Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates

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Objective: To evaluate the percentage (%) of mature oocytes retrieved in patients with a previous history of >25% immature oocytes retrieved who were triggered with gonadotropin-releasing hormone agonist (GnRH-a) and human chorionic gonadotropin (hCG) to induce oocyte maturation.
Design: Retrospective cohort study.
Setting: A university-based tertiary fertility center.
Patient(s): Patients with a history of >25% immature oocytes retrieved in a prior in vitro fertilization cycle who were triggered with GnRH-a and hCG 5,000 IU or 10,000 IU in a subsequent cycle from January 2008 through February 2012.
Intervention(s): Dual trigger of GnRH-a and hCG 5,000 or 10,000 IU.
Main Outcome Measure(s): Percent of mature oocytes retrieved and fertilization rate.
Result(s): The proportion of mature oocytes retrieved was significantly higher with a dual trigger compared with the subject's previous cycle (75.0%, interquartile range 55.6%–80.0% vs. 38.5%, interquartile range 16.7%–55.6%). The odds of a mature oocyte retrieved for patients who received a dual trigger was 2.51 times higher after controlling for stimulation protocol, hCG dose, gonadotropin dose, and oocyte retrieval time interval (odds ratio 2.51; confidence interval 1.06–5.96). The implantation, clinical, and ongoing pregnancy rates for the dual trigger were 11.8%, 26.1%, and 17.4%, respectively.
Conclusion(s): In patients with a low percentage of mature oocytes retrieved who are triggered with a combination of GnRH-a and hCG, the % of mature oocytes retrieved improved. in vitro fertilization outcomes, however, remain poor, suggesting an underlying oocyte dysfunction. (Fertil Steril® 2014;102:405–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: Dual trigger, gonadotropin-releasing hormone agonist, oocyte maturity, in vitro fertilization

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In vitro fertilization involves stimulating the ovaries with gonadotropins to yield mature oocytes that are capable of fertilization. Oocyte maturation occurs in vivo after the luteinizing hormone (LH) surge during the menstrual cycle. The oocyte completes meiosis I and stops at metaphase II until fertilization, when meiosis II is completed (1). Oocyte maturation for in vitro fertilization cycles is commonly induced by human chorionic gonadotropin (hCG) as a surrogate for the natural LH surge. After controlled ovarian stimulation, some of the oocytes retrieved are arrested at the germinal vesicle or metaphase I stage despite correct administration of hCG.

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Patients who have >25% of immature oocytes retrieved have poorer IVF outcomes compared with patients who have a larger proportion of mature oocytes obtained (2, 3). Low oocyte maturity or the inability to retrieve mature oocytes has severe consequences, including having very few or no embryos available for transfer, which reduces the chance of conceiving with IVF.

Following the introduction of GnRH antagonists in clinical practice, the use of a gonadotropin-releasing hormone agonist (GnRH-a) bolus to induce an endogenous LH surge has been explored in many clinical scenarios, primarily for prevention of ovarian hyperstimulation syndrome (OHSS; 4). Among the advantages of using a GnRH-a to trigger oocyte maturation is the induction of a more physiologic release of LH and follicle-stimulating hormone (FSH), resembling what occurs in the natural menstrual cycle (4). In addition, some studies have suggested an increase in the percentage of mature oocytes retrieved when triggered with GnRH-a compared with hCG (4, 5).

Shapiro et al. (6) introduced the concept of "dual trigger" with a combination of GnRH-a and a low-dose hCG, primarily for the purpose of OHSS prevention. This approach was subsequently corroborated by Griffin et al. (7). More recently, Castillo et al. (8) reported the successful use of a dual trigger with GnRH-a and hCG in a patient showing repetitive immature oocytes and empty follicle syndrome. We hypothesized that the endogenous LH and FSH released by the GnRH-a bolus, in addition to the hCG, would result in a larger proportion of mature oocytes in patients with a history of poor oocyte maturation after the hCG trigger alone. As far as we are aware, this is the first study showing a series of patients in whom a dual trigger with GnRH-a plus a standard dose of hCG has been applied as a potential treatment in patients with a history of a large percentage of immature oocytes retrieved, and compared with an hCG trigger alone in a previous cycle.

