

Ovarian Hyper-Response to Administration of an GnRH-Agonist Without Gonadotropins

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Several case reports have indicated that a small subgroup of patients may develop ovarian hyperstimulation following the administration of gonadotropin-releasing hormone agonists (GnRHa) without gonadotropins. However, since only few such cases have been published, it is unclear what course to follow in subsequent cycles after ovarian hyperstimulation in the first cycle using only GnRHa. A 33-yr-old woman was referred to in vitro fertilization for oocyte donation. A depot preparation (3.75 mg) of triptorelin without gonadotropins induced ovarian multifollicular enlargement with high estradiol level, and was followed by human chorionic gonadotropin administration and oocyte retrieval. In a subsequent cycle of the same patient, a low dose of triptorelin (0.05 mg) did not induce ovarian hyperstimulation, and resulted in clinical pregnancy. This report shows potential management of ovarian hyperstimulation following the administration of GnRHa without gonadotropins.

Key Words: GnRH Agonist; IVF; Ovarian Hyperstimulation

INTRODUCTION

Since the first report on the use of the combination of gonadotropin-releasing hormone agonists (GnRHa) and gonadotropins for in vitro fertilization (IVF) in 1984 (1), GnRHa has widely been used in controlled ovarian stimulation cycles for assisted reproduction. One known complication of pituitary down-regulation using GnRHa in IVF treatment cycles is the formation of functional ovarian cysts (2). Several case reports have indicated that a very small subgroup of patients may experience ovarian hyperstimulation following the administration of GnRHa without gonadotropins (3-6).

However, since very few case reports have been published on this topic, it is unclear what course to follow in subsequent cycles after ovarian hyperstimulation using only GnRHa in the first cycle. In the present report, a depot preparation (3.75 mg) of triptorelin without gonadotropins induced ovarian multifollicular enlargement with high estradiol level, and was followed by human chorionic gonadotropin (hCG) administration and oocyte retrieval. In a subsequent cycle of the same patient, a low dose of triptorelin (0.05 mg) did not induce ovarian hyperstimulation, and resulted in clinical pregnancy.

CASE DESCRIPTION

Our patient was a 33-yr-old nulliparous Korean woman under-

going oocyte donation for her sister on March 2010. The patient reported irregular menstrual cycles, with only four to six periods each year. Her body mass index was 21.5 kg/m², with a gynecoid fat distribution. She had mild acne on her face, but no hirsutism, virilization, or acanthosis nigricans. Her exam results for the 53rd day of her cycle were as follows: negative u-hCG, follicle-stimulating hormone (FSH) 5.39 IU/L, luteinizing hormone (LH) 11.29 IU/L, estradiol 45 pg/mL, progesterone 0.66 ng/mL, and total testosterone 1.09 ng/mL. Thyroid-stimulating hormone (TSH) and prolactin levels were normal. Transvaginal ultrasound showed that the right ovary measured 3.9 × 3.5 × 2.8 cm (19 cm³) and the left ovary 3.0 × 2.8 × 2.5 (10 cm³). The diagnosis was polycystic ovary syndrome (PCOS). We scheduled a GnRHa long protocol for controlled ovarian stimulation. On the 54th day of the cycle, a depot preparation of triptorelin (3.75 mg Decapeptyl CR; Ferring, Malmo, Sweden) was administered subcutaneously. Seven days later, the patient complained of mild abdominal discomfort. An ultrasound revealed multiple follicles ranging from 15 to 28 mm in diameter (Fig. 1). Her exam results were: estradiol 2,560 pg/mL, LH 9.83 IU/L, FSH 2.24 IU/L, and progesterone 4.18 ng/mL. Since serum estradiol concentrations were considered appropriate for the number of follicles present, a decision was made to continue the oocyte donation cycle. The patient received 10,000 IU of hCG. Thirty-five hours later oocyte retrieval was performed and 5 oocytes were aspirated. Three oocytes fertilized and underwent subsequent cleavage. Three embryos

