Research Article
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Severe early ovarian hyperstimulation syndrome after spontaneous pregnancy and despite GnRH-agonist trigger during controlled ovarian stimulation in an oocyte donor cycle: a case report

Abstract

Background: GnRH agonist provides more physiological oocyte maturation while considerably reduces or abolishes the risk of Ovarian Hyperstimulation Syndrome. The risk of OHSS hence triggering oocyte maturation using a GnRH agonist bolus must be advised because, although exceptional, it is not completely abolished.

Case presentation: A 25 years old oocyte donor conceived during the course of a controlled ovarian stimulation cycle. Even after a final oocyte trigger with GnRH agonist and no exogenous luteal support, the patient developed a severe case of early ovarian hyperstimulation syndrome.

Conclusion: Trigger with GnRH agonist does not abolish completely the risk of OHSS. As far as we know, no real cases of severe early OHSS after GnRH agonist trigger have been reported. Candidates to oocyte donation programs should be fully informed of the risks of unprotected sexual intercourse during ovarian stimulation.

Keywords: hyperstimulation, spontaneous, donor, luteinisation, culdocentesis, paracentesis

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious and potentially lethal complication of In Vitro Fertilization (IVF) cycles.[1,2] OHSS is characterized by the shift of protein-rich fluid from the intravascular space to the third space that follows ovarian enlargement due to follicular stimulation. The pathogenesis involves an increased number of granulosa cells, due to multifollicular growth, and the resultant increased vascular endothelial growth factor (VEGF) production during the luteinization of these cells.[3] VEGF, which appears to be the main vascular mediator, is the main responsible for increase intravascular permeability.[4] hCG (endogenous or exogenous) has been proved to be the main contributor of OHSS.[5]

In the literature, two main types of OHSS are described according to the time of onset: Early OHSS and late OHSS. Early OHSS is associated with ovarian stimulation and the exogenous hCG trigger, it usually occurs within 9 days of oocyte retrieval. In the other hand, late-onset OHSS correlates to endogenous hCG produced by an implanting embryo and mostly occurs after the 10th day period.[6–9] In 2010, *Humaidan P*[10] proposed an objective method to classified OHSS according to its severity based on vaginal ultrasound and laboratory parameters.[10]

As part of assisted reproductive treatments, hCG is usually administered to mimic the midcycle surge of LH activity in order to achieve final oocyte maturation previous to collection.[1] although both activate the same receptor, its main difference resides in half-life. The longer half-life of hCG (>24 hours) compared with LH (<60 minutes) extends the luteinizing stimulus for the granulosa cells.[11]

It is well recognized that GnRH-agonist trigger in antagonist protocols results in prevention of clinically significant ovarian hyperstimulation syndrome (OHSS) by inducing quick and irreversible luteolysis hence preventing the secretion of vasoactive substances.[1–4] conversely, this results in decreased implantation and pregnancy rates due to its deleterious effects on the endometrium. While hCG trigger continues its action for up to 5 days, GnRH agonists provide a two phases gonadotrophins surge that persists up to 24-36h. Although the importance of the quality of the endometrium is limited in oocyte donors, it is assumed a minimum possibility of spontaneous pregnancy due to the negative effect of the GnRH agonist on the endometrium. Furthermore, because of an ineffective luteal phase and absence of support with exogenous progesterone the probability of an evolutive pregnancy might be reduced such as autologous cycle have demonstrated.[12]

Materials and methods

Case report

Clinical history: The patient was a 25-year-old, para 0, oocyte donor. She had regular menstrual cycles and no relevant medical or surgical history. Weight 60kg, BMI 23.4. She had had a previous donation cycle (short antagonist protocol and agonist trigger) resulting in 10 metaphase II and normal clinical outcome. Ovarian stimulation protocol: The patient was stimulated in a fixed GnRH antagonist protocol. Controlled ovarian stimulation (COS) started after a wash-out period of 4 days, following contraceptive pills, on day 2 of menstrual cycle. Stimulation started with rFSH 225 UI daily (Gonal®; Merck-Serono, Spain) and HMG 75 UI(Menopur®; Ferring, Spain) was added from day 1 to 3 and 9 to 10 of stimulation to achieve follicular growth in this particular case. The patient required a total of 2225 UI rFSH and 375 UI HMG. GnRH antagonist was administered from day 6 of stimulation (Ganirelix 0.25mg/0.5ml; Orgalutran; Merck-Serono, Spain). Triptorelin 0.3mg (Decapeptyl®) was used on day 10 to trigger oocyte maturation. A total of 30 metaphase II oocytes were retrieved.

