Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG

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STUDY QUESTION: Is severe early ovarian hyperstimulation syndrome (OHSS) completely prevented with the GnRH agonist trigger and 1500 IU hCG luteal rescue protocol?

SUMMARY ANSWER: Severe early OHSS can occur even after the GnRH agonist trigger and 1500 IU hCG luteal rescue protocol.

WHAT IS KNOWN ALREADY: Prior studies including over 200 women who received the GnRH agonist trigger and 1500 hCG luteal rescue protocol have reported complete prevention of severe early OHSS. Only a few late OHSS cases have been reported and it has been suggested that this protocol can be safely applied to any women under risk.

STUDY DESIGN, SIZE, DURATION: This retrospective cohort study included all women who were at high risk of OHSS and were given the GnRH agonist trigger plus hCG luteal rescue protocol between December 2008 and August 2012 in the two participating centers.

PARTICIPANTS/MATERIALS, SETTING, METHODS: There were 23 women with a mean estradiol level of 4891 ± 2214 pg/ml and a mean number of > 12 mm follicles of 20 ± 6 on the day of ovulation triggering. OHSS was categorized according to the Golan criteria.

MAIN RESULTS AND THE ROLE OF CHANCE: Overall 6 of the 23 (26%) women developed severe OHSS. Five women had severe early OHSS requiring ascites drainage and hospitalization and three of these women did not undergo embryo transfer. The number of follicles measuring 10–14 mm on the day of triggering was significantly different between women who developed severe early OHSS and those who did not.

LIMITATIONS, REASONS FOR CAUTION: The small number of women with severe early OHSS may have prevented identification of other significant risk factors.

WIDER IMPLICATIONS OF THE FINDINGS: Although the GnRH agonist plus 1500 IU hCG luteal rescue protocol significantly decreases the risk of severe OHSS, this life threatening complication can still occur in high-risk patients. It would be prudent to avoid hCG luteal rescue and freeze all embryos for future transfer in such women particularly when there are ≥ 18 follicles with 10–14 mm diameters even with few larger follicles.

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Key words: ovarian hyperstimulation syndrome / hCG / GnRH agonist / GnRH antagonist / in vitro fertilization

Introduction

Ovarian hyperstimulation syndrome (OHSS) is characterized by increased vascular permeability, hemoconcentration and fluid leakage to the third space (Ata and Tulandi, 2009). The vast majority of OHSS cases occur following ovarian stimulation for IVF. This potentially lethal iatrogenic condition is one of the most serious complications of assisted reproductive technologies.

The pathogenesis of OHSS involves an increased number of granulosa cells due to multifollicular growth and the extensive production of vascular endothelial growth factor following the luteinization of these cells.
(Soares et al., 2008). Traditionally, in ovarian stimulation cycles hCG is administered as a surrogate for the natural LH surge to induce final oocyte maturation. The longer half-life of hCG compared with LH is thought to extend the luteinizing stimulus for the granulosa cells and to play a crucial role in the development of OHSS (Ata and Tulandi, 2009). While the luteinizing stimulus exerted by exogenous hCG is the major driving force behind early OHSS that starts within 8 days after oocyte retrieval (OR), late OHSS, starting after the eighth day following OR, seems to be triggered by the endogenous hCG of pregnancy. When the patient is at risk of OHSS, withholding the hCG injection and aborting the ovarian stimulation cycle will prevent either form of the syndrome.

More recently the use of a GnRH agonist instead of hCG to trigger final oocyte maturation has been suggested as a preventive measure to avoid OHSS. This can only be achieved in controlled ovarian stimulation (COS) cycles in which a GnRH antagonist is used for pituitary suppression. GnRH agonist used in this context does not only induce final oocyte maturation but also acts as a luteolytic agent and prevents the secretion of vasoactive substances from corpora lutea (Fauser et al., 2002; Kol, 2004). However, pregnancy rates following fresh embryo transfer have been significantly decreased with this approach. Therefore, it has been suggested to deliver a 1500 IU hCG injection given 35 h after the agonist trigger to preserve luteal function (Humaidan et al., 2006, 2010). This lower dose of hCG is thought to be too low a stimulus to trigger OHSS (Humaidan et al., 2006, 2010).

Prior studies of GnRH agonist triggering combined with 1500 IU hCG (agonist trigger plus hCG support protocol) have reported complete prevention of severe early OHSS and excellent pregnancy rates following fresh embryo transfer even in high-risk patients (Humaidan, 2009; Radesic and Tremellen, 2011). Indeed, only two cases of late onset OHSS were reported in a total of 83 women deemed to be at risk of OHSS due to a high number of growing follicles (Humaidan, 2009; Radesic and Tremellen, 2011). The current status of the literature in this domain suggests that severe early OHSS can be completely prevented, and that late OHSS occurs sporadically with this protocol. The purpose of this investigation is to explore the risk of severe early OHSS associated with the GnRH agonist trigger plus hCG support protocol.

Materials and Methods

This is a retrospective analysis of women who received the GnRH agonist trigger plus hCG support protocol in a GnRH antagonist ovarian stimulation cycle at the McGill University Health Centre Reproductive Centre (MUHC RC), Montreal, Canada and the Anatolia IVF Centre, Ankara, Turkish Republic between December 2008 (when the first patient was given the agonist trigger + 1500 IU hCG protocol) and August 2012.