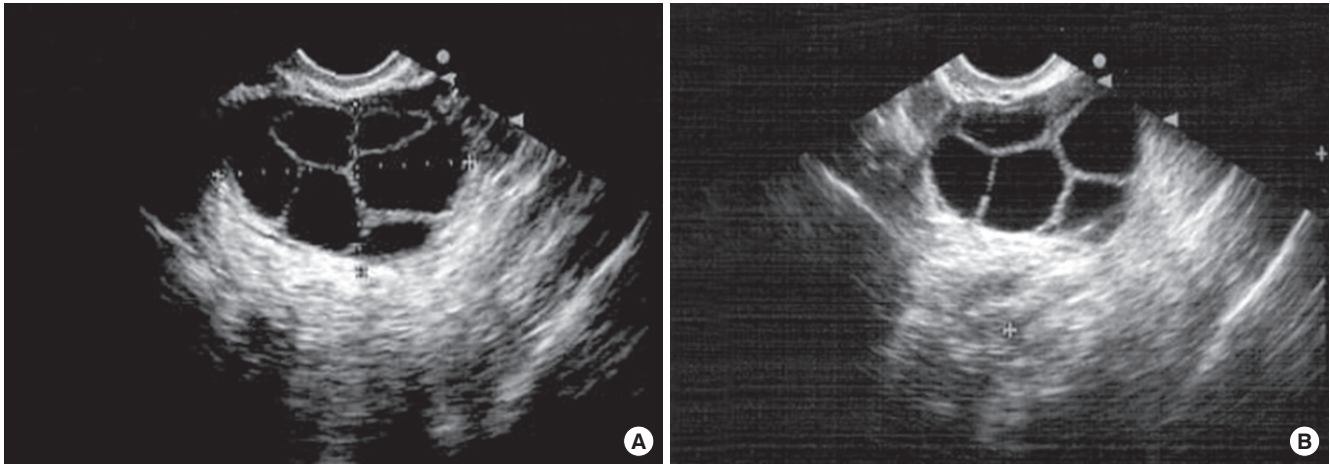


Fig. 1. Ultrasonographic finding of both ovaries. (A) Left ovary, (B) Right ovary.

were transferred to the recipient, none of which resulted in pregnancy.

Afterwards, the patient underwent another cycle. On the 42nd day of her cycle (FSH 5.96 IU/L, LH 10.78 IU/L, estradiol 41 pg/mL, progesterone 0.54 ng/mL), a short-acting preparation of triptorelin (Decapeptyl; Ferring) was administered s.c. at a dose of 0.05 mg per day, which is half of the conventional dosage. Three days later, her ovaries were quiescent on ultrasound. Seven and ten days after the initiation of GnRH α , an ultrasound revealed no evidence of functional ovarian cyst. Administration of 150 IU recombinant FSH (gonal-F; Serono Inc., Rockland, MA, USA) was started, which she received daily for 7 days. The dosage was later increased to 225 IU for an additional 5 days. On day 13, her estradiol concentration reached 1,756 pg/mL. She received 10,000 IU hCG and underwent oocyte retrieval 35 hr later. A total of 11 oocytes were retrieved, and three embryos were transferred to the recipient. A single gestational sac and fetal pulse was detected upon ultrasound at 7 weeks.

DISCUSSION

It is unclear what led to the exaggerated response to GnRH α in this case. One possible explanation is the initial flare-up caused by GnRH α , which induced the release of gonadotropins from the pituitary thereby stimulating the growth of ovarian follicles. These follicles acquired FSH-independent growth dynamics, which finally led to mature follicles by relatively abundant LH. The high serum concentrations of LH (9.83 IU/L) may support this scenario. It is accepted that in the late stages of follicle development, granulosa cells become receptive to LH stimulation and LH becomes active (7). Our patient was lean-PCOS. In PCOS, LH secretion is characterized by greater sensitivity to GnRH, as compared to women without PCOS. These responses to GnRH are more prominent in lean-PCOS (8); for this reason, we speculate that the serum LH concentration remained high for ten

days following the initiation of GnRH α due to an extremely high initial flare-up.

Alternatively, previous researchers have suggested a direct effect of GnRH α at the ovarian level (3, 5, 9). The concentration of native GnRH in the systemic circulation is relatively low. However, during treatment with GnRH α , high concentration of GnRH α circulate in the central and peripheral tissue. Many studies have investigated the effects of GnRH α on ovarian cell proliferation and steroidogenesis. In Bussenot et al. (10), 5 different GnRH agonists were compared based on their effect on estradiol secretion in human granulosa lutein cell cultures. The results showed that buserelin and leuproline significantly enhanced estradiol secretion. However, triptorelin, which was used in our case, had no effect on estradiol secretion in their study.

Recently, Azem et al. (11) reported a live birth following the administration of GnRH α without gonadotropins. They scheduled a conventional flare-up regimen on day 1 of the cycle (triptorelin 0.1 mg) and daily injections of gonadotropins from day 3 and on. Contrary to their expectation, they observed that continued GnRH α injection without gonadotropins induced follicular development with high estradiol levels until oocyte retrieval. However, it is unclear what course to follow in subsequent cycles, after ovarian hyperstimulation using only GnRH α in the first cycle, as very few case reports have been published on this topic. Weissman et al. (3) reported two cases of ovarian hyperstimulation following the administration of GnRH α without gonadotropins. They also reported that recurrent ovarian hyperstimulation occurred in subsequent cycles of the same patients. In the present report, the second cycle did not lead to ovarian hyperstimulation. The main difference between their cases and ours is the dose of GnRH α . While Weissman et al. (3) used a depot preparation of triptorelin (first cycle) and short acting preparation 0.1 mg/day in (subsequent cycle), we used triptorelin at 0.05 mg/day.

However, we cannot say that the dose of GnRH α is only respon-

sible for different results. Some differences regarding patient's characteristics and the timing of initiation of GnRHa should be considered.

In summary, a small subgroup of patients may develop ovarian hyperstimulation following the administration of GnRHa without gonadotropins. More attention should be paid to patient's complaints during the use of GnRHa.

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