International Journal of Gynecology and Obstetrics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Administering human chorionic gonadotropin injections for triggering follicle maturation could impact fertility during the subsequent menstrual cycle

Junichiro Fukuda *, Takashi Abe, Takashi Okuno, Tamotsu Kobayashi, Keiichi Kato

Kato Ladies Clinic, Tokyo, Japan

ARTICLE INFO

Article history:
Received 17 March 2015
Received in revised form 24 July 2015
Accepted 3 November 2015

Keywords:
Follicle maturation trigger
Human chorionic gonadotropin
Iatrogenic infertility
Natural-cycle in vitro fertilization
Persistent follicle
Subsequent menstrual cycle

ABSTRACT

Objective: To determine whether the use of a human chorionic gonadotropin (hCG) injection as a follicle-maturation trigger affects a patient's reproductive ability during their subsequent menstrual cycle. *Methods:* Patients that were infertile undergoing natural-cycle in vitro fertilization at Kato Ladies Clinic, Japan, between March and June 2012 were enrolled in a prospective cohort study. Patients who had received fertility treatments other than hCG injections were excluded from the study. The remaining patients were divided into two cohorts; patients who had received injection-administered hCG (study group) and patients who had not received any fertility treatment (control group) during their preceding menstrual cycle. The rates of oocyte retrieval, fertilization, clinical pregnancy, and live deliveries were analyzed using a Fisher exact test. *Results:* The rate of successful oocyte-retrieval ($P < 0.001$) and the delivery-rate ($P = 0.002$) were significantly lower in the study group in comparison with the control group. Additionally, the incidence of empty follicles ($P < 0.001$) and degenerated oocytes ($P = 0.002$) was significantly higher in the exposure group. *Conclusion:* Triggering follicle maturation with hCG during in vitro fertilization could impact patient fertility during their next cycle. Treatment with hCG injection has the potential to influence not only the cycle during which it is administered, but also the subsequent menstrual cycle.

1. Introduction

Human chorionic gonadotropin (hCG) injection, which has been used in fertility treatments for decades [1], is recognized widely as a trigger of oocyte meiosis and follicle maturation, and as an activator of luteal function. When used in triggering follicle maturation, hCG is typically administered to act as a substitute for the luteinizing-hormone surge in patients with ovulation disorders. In addition, hCG is sometimes used to synchronize the timing of ovulation with sexual intercourse or intrauterine insemination in women with a regular menstrual cycle. As a gonadotropin, hCG is produced primarily by the villi following embryo implantation and is virtually absent in non-pregnant individuals. Therefore, high levels of hCG circulate in the blood following the implantation of an embryo. Whereas, similar to the surge in luteinizing hormone, hCG injection induces ovulation effectively, the half-life of hCG differs markedly from that of luteinizing hormone [2–4]. Consequently, owing to its long-lasting strong influence on ovarian function, hCG may influence not only the menstrual cycle during which it is administered but also the subsequent cycle. However, to our knowledge, only one report to date has suggested that the subsequent cycle could be influenced by the administration of hCG [5].

The present study aimed to evaluate the effects of hCG injection on the menstrual cycle subsequent to the cycle it was administered during in patients undergoing natural-cycle in vitro fertilization (IVF) and single embryo transfer.

2. Materials and method

A prospective cohort study was performed at Kato Ladies Clinic, Tokyo, Japan, between March 1, 2012 and June 30, 2012 in patients undergoing natural-cycle IVF and single embryo transfer. The present study was approved by the Institutional Review Board of Kato Ladies Clinic and the participants provided written informed consent for participation in the study.

