasound evaluation at 7 weeks gestation demonstrated a single intrauterine pregnancy (CRL 6.6 mm with cardiac activity). She has since completed an uncomplicated pregnancy, and delivered a healthy term infant.

2) C.S. is a 28-year old obese, nulligravid female (BMI 35) with 3 years of infertility, a history of oligomenorrhea since menarche, and evidence of insulin resistance. Her insulin levels were 207 mIU/mL and 98 mIU/mL (reference 2–23 mIU/mL) 1 and 2 h, respectively, after a 75 g glucose challenge. The diagnostic evaluation included a normal semen analysis and an HSG with multiple intrauterine filling defects and patent tubes. Hysteroscopy revealed endometrial polyps, which were removed. Although C.S.