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CASE REPORT

Ovarian hyperstimulation syndrome following GnRH agonist trigger for final follicular maturation in a patient undergoing random start ovarian stimulation for egg-donation cycle with an inadvertent concomitant early pregnancy

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ABSTRACT

We report the first case of OHSS following GnRH agonist trigger for final follicular maturation in random start ovarian stimulation for egg-donation cycles during inadvertent concomitant early pregnancy. As an additional note, the sustained activity exerted by the increasing endogenous hCG production seemed to be responsible for the suboptimal performance in terms of oocyte yield in the current case. OHSS can occur in random-start stimulations protocols even after the use of a GnRH agonist for triggering in case of concomitant unnoticed early pregnancy especially if stimulation is commenced in the periovulatory/luteal phase. The present case report introduces a note of extreme caution when proceeding with this protocol in an otherwise fertile population (egg-donors, elective or oncologic oocyte cryopreservation).

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Introduction

Due to the almost total elimination of early-onset ovarian hyperstimulation syndrome (OHSS), combined with excellent reproductive outcomes in recipients, the use of GnRH-agonist (GnRHa) trigger in oocyte donors has become mandatory. When using this approach in conventional ovarian stimulation, we can consider OHSS in egg-donors to be virtually eradicated. Recently, random-start ovarian stimulation protocols have emerged as an alternative to conventional ovarian stimulation allowing treatment to begin independently of the day of the cycle. This approach could be of interest for the egg-donor population since it makes the synchronization with the recipient easier, avoiding the use of contraceptive pills. Importantly, the available data suggest that oocyte yield derived from random-start ovarian stimulation protocols initiated during any phase of the menstrual cycle are similar to conventional ovarian stimulation start protocols [1].

Herewith, we report a case of OHSS following GnRHa trigger for final follicular maturation in egg donors initiating ovarian stimulation in the luteal phase masking a concomitant early pregnancy.

Case

A 29-year-old donor, gravida 2, para 2 (one vaginal delivery and one C-section), underwent ovarian stimulation initiating on cycle day 25 as part of the random-start ovarian stimulation trial (NCT02821819). Stimulation was started after an ultrasound evaluation showed a secretory phase 10 mm endometrium, with no free pelvic fluid and confirmation of a unilateral corpus luteum. As per protocol, the donor was asked about any unprotected intercourse on the previous days since last menses, which she denied. The egg-donor started with 225 IU/day of uFSH (Fostipur®, Angelini Pharma Inc.), five days later a GnRH-antagonist (Cetrorelix 0.25 mg/day. Cetrotide®, Merck Serono Ltd.) was added. After 11 days of stimulation she was triggered with GnRHa (Triptorelin 0.2 mg, Decapeptyl®, IPSEN Pharma, Barcelona - España.) for final follicular maturation. The donor underwent ovum pick-up (OPU) 36 h following GnRHa trigger and although ~19 follicles > 11 mm were aspirated, only 01 egg was retrieved after an otherwise uneventful ovarian puncture. Four days following OPU, the patient was admitted into the local hospital for pain, abdominal distention and mild respiratory distress. Her transvaginal ultrasound revealed enlarged ovaries (10-11 cm) with significant pelvic and upper abdominal ascites and an image compatible with an intrauterine gestational sac (5 weeks + 5 days according to LMP). Blood was drawn for hCG, complete blood count and chemistry, revealing hematocrit of 47%, WBC 19870, platelets 679,000, normal kidney and liver function tests, and βhCG of 1909 UI/l. The patient requested a termination of pregnancy. She was discharged after 09 days for further outpatient surveillance, during which she demonstrated complete resolution of her OHSS. Consent was obtained from the patient authorizing the report of the clinical case as long as measures to prevent personal identification were adopted.

Discussion

To our knowledge, the present case is the first report on the occurrence of OHSS following a GnRH agonist trigger in the so-called random start protocol in egg-donor cycles due to the concomitant presence of an undetectable pregnancy during controlled ovarian stimulation.

