Pregnancy and Birth After GnRH Agonist Treatment for Induction of Final Oocyte Maturation in a Woman Undergoing Ovarian Stimulation for ICSI, Using a GnRH Antagonist (Orgalutran/Antagon) to Prevent a Premature LH Surge: A Case Report

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INTRODUCTION

In the normal menstrual cycle, the endogenous mid-cycle luteinizing hormone (LH) surge induces resumption of oocyte meiosis and dissociation of the cumulus, which leads to rupture of the follicular wall and ovulation of the oocyte from the Graafian follicle (1).

In conventional in vitro fertilization (IVF) programs, gonadotropin-releasing hormone (GnRH) agonists are used for pituitary "down-regulation" to prevent a premature LH surge. Because of its LH-like properties, human chorionic gonadotropin (hCG) is given to induce final oocyte maturation. However, the increased carbohydrate content of hCG in comparison to LH results in a longer circulating half-life and a longer biological effect (2).

In contrast to GnRH agonists, GnRH antagonists

induce an immediate suppression of pituitary gonadotropin release and a rapid recovery of normal secretion of endogenous LH and follicle stimulating hormone (FSH) (3). These analogues have recently been developed for the prevention of premature LH surges during ovarian stimulation for assisted reproduction (4–7). A GnRH antagonist regimen offers the opportunity to trigger the final maturation of the oocyte with pulsatile native GnRH administration (8) or with a single dose of a GnRH agonist (9). Indeed, it has been reported that the midcycle FSH and LH surge could thus be simulated in patients cotreated with a GnRH antagonist, undergoing ovarian hyperstimulation for intrauterine insemination (10). Therefore, triggering of final stages of oocyte maturation may be induced by administration of a GnRH agonist in patients undergoing ovarian stimulation and cotreated with a GnRH antagonist to prevent a possible LH surge for IVF.

This case report describes the characteristics of a woman who underwent ovarian stimulation for intracytoplasmic sperm injection (ICSI) cotreated with a GnRH antagonist and a single bolus of GnRH agonist for triggering the final stages of oocyte maturation, resulting in the birth of a healthy girl.

CASE REPORT

A 28-year-old normo-ovulatory woman (body mass index, 27.5 kg/m²) with an infertility duration

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of 4.5 years due to male factor underwent ovarian stimulation for ICSI in our unit. Before initiation of treatment, endocrine screening and sonographic examination appeared to be normal. The patient participated in a multicenter trial, approved by the local ethics review committee. Ovarian stimulation using daily subcutaneous injections of 150 IU recFSH (Puregon; N.V. Organon, Oss, The Netherlands) was started on cycle day (CD) 2. From CD 7 onward, daily subcutaneous injections of 0.25 mg GnRH antagonist (ganirelix; Orgalutran/Antagon; N.V. Organon) (11) were started. On CD 12 this patient showed three preovulatory (≥ 17 -mm) and nine intermediate-sized (10- to 16-mm) follicles on transvaginal ultrasound sonography. According to the protocol, after randomization, a bolus injection of 0.5 mg GnRH agonist leuporelin (Lupron; Abbott Laboratories, Montreal, Canada) was administered subcutaneously. Subsequently, blood samples were taken frequently after the GnRH agonist was administered, on the day of oocyte pickup, on the day of embryo transfer (ET), and 7 and 14 days thereafter.

Serum concentrations of LH, FSH, estradiol (E_2), and progesterone (P) are depicted in Fig. 1. In the late follicular phase, LH serum levels were 0.6 IU/L, whereas FSH serum levels remained steady at 5 IU/L. During the follicular phase, increasing E_2 (reaching 588 pg/mL) and steady P levels of 0.5 ng/ml were observed. After administration of the GnRH agonist leuporelin an increase in gonadotropin levels was observed, reaching a maximum of 103 and 12.2 IU/L for LH and FSH, respectively, at 8 hr after GnRH agonist administration.

Ovum pickup (OPU) resulted in 11 metaphase II oocytes and 1 germinal vesicle. Subsequently, the metaphase II oocytes were fertilized by ICSI. As per the center's current practice, embryo culture was performed to day 5 after OPU (12). Two blastocyst-stage embryos were transferred and three were cryopreserved. Daily intramuscular injections of 50 mg P were provided as luteal-phase support from the day the oocytes were transferred. Analyses of blood samples drawn in the luteal phase up to 14 days post-ET resulted in decreasing FSH and LH serum to levels which were below the limit of detection for their assays (<0.6 and <1.0 IU/L, respectively). From OPU up to 7 days post-ET, a decrease in E_2 levels (from 161 pg/ml to 45.4 ng/ml) was observed, followed by an increase to 126 pg/ml 14 days after ET. P levels increased from 2.61 at OPU to 36.7 ng/ml at 7 days post-ET,

followed by a decrease to 16 ng/ml at 14 days after ET.

A viable intrauterine twinpregnancy was observed at 8 and 12 weeks amenorrhea on ultrasound, which spontaneously reduced to a singleton pregnancy at 14 weeks amenorrhea. After a noncomplicated pregnancy and spontaneous vaginal delivery, this patient gave birth to a healthy girl at 40 weeks of amenorrhea.

DISCUSSION

The routinely applied "long protocol" for IVF, characterized by pituitary down-regulation by a GnRH agonist and ovarian hyperstimulation by exogenously administered gonadotropins, may lead to undesired complications such as the development of ovarian hyperstimulation syndrome (OHSS) (13). Alternative strategies for ovarian stimulation for IVF are needed (14). These include the application of GnRH antagonists for avoiding a premature LH rise and the use of GnRH agonists, native GnRH, and recombinant LH for induction of final stages of oocyte maturation (15).

The availability of GnRH antagonists may offer alternative strategies for countering imminent OHSS (16). Replacing hCG with a single bolus of GnRH agonist for final oocyte maturation may prevent OHSS and permit continuation of the treatment cycle (13). This possibility arises because the pituitary is not down-regulated and the GnRH receptors are still present. The efficacy of triggering final oocyte maturation and ovulation with GnRH agonists has been demonstrated in women undergoing ovarian stimulation with (10) or without (17) a GnRH antagonist followed by intrauterine insemination.

The present case describes the successful treatment of a woman who underwent ovarian stimulation for ICSI using a GnRH antagonist protocol and a single bolus of a GnRH agonist to trigger the final stages of oocyte maturation. A healthy baby was delivered at 40 weeks of amenorrhea.

The use of GnRH agonists for triggering final stages of oocyte maturation instead of hCG may further reduce the incidence of OHSS, reduce cancellation rates, and result in the safe treatment of high responders. Further controlled studies are required to assess whether such a regimen should be applied in daily routine practice.

Fig. 1. LH (●—●), FSH (◆—◆) (top), E₂ (■—■), and P (▲—▲) (bottom) serum levels in a single patient undergoing ovarian stimulation for IVF, using the GnRH antagonist ganirelix to prevent a premature LH surge. Recombinant FSH (recFSH) was initiated on cycle day (CD) 2; GnRH antagonist, on CD7. Final stages of oocyte maturation were induced by a single bolus of GnRH agonist on CD12 (*t* = 0 hr). Monitoring during the peri-ovulatory period was performed at 2, 4, 8, 12, and 20–24 hr after the GnRH antagonist was administered. Luteal-phase blood samples were withdrawn on the day of oocyte pickup (OPU), on the day of ET, 7 days after ET, and 14 days after ET.

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