Results

Five days after oocyte retrieval the patient consulted an external general emergency room complaining of severe abdominal pain. The mentioned health centre had no experience on Reproductive Medicine moreover, she did not put into advice her recent ovarian stimulation cycle. Ultrasound showed increased subhepatic-subsplenic and pelvic free fluid with enlarged ovaries (>80mm). Although no evidence of intrauterine pregnancy was found, seric β-hCG was 340.8 IU/l. Due to continuous denial of any procedure related to assist reproductive techniques, she was admitted under the suspicion of ectopic pregnancy versus ovarian mass. Blood tests revealed: Haematocrit 47%, Haemoglobin 15 mg/dl, total proteins 4.3g/L, ALT 68 IU/L, AST 73 IU/L andnormal renal function. Significantoliguria (600ml/24h) and generalized oedema were observed accompanied by progressively increased weight (72 kg/+12kg). Gradual oedema was complicated by a remarkable vulvar oedema which provided a much sense of discomfort to the patient. A new seric β-hCG revealed an increased (1068 IU/l) level and established the probability of an evolutive recent pregnancy. Her severely compromised medical status, and the strong suspicion of OHSS by the medical unit, forced her to declare the oocyte donation cycle. At this point, the patient was under treatment with furosemidedaily and intravenous fluid support afterwards, shows started on subcutaneous low molecular weight heparin (prophylactic dosage) and intravenous albumin 25% according to her actual weight. Clinical status worsened with continuous increased weight (74.5 kg/+14.5kg), dyspnoea and tense as cites. X-ray study did not showed pleural effusion. Due to the lack of experience on culdocentesis, paracentesis was performed retrieving only 300cc.Clinical status maintained until ten days after admittance clinical improvement was perceived. Data of hem concentration ameliorated: haematocrit decreased to 37%, and evidence of total proteins' normalization. Liver enzymes descending, normal renal function and diuresis increased to 4000ml/day. Five days later clinical progress was much encouraging, haematocrit 33%, haemoglobin 11.3 and weight recovery 70.7kg (+10.7kg). At this time, endovaginal ultrasound revealed a 13mm intrauterine gestational sac. Still increased pelvic free fluid was observed. Fifteen days after admittance the patient was discharged due to positive progress, at this time, her weight was 69.5kg and signs of oedema had disappeared at most. A week later, a follow-up consult confirmeda viable intrauterine gestation of 7+1 weeks and mild pelvic free fluid. According to the embryo's crown rump length, the estimated conception date corresponds to the controlled ovarian stimulation period, previously to introduction of GnRH antagonist. Displays β-hCG progression and its approximate equivalence in gestational weeks. Recently, the patient was call into our centre for a follow-up consult. She had had a spontaneous abortion a week after the last medical consult (8th gestational week approximately). Because she consulted a different centre in that occasion, there is no official data about this episode.

