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.

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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.

achieved regular predictable menstrual cycles and ovulatory levels of serum progesterone on metformin (1500 mg/day) and clomiphene citrate (100 mg, days 3–7), she failed to achieve pregnancy.

While still on metformin, ovulation induction was initiated with recombinant FSH (Follistim) at 150 IU/day after GnRH agonist suppression was achieved. On cycle day 10 of FSH, the ultrasound examination revealed 8 follicles >13 mm, 23 follicles <10 mm and a serum estradiol concentration of 1,965 pg/mL. FSH therapy was discontinued and she was given 200 IU hCG/day for 2 days. On cycle day 12, she had eight follicles >16 mm, three follicles between 10 and 14 mm, and seven follicles <10 mm. She received an ovulatory dose of hCG (5,000 IU) followed by a washed intrauterine insemination 36 h later. She was also instructed to report any symptoms of OHSS, and was subsequently interviewed by telephone to confirm the absence of OHSS symptoms.

Two weeks later, a serum quantitative hCG was positive at 463 mIU/mL, with appropriate rise 2 days later. An endovaginal ultrasound performed at 8 weeks gestation demonstrated a viable triplet intrauterine pregnancy. She has since delivered triplets at 31 weeks gestation.

3) S.A. is a 36-year old obese nulligravid female (BMI 31) with 6 years of infertility, a history of oligomenorrhea since menarche and evidence of insulin resistance. Her insulin levels were 170 mIU/mL and 98 mIU/mL (reference <27 mIU/mL) 1 and 2 h, respectively, after a 75 g glucose challenge. The diagnostic evaluation included a normal semen analysis and a normal hysterosalpingogram. Her family history includes a sister with estrogenic ovulatory dysfunction, who recently underwent a single cycle of IVF in Pakistan that was complicated by severe ovarian hyperstimulation requiring a prolonged hospitalization and sequential paracentesis and thoracentesis.

Ovulation induction was initiated at an outside hospital with parenteral gonadotropins after she failed to resume normal cycles while taking clomiphene citrate (150 mg days 3–7). In her first gonadotropin cycle, she had poor follicular recruitment after receiving a daily dose of 3 ampoules hMG. Her dose was increased to 4 ampoules daily. She then recruited 4 dominant follicles and reached a peak serum estradiol level of 6,000 pg/mL. The outside records did not notate the number and sizes of smaller follicles. She did not conceive but developed

OHSS. Her next gonadotropin cycle, initiated with 4 ampoules of hMG daily, was converted to IVF and all of the embryos were cryopreserved (17 oocytes retrieved/10 fertilized 2pn/3 blastocysts) due to the perceived recurrent risk of OHSS with a peak serum estradiol concentration of 7,400 pg/mL. The transfer of her cryopreserved embryos did not result in pregnancy. Her third gonadotropin cycle followed a 1-month interval of GnRH agonist suppression and was supplemented by metformin (1,000 mg daily). Her hMG dose was tapered from 3 ampoules daily to 1 ampoule daily over 12 days, followed by 3 days of coasting. Her estradiol level fell from 6,174 to 1469 pg/mL and she received an ovulatory dose of hCG (5,000 IU). Eight oocytes were retrieved, one 2-pn embryo resulted, but she did not conceive. Her fourth gonadotropin cycle followed a 1-month interval of oral contraceptives followed by GnRH suppression. She received 2 ampoules hMG daily for 3 days, followed by a decrease to 1 ampoule daily. After 13 days, endovaginal ultrasound demonstrated a single dominant follicle and 20 follicles <10 mm. This cycle was downgraded to an insemination, and again, pregnancy was not achieved. Her fifth gonadotropin cycle began with a prolonged course of GnRH agonist suppression followed by 2 ampoules of gonadotropin daily (75 IU recombinant FSH and 75 IU hMG). On cycle day 10, the ultrasound examination revealed 8 follicles >12 mm diameter, 12 follicles <10 mm diameter, and a serum estradiol of 1411 pg/mL. Gonadotropin therapy was discontinued, and she given 200 IU hCG daily for 2 days. On cycle day 12, ultrasound revealed nine follicles >15 mm diameter, two follicles between 12 and 14 mm diameter, six follicles <8 mm diameter and a serum estradiol of 4207 pg/mL. She received an ovulatory dose of hCG (5,000 IU) followed by a transvaginal oocyte retrieval 37 h later. Ten oocytes were retrieved, eight underwent intracytoplasmic injection, and five 2-pn embryos resulted. She had 4 embryos transferred on culture day 3 and received daily intramuscular progesterone luteal support. Her serum hCG was positive (480 mIU/mL) 14 days later and rose appropriately. Because of her multiple risk factors for OHSS, she was queried by telephone to assess for OHSS. She denied any adverse symptoms. Endovaginal ultrasound performed 3 weeks later revealed 2 gestational sacs, each with an appropriately sized embryo. She has since delivered twins at term, with pregnancy complicated by gestational diabetes.