All patients presenting to the Kato Ladies Clinic for natural IVF during the study period were assessed for study eligibility. Information regarding the administration of fertility drugs or hormones during a patient's preceding menstrual cycle was gathered by patient questionnaires and an interview with the attending physician (J.F. or T.A.). In addition, details on patient age, the duration of infertility experienced by patients, patients' past pregnancy history, details of patient menstrual periods, and indications for IVF were collected. To minimize variation in

* Corresponding author at: Kato Ladies Clinic, 7-20-3 Nishishinjuku, Shinjuku-ku, Tokyo 160–0023, Japan. Tel.: +81 3 3366 3777; fax: +81 3 5332 7373.
E-mail address: j-fukuda@towako-kato.com (J. Fukuda).

http://dx.doi.org/10.1016/j.ijgo.2015.08.001
0020-7292/

the study population, only patients with a history of fertility treatment involving hCG injections were included. Patients who had received an hCG injection to trigger follicle maturation prior to timed intercourse or for intrauterine insemination during the pre-ovulation phase of the preceding cycle only were assigned to the study group. Patients who had not received any agents for fertility treatment during the preceding menstrual cycle were assigned to the control group. Patients who had received other fertility drugs or hormones alone or in addition to hCG (e.g., clomiphene citrate, human menopausal gonadotropin, and recombinant follicle-stimulating hormone [FSH]), or who had received hCG during the luteal phase, were excluded.

Serum β-hCG was measured to confirm patients were not pregnant at the start of the IVF cycle. For the natural-cycle IVF protocol, the only pharmaceutical intervention permitted was the induction of final follicle maturation using a gonadotropin-releasing hormone (GnRH) agonist. Patient monitoring consisted of an ultrasound scan and hormone profiling (estradiol, progesterone, and luteinizing hormone), and was usually started on day 10 or day 12 of a patient's cycle, based on the duration of the patient's menstrual cycle. Oocyte retrieval was scheduled when the leading follicle reached a size of 18 mm with a concomitant estradiol level of more than 250 pg/mL. Ovulation was triggered using the GnRH agonist buserelin (600 μg) (Hoechst AG, Frankfurt, Germany), administered as a nasal spray. When the luteinizing-hormone surge was detected, oocyte retrieval was conducted 20–30 hours after triggering ovulation; when the start of the luteinizing-hormone surge was not detected, oocyte retrieval was performed 32–35 hours after ovulation was triggered [6–9].

The absence of a dominant follicle, observed using ultrasound prior to oocyte retrieval, was assumed to result from premature ovulation. Oocyte retrieval of a single dominant follicle was performed using a 21-gauge needle (Kitazato, Tokyo, Japan); follicular flushing was not performed during the retrieval. Conventional insemination was performed approximately 3 hours after retrieval and intracytoplasmic sperm injection was performed after a 5-hour interval. P1 medium, supplemented with 10% synthetic serum substitute, (Irvine Scientific, Santa Clara, CA, USA) was used as a culture medium. Intracytoplasmic sperm injection was the preferred insemination method in the presence of moderate-to-severe male factor infertility and for oocytes that matured in vitro following oocyte retrieval.

A fertilization assessment was performed 16–20 hours after insemination. Zygotes exhibiting normal fertilization, with two pronuclei, were cultured in 20 μL of Quinn's Advantage Protein Plus Cleavage Medium (Cooper Surgical, Trumbull, CT, USA) during days 1–3 post-fertilization. If necessary, the embryos were subsequently transferred to Quinn's Advantage Protein Plus Blastocyst Medium (Cooper Surgical) during post-fertilization days 4–6. All embryos were cultured at 37°C in 5% O_2, 5% CO_2, and 90% N_2, with 100% humidity; embryo culturing was performed in small, water-jacketed multi-gas incubators (Astec, Fukuoka, Japan).

In general, a fresh cleavage-stage embryo (2–8 cells) was transferred to patients 2 days after oocyte retrieval. However, a fresh blastocyst transfer was performed 5 days after oocyte retrieval for patients with bilateral fallopian tube obstruction, hydrosalpinx, or a history of extra-uterine pregnancy. All embryo-transfer procedures were performed under ultrasound guidance using a specially designed soft catheter (Kitazato) by placing a single embryo, in a minimal volume of medium, into the mid-uterine cavity. Oral dydrogesterone (30 mg/day) (Abbott Japan, Tokyo, Japan) was routinely administered following embryo transfer.

