Gonadotropin-releasing hormone agonist trigger in oocyte donors co-treated with a gonadotropin-releasing hormone antagonist: a dose-finding study

Objective: To determine the optimal GnRH agonist dose for triggering of oocyte maturation in oocyte donors.


Setting: IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam.

Patient(s): One hundred sixty-five oocyte donors (aged 18–35 years, body mass index [BMI] < 28 kg/m², antimüllerian hormone level > 1.25 ng/mL, and antral follicle count ≥ 6).

Intervention(s): Ovulation trigger with 0.2, 0.3, or 0.4 mg triptorelin in a GnRH antagonist cycle.

Main Outcome Measure(s): The primary end point was number of metaphase II oocytes. Secondary end points were fertilization and cleavage rates, number of embryos and top-quality embryos, steroid levels, ovarian volume, and ongoing pregnancy rate (PR) in recipients.

Result(s): There were no significant differences between the triptorelin 0.2, 0.3, and 0.4 mg trigger groups with respect to number of metaphase II (16.0 ± 8.5, 15.9 ± 7.8, and 14.7 ± 8.4, respectively), embryos (13.2 ± 7.8, 11.7 ± 6.9, 11.8 ± 7.0), and number of top-quality embryos (3.8 ± 2.9, 3.6 ± 3.0, 4.1 ± 3.0). Luteinizing hormone levels at 24 hours and 36 hours after trigger was significantly higher with triptorelin 0.4 mg versus 0.2 mg and 0.3 mg (9.8 ± 7.1 IU/L vs. 7.3 ± 4.1 IU/L and 7.2 ± 3.7 IU/L, respectively; 4.6 ± 3.2 IU/L vs. 3.2 ± 2.3 IU/L and 3.3 ± 2.1 IU/L, respectively). Progesterone level at oocyte pick-up + 6 days was significantly higher in the 0.4-mg group (2.2 ± 3.7 IU/L) versus 0.2 mg (1.1 ± 1.0 IU/L) and 0.3 mg (1.2 ± 1.6 IU/L). One patient developed early-onset severe ovarian hyperstimulation syndrome (OHSS).

Conclusion(s): No significant differences between triptorelin doses of 0.2, 0.3, and 0.4 mg used for ovulation trigger in oocyte donors were seen with regard to the number of mature oocytes and top-quality embryos.

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Key Words: In vitro fertilization, gonadotropin-releasing hormone agonist trigger, oocyte donor, dose-finding, triptorelin

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Use of a GnRH agonist (GnRH-a) has previously been shown to effectively stimulate ovulation and final oocyte maturation, and the trigger concept was initially described in IVF during the early 1990s when no GnRH analogue cotreatment was used for IVF (1, 2). However, soon after the introduction of GnRH-a to trigger oocyte maturation, its use was hampered by the introduction of GnRH-a for pituitary down-regulation. Obviously when GnRH-a was used for pituitary down-regulation to avoid a premature endogenous LH surge, the GnRH-a triggering concept was no longer applicable because the simultaneous use of GnRH-a for down-regulation and triggering of final oocyte maturation is not possible.

The introduction of GnRH antagonists for the prevention of a premature LH surge in the late 1990s sparked new interest in the use of GnRH-a for triggering of final oocyte maturation (3–6). From a physiological point of view, a bolus of GnRH-a will displace the GnRH antagonist from the GnRH receptor in the pituitary, eliciting an endogenous surge of FSH, as well as LH, that is similar, although not identical, to the natural midcycle surge of gonadotropins—before down-regulation of the receptor (1, 2, 7). In this respect triggering of final oocyte maturation with a bolus of GnRH-a could be considered more physiological than the use of hCG for trigger because GnRH-a trigger also introduces a surge of FSH. Although the exact role of the midcycle FSH surge remains to be fully explored, and its role may not be completely essential, FSH is known to promote cumulus expansion, nuclear maturation, and LH receptor induction on the granulosa cell (GC), securing the function of the corpus luteum (CL) (8–12). Interestingly, the retrieval of more metaphase II (MII) oocytes after GnRH-a trigger in randomized clinical trials comparing GnRH-a trigger with hCG trigger has previously been attributed to the presence of a surge of FSH (13–15).