MATERIALS AND METHODS

A retrospective chart review was performed on all patients who received the dual trigger of a GnRH-a and a standard dose of hCG for oocyte maturation during their IVF cycle from January 2008 until February 2012. Institutional review board approval was obtained at the University of Connecticut Health Center. Patients who were eligible for the study had a prior IVF cycle with >25% immature (germinal vesicle or metaphase I) oocytes retrieved, and a subsequent IVF cycle using a dual trigger to induce oocyte maturation. All patients must have used the intracytoplasmic sperm injection (ICSI) technique for fertilization, so that the oocyte maturation could be assessed. Exclusion criteria included patients who used a standard IVF insemination technique for oocyte fertilization.

Patients underwent various IVF stimulation protocols including microdose leuprolide (9) or pituitary down regulation with leuprolide as previously described (10) during their prior cycle, and this was compared with the dual-trigger cycle. Stimulation protocols were selected based on physician's preference. During the previous cycle, patients were triggered with hCG only. The dose of hCG was either 5,000 IU or 10,000 IU.

For the dual-trigger cycle, all patients used a GnRH antagonist controlled ovarian stimulation protocol. All patients presented for a baseline transvaginal ultrasound on day 2 of their menstrual cycle and started recombinant FSH (rFSH; Follistim; Organon USA Inc. or Gonal-F; Serono Inc) with or without human menopausal gonadotropin (Menopur; Ferring Pharmaceuticals). The starting gonadotropin dose of 225–600 IU was based on patient age, body mass index, day-3 FSH, antral follicle count, anti-Müllerian hormone level, and prior response to gonadotropins. Patient response was monitored during the IVF cycle with serial transvaginal ultrasounds for follicular measurements and serum E_2 levels.

The dose of gonadotropins was adjusted according to a patient's response. A daily subcutaneous (SC) dose of 0.25 mg GnRH antagonist (Ganirelix; Organon USA Inc.) was started after a follicle reached ≥14 mm in diameter or serum E_2 level was >350 pg/mL; the dose was continued until the day of the oocyte maturation trigger. Patients were triggered when at least 3 follicles reached ≥17 mm in diameter, with a combination of 1 mg SC leuprolide acetate plus 5,000–10,000 IU SC hCG. Transvaginal ultrasound-guided oocyte retrieval was performed 35–37 hours after trigger injection. Serum LH, E_2, P, and hCG levels were assessed the day after trigger to ensure adequate LH surge response and hCG absorption.

Luteal support included 50 mg intramuscular P daily, commencing the day after oocyte retrieval until either a negative pregnancy test or 8 weeks' gestation. Patients had either a cleavage stage or a blastocyst stage embryo transfer (ET) 3 or 5 days after the oocyte retrieval. The type and number of embryos transferred were based on embryo quality and the age of the patient.

The primary outcome measures were the number and percentage of mature oocytes retrieved with the dual-trigger protocol, compared with the patient's prior cycle. Secondary outcome measures included fertilization rate, implantation rate, clinical and ongoing pregnancy rates, as well as live birth rate. Implantation rate was defined as the number of gestational sacs, as assessed by ultrasound at 7 weeks' gestation, divided by the number of embryos transferred for each patient. Clinical pregnancy was defined as evidence of fetal cardiac activity on ultrasound at 7 weeks' gestation.

Statistical Analysis

Statistical analyses were performed using SPSS Release 21.0 (SPSS Inc.). A Chi-square or Fisher's exact test was used for categorical variables, as appropriate. Wilcoxon's rank sum test was used for continuous variables, as appropriate, between the subject's prior IVF cycle and dual-trigger cycle. A general estimation equation with logistic regression link was used to identify and control for any confounding variables and their effect on the primary outcome. Nonparametric data are presented as the median with interquartile range (25th–75th percentile). All *P* values are two-sided, and values <.05 indicate statistical significance.

RESULTS

The baseline characteristics for the patients are shown in Table 1. The stimulation protocols differed between the two groups. In the dual-trigger cycle, all patients used an