Following the introduction of GnRH antagonist protocols combined with a GnRH agonist trigger the occurrence of OHSS has drop dramatically, this fact is especially evident in the egg-

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donor population and although a case of OHSS following GnRHa trigger for final oocyte maturation in an egg-donor has been reported [2]; this potentially life-threatening complication can be considered virtually eradicated in the egg-donor population. Since OHSS almost always requires circulating exogenous administration or endogenous hCG secretion (e.g. early pregnancy) [3,4] its occurrence following GnRHa trigger should be an alert to search for circulating hCG as recently showed by Orvieto *et al.* describing a case of OHSS following IVF treatment using a GnRHa trigger for final follicular maturation, masking an ectopic pregnancy [3].

In 2003, the concept of the "follicular waves" [5] opened the possibility of initiating ovarian stimulation at any moment during the menstrual cycle. The so-called random start ovarian stimulation protocol has been described in patients looking for oocyte cryopreservation for non-medical reasons (elective or "social" egg freezing) [1] and in the egg-donor population [6,7]. Importantly, the available data suggest that oocyte yield and competence derived from random-start ovarian stimulation protocols initiated during any phase of the menstrual cycle are similar to conventional ovarian stimulation start protocols [1,7–9]. Random start protocols might offer advantages for the egg-donor population in terms of facilitating schedules and avoiding the use of contraceptive pills. However, we should bear in mind that egg-donors are essentially fertile females and unexpected pregnancies are not uncommon in this population. In our center, egg donors not taking the contraceptive pill (60% of the egg-donor population) and planning to enter the random start stimulation protocol are strongly advised about the use of barrier contraceptive methods and asked about unprotected intercourse, ovarian stimulation is canceled if any risk is detected. In the present case, medically important information was withheld by the donor, which is unfortunately not uncommon according to two recent surveys showing that a high proportion of users admitted they had not been forthcoming with doctors about information that could be relevant to their health [10].

Detecting a pregnancy at this early stage before commencing COS appears virtually impossible. Although pioneering studies focused on early implantation described the use of a hypersensitive chemiluminescence assay (Amerlite, Amersham Int, Arlington Heights, IL) capable of detecting values as low as 0.3 IU/L as an early sign of embryo implantation [11], to the best of our knowledge the test is no longer available. This case illustrates that clinicians should be very careful when considering beginning ovarian stimulation randomly especially in the luteal phase, perhaps targeting this option solely for lesbian donors, donors with azoospermic partner or donors using intrauterine devices as contraceptive method or with documented tubal blockage.

An additional note to consider is the suboptimal egg yield obtained after egg collection in the present case. As shown earlier during the pre-GnRHa trigger era [12,13], follicle development and even the production of a large cohort of follicles >18 mm in diameter are possible in pregnancy; however, the quality and quantity of oocytes are poor, which is possibly related to high serum titers of beta-hCG from the preexisting pregnancy [14]. More recently two case reports showed that GnRHa can trigger final follicular maturation during pregnancy in the presence of circulating hCG leading to the obtention of (apparently) competent eggs [3] and zygotes [15] in both cases the circulating levels of hCG were probably low (one stimulation commenced after termination of pregnancy for fertility preservation and the other during a concomitant ectopic pregnancy). The suboptimal oocyte yield in our case could possibly be related to a detrimental effect on follicular development due to a sustainably high hCG levels as described by others [14,16] or hypothetically to a suboptimal LH response from the hypophysis after GnRHa trigger in the presence again of elevated endogenous hCG levels. Therefore, a suboptimal oocyte yield during an otherwise uneventful random start ovarian stimulation protocol following GnRHa trigger should alert physician to check for serum hCG levels, aiming to exclude the endogenous secretion of hCG by an early pregnancy.

Finally, the information from this case report provides some lessons of relevance for other populations currently undergoing random start protocols such as: the "elective" egg-freezing population or the oncologic female population considering fertility preservation. In both scenarios not only a superimposed OHSS but also the probability of a poor oocyte harvest could be highly detrimental.

To conclude, OHSS can occur in random-start stimulations protocols even after the use of a GnRH agonist for triggering in case of concomitant unnoticed early pregnancy, especially if stimulation is commenced in the periovulatory/luteal phase. A note of extreme caution is warranted when proceeding with this protocol in otherwise fertile population since a complete prevention appears unfeasible except for documented cases of tubal blockage. As an additional note, the sustainably high LH-like activity exerted by the increasing endogenous hCG production seemed to be responsible for the suboptimal performance in terms of oocyte yield in the present case.

Disclosure statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. No external funding was sought or obtained for this study. All authors agree for the submission of the manuscript.

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