Important, the sustained luteotropic effect of hCG at doses of 5,000–10,000 IU facilitates the development of early-onset ovarian hyperstimulation syndrome (OHSS) after ovarian stimulation with exogenous gonadotropins. Conversely, the short half-life of the endogenous LH surge elicited by a bolus of GnRH-a will result in a swift CL demise, and an almost complete elimination of early-onset OHSS (16).

Due to the almost total elimination of early onset OHSS, diminished early luteal abdominal distension, and rapid occurrence of a withdrawal bleeding, combined with excellent reproductive outcomes in recipients, the use of GnRH-a trigger in oocyte donors has gradually become common practice worldwide (14).

With the increasing use of GnRH-a trigger for oocyte donors as well as for patients undergoing IVF, data on the most appropriate GnRH-a dosages used for trigger are needed. However, until present, only a few early dose-finding studies have been reported in the literature (16, 17), performed in intrauterine insemination (IUI) patients for whom no information is available regarding luteal steroid profiles, oocytes, and embryonic development.

The aim of the present study was to explore possible differences regarding the maturity rate of retrieved oocytes, the developmental competence of embryos, and the early luteal phase gonadotropin and steroid profiles of the nonsupplemented donor cycle after the use of three different doses of GnRH-a (triptorelin) for trigger in oocyte donors co-treated with a GnRH antagonist. The primary end point of this dose-finding study was the number of MII oocytes and the goal was to try to define the optimal dose of GnRH-a to be used for trigger in an oocyte donation setting.

MATERIALS AND METHODS

This single-center, randomized controlled trial was conducted from August 2014 to March 2015 at IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam. All patients provided written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The Institutional Review Board (reference number: NCKH/CGRH_01_2014) and Ethics Committee approved the study protocol on 21 July 2014.

Study Population

All oocyte donors who met the following criteria were eligible for inclusion in the study: aged 18–35 years as the Vietnamese Ministry of Health regulations state that oocyte donors must have an age within this range; body mass index (BMI) <28 kg/m²; normal ovarian reserve, defined as anti-müllerian hormone level >1.25 ng/mL or antral follicle count ≥6 (18) measured within 2 months before the start of stimulation; first oocyte donation cycle as the Vietnamese Ministry of Health regulations state that oocyte donors can only donate once; donors should receive GnRH antagonist cotreatment during ovarian stimulation, and be willing and able to comply with the protocol requirements for the whole duration of the study. Patients were excluded from the study if they had polycystic ovary syndrome (PCOS), were classified as World Health Organization group 1, had a chronic medical condition (e.g., diabetes, Crohn disease, thyroid disease, hepatitis B, or sexually transmitted diseases), had already participated in another clinical trial, or had concomitant use of either LH or hMG/urinary FSH preparations during the study cycle.

Stimulation, Monitoring, and Oocyte Pick-up

On cycle day 2 (before starting stimulation) donors were randomized to one of three groups. Randomization was performed using sealed envelopes developed by a computer-generated list with blocks of nine. Physicians, but not patients and nurses, were blinded to treatment allocation. Patients were randomized to trigger with SC triptorelin (Ipsen Pharma Biotech) using the following doses, 0.2 mg (group 1), 0.3 mg (group 2), and 0.4 mg (group 3).

Stimulation was performed according to the standard protocol of the unit, using a depot injection of corifollitropin alfa (Elonva) for stimulation on cycle day 2, followed by co-treatment with ganirelix (starting on day 5 after stimulation) and follicitin-β. The corifollitropin alfa dose used for stimulation was either 100 or 150 µg, depending on body weight, and the corresponding follicitin-β dose was 150 or 200 IU/d, starting from day 8 of stimulation until the day of triggering. The first transvaginal ultrasound scan was performed 7 or