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CASE REPORT

Severe Early-onset Ovarian Hyperstimulation Syndrome following Use of GnRH Agonist Trigger along with Low-dose hCG

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ABSTRACT

Controlled ovarian hyperstimulation, which is a key component of assisted reproductive technology (ART) treatment, can be excessive in certain cases and can lead to massive cystic enlargement of the ovaries and biochemical changes, leading to ovarian hyperstimulation syndrome (OHSS). Traditionally, human chorionic gonadotropin (hCG) has been used as ovulation trigger in ART cycles but its sustained luteotrophic effect is associated with an increased risk of OHSS in high-risk patients. Gonadotropin-releasing hormone (GnRH) agonist trigger can be used as an alternative to hCG in GnRH antagonist downregulated cycles. However, the use of GnRH agonist was associated with a lower pregnancy rate due to deficient luteal phase, and hence, use of low-dose hCG to rescue the deficient luteal phase has been used. Various studies showed that using low-dose hCG did not increase the risk of OHSS even in high-risk patients. Here, we present a case report of severe early-onset OHSS following GnRH agonist trigger with low-dose hCG.

Keywords: Gonadotropin-releasing hormone agonist trigger, Human chorionic gonadotropin, Ovarian hyperstimulation syndrome.

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is one of the life-threatening complications of assisted reproductive technology (ART). The incidence of OHSS varies, with mild and severe OHSS being reported in 33 and 3% of ART cycles respectively.[1] The pathognomonic feature of OHSS is an increased number of granulosa cells due to multifollicular growth and extensive production of vascular endothelial growth factor (VEGF) following lutenization of these cells.[2] It is characterized by a shift of protein-rich fluid from the intravascular space to the third space (mainly the abdominal cavity) that occurs when the ovaries become enlarged owing to follicular stimulation.

Ovarian hyperstimulation syndrome may be associated with massive ovarian enlargement, ovarian torsion, ascites, hydrothorax, liver and renal dysfunction, thromboembolism, and electrolyte imbalance.[3] These complications can lead to cancellation of an *in vitro* fertilization (IVF) cycle, as well as prolonged hospitalization which can lead to significant psychological stress for the couple. The important risk factors for OHSS include age <33 years, polycystic ovary appearance on ultrasound (>24 antral follicles in both ovaries combined), high antimullerian hormone (AMH >3.5 ng/mL), and previous history of OHSS.[4]

The common preventive measures for OHSS used in clinical practice are: GnRH antagonist protocol, GnRH agonist trigger with or without low-dose human chorionic gonadotropin (hCG), freeze-all policy and avoiding fresh transfers, coasting, administration of albumin, hydroxy ethyl starch (HES), and cabergoline.[4] Human chorionic gonadotropin has been used as a surrogate for luteinizing hormone (LH), to induce final oocyte maturation. However, due to its extended half-life leading to high endogenous LH activity, which in turn upregulates VEGF, its use has been tailored in patients at high risk of OHSS. The use of GnRH agonist (GnRHa) as trigger in GnRH antagonist downregulated cycles to prevent OHSS in high responders was realized as early as 1991.[5] The LH surge induced by GnRHa trigger lasts even shorter than the endogenous LH surge in a natural cycle, and half-life of LH is much shorter than that of hCG. These two characteristics decrease the luteinizing stimulus to the granulosa cells, thereby limiting the production of vascular endothelial growth factor.[6,7] However, decreased luteinization was found to be associated with significantly decreased estradiol and progesterone production, leading to a defective luteal phase and decreased pregnancy

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rates compared to hCG trigger.[8] Various measures were undertaken to overcome this drawback, such as addition of low-dose hCG either as concomitant trigger (dual trigger) or one dose post oocyte retrieval (OR), along with additional dose of estradiol and progesterone in the luteal phase.[9,10] Prior studies of GnRH agonist triggering combined with 1500 IU hCG post-OR have reported complete prevention of severe early OHSS and excellent pregnancy rates following fresh embryo transfer even in high-risk patients.[6,7] However, there were few cases of occurrence of early OHSS following GnRH trigger and low-dose hCG post-OR in literature.[11] We present a case report on severe early-onset OHSS after GnRH agonist trigger with low-dose hCG following oocyte pickup.

CASE REPORT

A 42-year-old woman, married for 10 years, was evaluated for infertility along with her husband at reproductive medicine unit of a tertiary level hospital. She gave history of irregular cycles and was a known case of hypertension on antihypertensive. She was also on Tablet Eltroxin (75 µg) for hypothyroidism. On examination, her body mass index (BMI) was 30.7 kg/m^2 with normal general and pelvic examination findings. A transvaginal ultrasound report revealed polycystic ovaries (antral follicle count in each ovary >12) with a volume of 10 cm^3 each and an anterior wall myoma measuring 5×5 cm which was close to the endometrial cavity. Her husband's semen analysis revealed normozoospermia. She was diagnosed as a case of polycystic ovarian syndrome according to the Rotterdam criteria. She had undergone multiple cycles of ovulation induction with clomiphene citrate elsewhere.

