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GnRH antagonist rescue of a short-protocol IVF/ICSI cycle and GnRH agonist triggering to prevent ovarian hyperstimulation syndrome: two case reports

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Summary

Objective: To describe two clinical cases concerning patients at risk of developing severe ovarian hyperstimulation syndrome (OHSS) during in vitro fertilization (IVF) stimulation. Design: Description of clinical management and outcomes of patients using an IVF antagonist rescue protocol to prevent OHSS. Setting: Reproductive medicine unit, University Hospital. *Materials and Methods:* Two infertile patients undergoing controlled ovarian stimulation (COS) for IVF/intracytoplasmic sperm injection (ICSI) presenting with high risk of OHSS. IVF/ICSI patients following COS under short protocol and high risk of OHSS were managed by withdrawing the agonist and replacing it with an antagonist and triggering ovulation with an agonist bolus. Main outcome measures included incidence of OHSS, oocytes retrieved, and pregnancy rates. *Results:* None of the two patients developed OHSS. None of the patients had metaphase II retrieved oocytes at oocyte retrieval. *Conclusions:* Use of COS with short protocol in an IVF/ICSI cycle carries a risk of severe OHSS. Rescuing the cycle by withdrawing the agonist and replacing it with an antagonist and triggering ovulation with an agonist bolus is not always effective and should not be used if short time interval between agonist replacement with antagonist and ovulation triggering is available.

Key words: GnRH antagonist; Rescue; Agonist; Agonist trigger; OHSS; IVF.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most severe complications in the context of assisted reproductive technologies [1]. The clinical aspect of this condition can vary from mild to severe with multiple organ dysfunction and life-threatening events [2]. Clinically, it is characterized by an increased vascular permeability and ovarian augmentation. Rarely, this syndrome can occur spontaneously [3], but the majority of cases are observed in association with controlled ovarian stimulation (COS) procedure [4]. Therefore, it is crucial to understand and find a way to prevent OHSS. In the literature, the use of GnRH antagonist rescue protocol utilising GnRH agonist for ovulation triggering has been proposed in order to prevent development of OHSS [5] in patients undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles with GnRH agonist downregulation of the pituitary gland. The authors describe the management and outcome of two clinical cases involving patients at high risk of developing severe OHSS during IVF/ICSI stimulation. These patients were under short protocol with triptorelin in a dose of 0.1 mg, sc, once daily for pituitary downregulation and GnRH antagonist rescue protocol and ovulation triggering was performed with a bolus of agonist given (triprorelin 0.2 mg, sc) 36 hours prior to oocyte retrieval. In both patients, when a high risk of OHSS was suspected, all the available options of management were presented including: cycle cancellation, coasting with fresh embryo transfer or freezing of all embryos, hCG triggering followed by oocyte retrieval, and freezing all embryos. In addition, the option to replace the agonist with an antagonist until the hCG administration criteria were met and performance of ovulation triggered with a bolus of an agonist was discussed. When at least three follicles >18 mm in mean diameter were observed, a single dose of 0.2 mg triptorelin subcutaneously was given, and oocyte retrieval was performed 36 hours later. Institutional Review Board was not obtained, because this is a retrospective review of medical records to which all patients had previously given written consents.

Materials and Methods

Case 1

The patient was 32-years-old with a BMI of 23 kg/m^2 and her FSH, LH, AMH and antral follicle count (AFC) on day 3 of her previous menstrual cycle were respectively: 6.3 iu/L, 3.8 iu/L, 4.1 ng/ml, and 16. The patient underwent COS with follitropin alfa with an initial dose of 175 IU per day, sc, beginning from the third day of the cycle (first day of the cycle was considered the first day of menses). Pituitary downregulation was achieved with the use of triptorelin in a dose of 0.1 mg, sc, once daily, beginning

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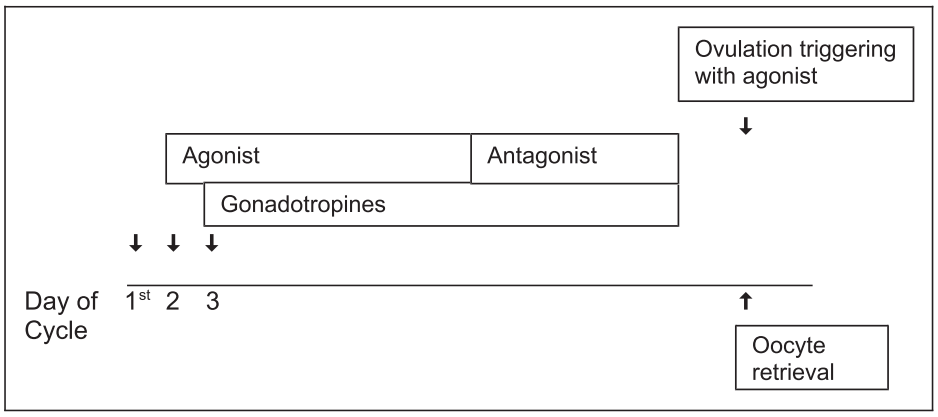