Discussion

Ovarian hyperstimulation syndrome has long been feared because of its potentially lethal effect. According to our research, there are not documented cases of allegedly severe early-onset OHSS after GnRHa trigger.[13] Most of the published cases are mild or not real OHSS.[14] Although, compared with hCG trigger, a bolus of GnRH agonist induces a more physiological oocyte maturation and considerably reduces the risk of early-onset OHSS, it is not completely avoided. In oocyte donation cycles, GnRH antagonist protocols have replaced agonists due to a shorter duration of stimulation and decreased cyst formation and hormonal withdrawal symptoms.[15,16] More importantly, this allows the possibility of using GnRH agonist as an alternative trigger to hCG, which could minimize the exposure to unnecessary treatment risks as ovarian hyperstimulation syndrome (OHSS). GnRH agonist can stimulate the release of LH from the pituitary, triggering final oocyte maturation; this cannot be achieved when agonists have already been used for down-regulation.[17–19] While GnRH antagonist causes a competitive blockage of GnRH receptors, it still allows the stimulation of the hypophysis with GnRH agonists and the subsequent secretion of endogenous gonadotrophins.[12–23]

Currently, the use of Gonadotrophin-realising hormone agonist (GnRH agonist) has come to a frequent and common use as an alternative trigger to hCG. This has claimed to be of utmost importance especially in oocyte donation cycles in which the safety for the patient and efficacy in results most be assured. The administration of GnRH agonist activates the GnRH receptor resulting in a two phase's surge of gonadotrophins with duration of 24-36h in contrast to that of hCG which continues for 5 days.[24] These differences have had no proved detrimental effect on oocyte maturation neither on its quality. However, during early luteal phase the reduced endogenous LH concentration causes a negative impact on corpus luteal function and the capacity of the endometrium for implantation.[20]According to this, after agonist trigger luteal phase support might depend exclusively on exogenous progesterone and oestrogen, although, these may not be sufficient in the early stages. Although the avoidance of hCG in oocyte donation cycles associates an almost complete elimination of OHSS, in autologous cycles, even if combined with luteal support, associates a remarkable reduction in pregnancy rates and increased risk of miscarriage.[12,25–27]

Such as Gurbuz have recently exhibited in a report of 4 cases, luteolysis post GnRH agonist trigger might be individual dependant and not all of these patients will develop complete luteolysis.[2] After GnRH agonist has been administered, some patient's corpora luteum have the capability of recovering its function even after 7 days from LH deprivation. Moreover, after fertilisation hCG is produced by the embryo previous to its implantation. According to Humaidan et al. grading proposal, this case might be categorized in a severe OHSS form due to the clinical and laboratory parameters.[10] she was not moved to the Intensive Care Unit due to absence of pleural effusion and clotting disorders. The slow and torpid clinical progression of this patient might be justified since the initial approach of this patient was not focused on managing OHSS. Although, paracentesis might not have been the correct approach, hence increases pelvic free fluid was still found at discharge, clinical improvement was evident after only 300ml were obtained.

Conclusion

Because of the, even slight, likelihood of spontaneous pregnancy in oocyte donors it is of extreme importance to offer strong counsel and advise firm compromise to candidates. It is essential to consider the risk of spontaneous ovulation during controlled ovarian stimulation or the possibility of missing an oocyte after follicular aspiration in high responder patients such as oocyte donors. Commitment concerning oocyte donors should involved every member of the reprod4uctive team. It is of paramount importance to ensure that the patients are fully informed of the risks of unprotected sexual intercourse at every visit. Finally, the aim of the present paper is to advice reproductive specialist about the risk of OHSS hence triggering final oocyte maturation using a GnRH agonist bolus. Although real OHSS is exceptional, it is not completely abolished. Although, this cycle triplicate the quantity

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of metaphase II, the severity of a likely OHSS might have been diminished, perhaps abolished, by the GnRH agonist trigger. Yet the early embryo implantation prompted a severe premature response that took everyone by surprise. We have no official data about the circumstance of abortion. The patient referred a diagnosis of non-viable pregnancy a week after the last follow up consult. Could this have been a consequence of GnRH agonist or OHSS treatment? Does GnRH agonist trigger really requires "freeze-all policy" or is there a selected group of patients in which luteal phase remains acceptable for fresh embryo transfer? Some authors, like Iliodromiti et al., have already suggested new protocols to diminish the endometrial effect of GnRH agonist trigger.[20] Questions surge from this manner.

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Conflict of interests

The authors declare that there is no conflict of interest that could prejudice the impartiality of the present research.

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