She underwent laparoscopic myomectomy and was advised ART in view of advanced age and anovulation. Pretreatment with combined oral contraceptive pills was done, and following onset of menstruation, controlled ovarian hyperstimulation was started with 200 IU of recombinant follicle stimulating hormone (Recagon, Organon pharmaceuticals, Dublin, Ireland) in view of her age and high BMI. Multiple dose flexible antagonist (0.25 mg) regimen was followed. She underwent stimulation for 8 days and there were approximately 13 dominant follicles and another 8 intermediate follicles. When more than three follicles reached a diameter of 17 mm, GnRH trigger, 2 mg, subcutaneously (Injection Lupride, Sun Pharmaceuticals, India) was administered for final oocyte maturation after measuring the serum estradiol (E2) which was 15.7 nmol/L (4,276 pg/mL). She underwent ultrasound-guided transvaginal OR and a total of 20 metaphase II oocytes were retrieved. Injection hCG 2000 IU (Pregnyl, Organon Pharmaceuticals, Dublin, Ireland) intramuscularly and 500 mL of HES (6%) was administered prophylactically after OR. Intracytoplasmic sperm injection (ICSI) was performed and fertilization check revealed 15 fertilized oocytes the next day. The patient was advised to take high-protein diet and to maintain total fluid intake–output records. On postretrieval, day 2, she presented with complaints of severe abdominal discomfort and decreased urine output. Her blood pressure was 140/106 mm Hg, pulse rate and respiratory rate was 96/minute and 24/minute respectively. Her abdominal girth was 100 cm and body weight was 71 kg. Her blood investigations revealed hemoconcentration (packed cell volume – 43.6 gm%) and all other biochemical parameters like hepatic, renal functions tests, coagulation parameters, and electrolytes were normal (Table 1).

An ultrasound of the abdomen revealed bilateral enlarged ovaries (right ovarian size – 11×10.5×9 cm and left ovarian size – 11×11.6×10 cm) with significant ascites. The patient was diagnosed with severe early-onset OHSS and admitted. Standard measures, such as intravenous fluid administration, analgesics, antiemetics, and prophylactic anticoagulation with low molecular

Table 1: Blood investigations

	Day 2	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 10*
Hematocrit (PCV %)	43.6	45.2	39.2	40.7	37.5	31	31.3
Total WBC count (mm)	15,800	29,700	14,300	–	–	–	–
Creatinine (mg%)	0.7	–	0.9	–	–	–	–
SGOT (U/L)	8	–	–	9	–	–	–
SGPT (U/L)	18	–	–	10	–	–	–
T. Protein (g/dL)	5.4	–	–	4.0	–	–	–
S. Albumin (g/dL)	3.3	–	–	2.4	–	–	–
Na/K	133/4.3	–	–	–	–	–	–
T. Bilirubin (mg/dL)	0.22	–	–	0.27	–	–	–
APTT (seconds)	32.4	–	–	–	–	–	–
PT (seconds)	9.7	–	–	–	–	–	–
INR	0.89	–	–	–	–	–	–
Alkaline phosphatase (U/L)	118	–	–	99	–	–	–

weight heparin 2500 IU subcutaneously were initiated. She was also started on antibiotics in view of respiratory tract infection. In view of worsening abdominal distension and decreasing urine output, she underwent ultrasound-guided abdominal paracentesis on day 4 postretrieval. A total of 1.8 L of ascitic fluid was drained. The patient's symptoms were relieved temporarily. Her clinical and biochemical parameters were monitored on a daily basis. The patient was advised to wear elastic stockings along with high-protein diet intake and was transfused with four units of thawed plasma to replace the protein. A day later she again developed recurrence of abdominal distension and respiratory distress and a repeat paracentesis was carried out and further 2.5 L of fluid was drained out. Due to low albumin levels (2.9 gm/dL), she was transfused with additional four units of thawed plasma. Hematocrit was falling and other biochemical parameters remained stable. She was also started on Tablet Cabergolin 0.5 mg vaginally once daily and Injection Ganirelix 0.25 mg subcutaneously once daily, and the embryos were cryopreserved. Two days later, she again developed abdominal distension with reaccumulation of ascites and hence, underwent ultrasound-guided abdominal tapping for the 3rd time and 3 L of ascitic fluid was removed. She was again transfused with four units of thawed plasma. The patient's general condition started improving and biochemical parameters stabilized and hence, she was discharged on postretrieval day 11. In view of severe early-onset OHSS, a total of seven blastocysts were cryopreserved for frozen embryo transfer at a later date.

DISCUSSION

Ovarian hyperstimulation syndrome is an iatrogenic complication following ovarian stimulation and multifollicular development. Early OHSS usually starts within 7 to 8 days after OR and is due to the luteinizing stimulus exerted by exogenous hCG, whereas late OHSS starts after the 8th day following OR and is related to the endogenous hCG following conception.