Figure 1. — Management protocol.

from the second day of the cycle (Figure 1). On the fourth stimulation day, the patient had estradiol level 1,100 pg/ml, progesterone:0.9 ng/ml, and LH: 3.9 IU/L, while on transvaginal ultrasound there were about ten follicles of nine to ten mm in right ovary and 14 follicles of nine to ten mm in left ovary. The follitropin alfa dose was reduced to 150 iu per day and on day 6 of stimulation the patient had estradiol level 2,321 pg/ml, progesterone 1.3 ng/ml, and LH 3.4 IU/L, while on transvaginal ultrasound there were about ten follicles of 15 mm and six follicles of 12 mm in right ovary and 12 follicles of 15 mm and five follicles of 12 -13 mm in left ovary. The follitropin alfa dose was reduced to 125 iu per day and was given only on day six and seven, while the agonist was replaced from antagonist which was given 12 hours before the usual administration time of the agonist. The antagonist used was ganirelix at a dose of 0.25 mg per day, sc. On day 8 of stimulation, the patient had estradiol level 8,530 pg/ml, progesterone 1.4 ng/ml, and LH 4.5 IU/L, while on transvaginal ultrasound there were about eight follicles of 18-19 mm and five follicles of 15-16 mm and four follicles of 12 mm in right ovary and 11 follicles of 18-20 mm and six follicles of 14-16 mm and five follicles of 12 mm in left ovary. The patient underwent coasting with antagonist for one day (day 8 of stimulation). The next day (day 9 of stimulation) she had estradiol level 8,287 pg/ml, progesterone 1.7 ng/ml, and LH 2.9 IU/L. A bolus of 0.2 mg triptorelin subcutaneously was given the same night (day 9 of stimulation) and oocyte retrieval was performed 36 hours later. No oocytes were recovered but one which was immature despite two washes. The patient had an uneventful recovery from the stimulation cycle.

Case 2

The patient was 27-years- old with a BMI of 21 kg/m^2 and her FSH, LH, AMH, and AFC on day 3 of her previous menstrual cycle were respectively: 4.5 iu/L, 4.2 iu/L, 3.2 ng/ml and 12. She underwent COS with follitropin alfa with an initial dose of 200 IU per day, sc, beginning from the third day of the cycle (first day of the cycle was considered the first day of menses). Pituitary down-regulation was achieved with the use of triptorelin in a dose of 0.1 mg, sc, once daily, beginning from the second day of the cycle. On the fourth stimulation day the patient had estradiol level 370 pg/ml, progesterone 0.6ng/ml, and LH 4.1 IU/L, while on transvaginal ultrasound there were about nine follicles of nine to ten mm in right ovary and five follicles of nine to ten mm in left ovary. She continued with the same dose of follitropin alfa and triptorelin for the fourth, fifth, and sixth stimulation days and on the seventh stimulation day, the patient had estradiol level 2,509 pg/ml, progesterone 1.16 ng/ml, and LH 4.4 IU/L, while on transvaginal ultrasound there were about eight follicles of nine to ten mm and eight follicles of 12 mm in the right ovary and five follicles of nine to ten mm and seven follicles of 12 mm in the left ovary. The triptorelin was changed to ganirelix at a dose of 0.25 mg per day, sc. The dose of follitropin alfa was reduced to 150 iu once daily. On the ninth day of stimulation the patient had estradiol level 5,025 pg/ml, progesterone 1.49 ng/ml, and LH 4.7 IU/L, while on transvaginal ultrasound there were about nine follicles of 15 mm and five follicles of 12 mm in the right ovary and five follicles of 15 mm and four follicles of 14 mm and five follicles of 12 mm in the left ovary. On the ninth and tenth days she continued with the administration of ganirelix at the same dose, while the dose of follitropin alfa was reduced to 125 iu once daily on ninth and tenth days. On the 11th day of stimulation the patient had estradiol level 8320 pg/ml, progesterone 1.9 ng/ml, and LH 4.8 IU/L, while on transvaginal ultrasound there were about five follicles of 18-19 mm and five follicles of 16 mm and four follicles of 12-14 mm in the right ovary and six follicles of 18-19 mm and six follicles of 16 mm and five follicles of 12 -14 mm in the left ovary. At 22.00 pm of the same day, a bolus of 0.2 mg triptorelin subcutaneously was given and oocyte retrieval was performed 35 hours later. No oocytes were recovered despite three washes. The patient had an uneventful recovery from the stimulation cycle.