The primary outcomes of the present study were the rate of successful oocyte retrieval, the rate of fertilization, and the rate of embryo development prior to embryo transfer. The secondary outcomes were the clinical-pregnancy and live-delivery rates, per treatment cycle. An intrauterine gestational sac, observed using an ultrasound scan approximately 3 weeks after transfer, was considered to indicate clinical pregnancy. Documentation was subsequently received from the patients to confirm the live-delivery rate.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). Patient characteristics were compared between the study and control groups using the Student t test and the χ^2 test. Differences in IVF outcomes were evaluated using the Fisher exact test. $P < 0.05$ was considered to indicate a statistically significant difference.

3. Results

During the enrollment period, 408 patients were assessed for eligibility for inclusion in the present study. Of these, 142 patients had received fertility drugs or hormones during their preceding cycle; 65 patients had received only an hCG injection to trigger follicle maturation for timed intercourse or intrauterine insemination and were enrolled to the study group, and 77 patients were excluded because they had received other fertility drugs or hCG injections during the luteal phase. In the study group, one patient was excluded from the analyses after this patient withdrew from the study for personal reasons, and one patient was excluded owing to premature ovulation. This resulted in 63 patients being included in the study group for analyses. Of the 266 patients who had not received any fertility drugs or hormones during their preceding cycle, six were excluded from analysis after withdrawing from the study owing to personal reasons and four were excluded following premature ovulation. Consequently, 256 patients formed the control group for analyses (Fig. 1).

No significant differences were observed with regard to patient age, the duration of infertility experienced by patients, or the proportion of patients who reported a history of pregnancy or an ovulation disorder. There was no significant difference in the indications for IVF between the two groups (Table 1).

A significantly lower rate of successful oocyte retrieval was recorded in the study group than in the control group ($P < 0.001$). The study group also exhibited a significantly higher percentage of degenerated oocytes ($P = 0.002$) and empty follicles ($P < 0.001$) than the control group. There was no significant difference in the day of oocyte retrieval between the two groups (Table 2). There was no correlation between the presence or absence of the luteinizing-hormone surge in patients when compared with any of the measured outcomes.

Of the 30 patients that underwent successful oocyte retrieval in the study group, the oocyte failed to mature in one patient. Of the remaining 29 patients, 16 (55.2%) and 13 patients (44.8%) underwent conventional IVF and intracytoplasmic sperm injection, respectively. In the control group, oocyte retrieval was successful in 211 patients; maturation failed to occur in two patients. Of the remaining 209 patients, 96 (45.9%) and 113 (54.1%) patients underwent conventional IVF and intracytoplasmic sperm injection, respectively. There was no significant difference in the rate of fertilization for patients who underwent either conventional IVF or intracytoplasmic sperm between the study and control groups. However, the rate of embryo development prior to embryo transfer, per cycle, was significantly higher in the control group ($P < 0.001$) (Table 2).

Clinical pregnancy was recorded in 9 (14.3%) and 61 (23.8%) patients in the study and control groups, respectively; the rate of clinical pregnancy was not significantly different ($P = 0.126$). Spontaneous abortion occurred in 5 (7.9%) and 12 (4.7%) patients in the study and control groups, respectively. Live deliveries were recorded in 4 (6.3%) and 49 (19.1%) patients in the study and control groups, respectively, with a significant difference observed between the two groups ($P = 0.002$) (Table 2). All deliveries resulted from singleton pregnancies.

4. Discussion

The findings of the present study indicate that the use of an hCG injection, to stimulate follicle maturation or for intrauterine insemination, during the pre-ovulation phase of the menstrual cycle, could have negative effects on the reproductive system during an individual's subsequent menstrual cycle. Of particular note is the live-delivery rate,

Please cite this article as: Fukuda J, et al, Administering human chorionic gonadotropin injections for triggering follicle maturation could impact fertility during the subsequent menstrual cycle, Int J Gynecol Obstet (2015), http://dx.doi.org/10.1016/j.ijgo.2015.08.001