The use of antagonist protocol during ART cycle reduced OHSS incidence by 50%.[12] Further, antagonist protocol allows usage of GnRH agonist trigger for final oocyte maturation instead of hCG, further reducing the incidence of early OHSS to even lower levels.[13]

However, due to lower pregnancy rates following GnRH trigger, various strategies have been put forward to rescue the luteal phase with or without hCG activity. Shapiro et al[10] introduced the concept of dual trigger in which GnRHa and low-dose hCG was given as a combined trigger for final oocyte maturation, whereas Humaidan et al[9] used a modified luteal support in which following GnRHa trigger, one dose of low-dose hCG was given for rescuing the luteal phase. Both the protocols, however, entail the use of low-dose hCG and hence do raise the small risk of OHSS even though the timing of hCG administration might differ. Various studies have suggested that the occurrence of early OHSS with this strategy is almost eliminated. A large prospective randomized trial evaluating the clinical effect of the use of GnRH agonist to trigger final oocyte maturation along with low-dose hCG post retrieval in normogonadotrophic women undergoing IVF/ICSI showed that early pregnancy loss rate was significantly reduced to a level comparable to that of standard hCG-triggered cycles and there were no cases of moderate or severe OHSS in the GnRH agonist group as compared with three cases in the hCG group, despite one-third of the patients in each group having >14 follicles >11 mm in diameter.[9] Two reviews by Humaidan et al[14] and Youssef et al[13] showed that the use of GnRH agonist for triggering of final oocyte maturation compared to hCG was associated with a statistically significantly reduction in the incidence of OHSS. A randomized controlled multicenter study by Humaidan et al[15] where 60 women at risk of OHSS received 0.5 mg Buserelin (GnRHa) subcutaneously followed by a single bolus of 1500 IU hCG, intramuscular, post-OR and 58 women received 5000 IU hCG as standard trigger showed that there were no cases of OHSS in the group that received GnRHa with the low-dose hCG, whereas two cases of moderate late-onset OHSS occurred in group that received 5000 IU of hCG. Radesic et al[7] conducted a retrospective study in which 71 women who were at high risk of severe OHSS (≥14 follicles ≥12 mm) received an agonist trigger followed by hCG and single embryo transfer and found only one case of severe late-onset OHSS. Although GnRH agonist along with 1500 IU hCG luteal rescue protocol significantly decreases the risk of severe OHSS, this life-threatening complication can still occur in high-risk patients. Seyhan et al[11] conducted a retrospective cohort study including 23 women who were at high risk of OHSS (according to the estradiol levels and/or number of follicles more than 12 mm during stimulation). In their study, the mean estradiol level was 4891 + 2214 pg/mL and a mean number of >12 mm follicles were 20 ± 6 on the day of ovulation triggering. They had taken additional preventive measures, like the use of metformin, coasting, dopamine agonist, and postponing fresh embryo transfer until day 5. However, six among 23 (26%) women developed severe OHSS. Five women had severe early OHSS and three of these five women did not have a fresh embryo transfer. They concluded that although there is strong evidence that GnRH agonist triggering in antagonist cycles significantly decreases the risk of OHSS, a single

1500 IU hCG injection which is used to rescue the luteal phase can trigger severe early OHSS in some patients. A segmented approach, including GnRH agonist trigger in antagonist cycle without low-dose hCG along with freeze-all strategy has been recommended for complete prevention of early and late OHSS.[11,16] However, this approach may also lead to rare OHSS as shown by Fatemi et al[17] and Gurbuz et al[18] where they reported few cases of severe early onset OHSS in spite of the segmented approach. However, in the case report by Gurbuz et al, two among the three cases received high dose of gonadotropin (225–300 IU).

Our case report also shows that high-risk patients can develop severe early-onset OHSS following GnRH agonist trigger with low-dose hCG. Hence, it would be appropriate to avoid hCG injection altogether in patients deemed to be at very high risk. Many times in practice, administration of hCG post OR is used in moderate to high-risk cases like in our case. Though it seems prudent to altogether omit low-dose hCG, but such decision would mean complete reliance on freeze-all strategy and subsequent transfer at a later date. However, sometimes surprisingly poor fertilization and embryo development may make a case for fresh embryo transfer than cryopreservation, hence the clinician tends to use low-dose hCG for additional luteal support when GnRHa trigger is administered, to avoid forgoing the option of fresh transfer altogether. Also freeze-all strategy needs a very reliable cryopreservation program. It will be worth exploring if the decision for administering the low-dose hCG can be deferred until next day morning (day 1) when the fertilization status is known and clinician can omit the hCG administration altogether if the report is on expected line and commit for freeze-all policy more confidently.

The aim of this report was to alert clinicians regarding the risk of early-onset OHSS in moderate- to high-risk patients with the use of concomitant low-dose hCG. There is definitely a need to consider freeze-all policy and withhold the use of low-dose hCG in patients with high risk of OHSS. However, there is also a need to evolve a system of categorizing OHSS risk patients into moderate and high risk. This will help in deciding which group of patients needs freeze-all policy (without any exposure to exogenous and endogenous hCG) and which can be offered combined GnRHa and single low-dose hCG rescue.

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