Results

Case 1: In this case the patient was on antagonist for four days prior to ovulation triggering with the agonist, while she had 24 hours coasting with antagonist prior to ovulation triggering with the agonist. No oocytes were recovered at oocyte retrieval despite multiple follicular washings.

Case 2: The patient was on antagonist for five days prior to ovulation triggering with the agonist and 35 hours after ovulation triggering, but no oocytes were recovered despite multiple follicular washings.

Discussion

COS is almost always used during assisted reproductive techniques aiming to retrieve more oocytes in an attempt to improve the reproductive outcome. However this practice

has the risk of iatrogenic occurrence of OHSS. Although the precise cause of OHSS is not completely known, it appears that the release of vasoactive substances such as vascular endothelial growth factor (VEGF) secreted by the ovaries under hCG stimulation could play an important role in the development of this syndrome [6]. Although several preventing strategies have been suggested, it not always possible to avoid the development of OHSS and in order to avoid cycle cancellation among other options, in recent years, it has been suggested to use a GnRH antagonist rescue protocol in patients undergoing pituitary downregulation. Searching the literature, two different strategies for the application of antagonist rescue protocol have been suggested and therefore the term could be confusing in some cases. Firstly, it has been suggested to replace the GnRH agonist with GnRH antagonist (250 g subcutaneously once daily; ganirelex acetate) that is administered for one to three days to decrease the estradiol concentration and permit further follicular growth prior to hCG administration for oocyte maturation [7]. Secondly, other researchers have suggested that it is possible in IVF patients treated under long protocol and presenting high risk of OHSS to have their cycles rescued by withdrawing the agonist and replacing it with an antagonist and triggering ovulation with an agonist bolus [8]. In this study, they report three cases treated with antagonist rescue protocol. In the two out of three cases the antagonist was used for three days (84 hours) and six days (144 hours) and 14 oocytes and 32 oocytes were retrieved, respectively, 36 hours after oocyte triggering. In the third case, ovarian triggering was performed after five days of treatment with antagonist and oocyte retrieval was performed 36 hours later, but no oocytes were retrieved despite several washes and an LH elevated value 12 hours later. The inability to recover any oocytes was not attributed to insensitivity of the pituitary to respond to the agonist bolus with the LH endogenous peak elevation, but to a possible coasting effect of FSH dose reduction to the ovaries [8].

In the first presented case the patient was on antagonist for four days prior to ovulation triggering with the agonist, while she had 24 hours coasting with antagonist prior to ovulation triggering with the agonist. Coasting with the use of an antagonist protocol has been used effectively in the past and it does seem to affect the stimulation cycle outcome [9, 10]. In the second presented case, the patient was on antagonist for five days prior to ovulation triggering with the agonist and 35 hours after ovulation triggering no oocytes were recovered. Also, the use of step down protocol is supported by the literature, which is applied with a gradual reduction in the administered levels of gonadotropins, is not associated with any recovery of any oocytes at oocyte retrieval [11] and the suggested possible coasting effect of gonadotropins [8] could not be the explanation in all cases with the use of antagonist rescue protocol and with no oocyte recovery. On the other hand, the described recovery of oocytes [12] after three and six days of antagonist use in the antagonist rescue protocol before GnRH agonist administration could be attributed to special characteristics of the individuals in relation to the recovery of pituitary GnRH receptors after GnRH downregulation with an GnRH agonist and these findings cannot be extrapolated for use in other patients. The findings from the present cases suggest that an interval time of four and five days of GnRH agonist replacement from a GnRH antagonist in an antagonist rescue protocol could not provide adequate time for recovery of GnRH receptors in the pituitary, so that the GnRH agonist could provoke LH surge. Clinicians should be aware of this possible situation before they advise their patients in the decision-making process in order to avoid severe OHSS. Because it remains unknown how much time is needed for recovery of pituitary receptors after downregulation with GnRH agonists in humans, and which factors could affect this recovery time, further research is required to answer these questions and provide information about possible use of GnRH antagonist rescue protocol.

Conclusion

Rescuing the cycle by withdrawing the agonist and replacing it with an antagonist and triggering ovulation with an agonist bolus is not always effective and should not be used if short time lapses between agonist replacement with antagonist and ovulation triggering is available. If it is used, the patient should be aware that no oocyte retrieval could be an unfavourable outcome.

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