DISCUSSION

Several recent studies have demonstrated success in ART and gonadotropin-stimulated COH cycles using LH-activity in lieu of FSH in the terminal portion of the follicular maturation phase (1–3). Physiologically, this scheme may mimic the natural spontaneous cycle better. During the mid and late follicular phase of a natural cycle, preovulatory follicular development continues, despite a decrease in systemic FSH levels. Once a follicle reaches a threshold of development, LH can stimulate granulosa function, due to the induction of LH receptors on FSH and estrogen primed granulosa cells. All prior reports on successful pregnancy after this type of induction scheme have utilized normal ovulatory women. Women with ovulatory dysfunction were excluded. Patients with estrogenic anovulation have traditionally posed a challenge in ovulation induction due to an exaggerated number of small preovulatory follicles, escalating estradiol levels, and the associated high risk for severe OHSS. We demonstrate that the discontinuation of FSH during the late follicular phase is feasible, and leads to a decreased number of small preovulatory follicles without detriment to larger follicles. While this is only a case report, we hypothesize that this regimen might improve the safety profile of ovulation induction in this group of anovulatory patients.

Previously, patients with high risks for OHSS have had the options of cycle cancellation, “coasting” (withholding all gonadotropin activity and awaiting the fall in estradiol levels), or induction protocols utilizing a long and slow increase in gonadotropins. Cycle cancellation is usually a last resort and difficult for patients after they have invested a large amount of time and finances to a cycle. This low dose hCG protocol is different from traditional coasting protocols; unlike the plummeting estradiol levels seen with coasting, estradiol levels actually continued to rise with hCG treatment. Although coasting is a safe alternative, the success rate following coasting is controversial (7,8), with the decrease in estradiol possibly associated with a decrease in follicular health. Finally, the incremental “low, slow” method of gonadotropin treatment has the unfavorable profile of prolonging the stimulation period, increasing the number of doctor visits and ultrasounds, and thereby increasing the costs of a cycle. Furthermore, patients with estrogenic anovulation are so sensitive to gonadotropins that despite minute adjustments in gonadotropin doses, growth and recruitment of smaller preovulatory follicles still occur.

Our rationale for using hCG in place of recombinant LH is based on the rationale that hCG has a prolonged half-life, and is economically favorable. The optimal dose of hCG for late follicular development has not been determined. We based our use of 200 IU hCG on prior studies comparing various hCG doses in relationship to FSH doses (1).

In summary, this case report provides important pilot data regarding the use of low dose hCG following FSH priming in patients with estrogenic anovulation. This regimen resulted in continued follicular development, a continual rise in serum estrogen, a reduction in small preovulatory follicles and positive pregnancy outcome. The results of this preliminary data is consistent with our hypothesis that this protocol may simultaneously control the number of small preovulatory follicles which may decrease the risk of OHSS, and allow for growth and maturation of larger follicles which may improve pregnancy success rates. However, future studies utilizing randomized controlled trials are needed to test these hypotheses.

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