Daily gonadotrophin injections were started on the second or the third day of either a spontaneous or an induced menstrual bleeding; the starting dose was determined according to female age, weight, markers of ovarian reserve, including follicular phase serum FSH level and antral follicle count (AFC), as well as previous ovarian response if there had been a prior COS cycle. GnRH antagonist injections at a dose of 0.25 mg/day were started either on the sixth day of stimulation or when the leading follicle reached 14 mm. Injections were continued until ≥2 follicles reached ≥17 mm diameter.

Participants were identified as being at high risk of OHSS by a high number of follicles measuring ≥12 mm and/or high serum estradiol levels during the late follicular phase of the ovarian stimulation cycle. The decision to apply the GnRH agonist trigger plus hCG support protocol rather than the traditional hCG trigger was at the discretion of the treating physician as this was not a protocol driven prospective study.

The GnRH agonist trigger plus hCG support protocol consisted of a s.c. injection of 1 mg buserelin acetate (Suprefact, Sanofi Aventis) at the MUHC RC or 0.2 mg triptorelin (Decapeptyl, Ferring) at the Anatolia IVF Centre, both followed by 1500 IU of hCG (Chorionic Gonadotropin, Pharmaceutical Partners of Canada, Canada or Pregnyl, MSD, Turkey) 35 h after the agonist trigger. Transvaginal oocyte retrieval was performed 1 h after the hCG injection.

Additional measures used to prevent OHSS included withholding gonadotrophin injections for one or more days before the GnRH agonist trigger, i.e. coasting, administration of a dopamine agonist, cabergoline, at a dose of 0.5 mg/day orally for 7 days starting from the day of agonist trigger, and starting metformin before the COS cycle for some patients with polycystic ovarian syndrome (PCOS). One or more of the additional measures were taken at the discretion of the treating physicians.

The decision to proceed with a fresh embryo transfer or to freeze all available embryos was jointly taken by the treating physicians and the patients, taking into account the risk of pending OHSS or already present symptoms before or on the day of embryo transfer. Women who underwent fresh embryo transfer received luteal phase support with vaginal micronized progesterone (90 mg/day vaginal gel) and oral estradiol valerate tablets (6 mg/day at MUHC RC and 4 mg/day at Anatolia IVF).

OHSS was defined according to the Golan criteria (Golan et al., 1989). Diagnosis of mild OHSS required the presence of abdominal distension and discomfort with or without nausea, vomiting and/or diarrhea. Moderate OHSS was diagnosed when ultrasonographic ascites was present in addition to the above features. Severe OHSS was diagnosed when there was clinical evidence of ascites and/or hydrothorax or breathing difficulties with or without hemoconcentration, coagulation abnormalities and diminished renal function.

Continuous variables were described by the mean and standard deviation or the median and interquartile ranges, depending on the distribution characteristics. Minimum and maximum values were also presented to better inform the reader about patient characteristics. Mann–Whitney U and χ² test with Yate’s correction was used to compare continuous and categorical variables, respectively, between the two participating centers.

In order to determine which patients could be at high risk of severe early OHSS following the GnRH agonist trigger plus hCG support protocol, demographic and clinical characteristics were compared between women who developed severe early OHSS and those who did not.

Results

The study population included 23 consecutive women who received the GnRH agonist trigger + hCG support protocol, 15 from the MUHC Reproductive Centre and 8 from the Anatolia IVF centre. They represent all patients treated with this protocol at both centers until the close of the study.

The mean (standard deviation) female age was 32.0 (3.1) years. The most common indication for treatment was PCOS, which was diagnosed as per Rotterdam criteria and was present in 9 (39.1%) of participants. The mean AFC was 35.4 (18.9) indicating high ovarian reserve. Clearly, women treated with the GnRH agonist trigger plus hCG support protocol were at high risk of OHSS. There were 14 (69.1%) undergoing their first IVF cycle. The baseline patient characteristics were comparable between the two centers and are presented in Table I.

IVF cycle characteristics and outcomes are presented in Table II. Fresh embryo transfer was canceled for five women. Of the remaining 18 women who underwent fresh embryo transfer, 7 (5 from McGill and 2
A total of 6 (26.1%) women developed severe OHSS and 5 (21.7%) of these women had severe early OHSS. Of these five women with severe early OHSS, two had fresh embryo transfer and the other three women had all their embryos cryopreserved due to the presentation of OHSS prior to the planned embryo transfer. The two women who had fresh embryo transfer failed to conceive.

The patient with severe late OHSS was a 27 years old woman undergoing IVF due to a male factor, and was stimulated with 112 IU/day recombinant FSH (rFSH, Gonal-F, EMD Serono, Canada). She had 30 follicles ≥ 12 mm and a serum estradiol level of 4959 pg/ml on the day of trigger. A total of 65 oocytes were collected, 41 of which was at the metaphase II stage. She was simultaneously started on 0.5 mg cabergoline (Dostinex, Pfizer, Canada) once a day, orally for 7 days. Three days after retrieval, she was asymptomatic and had no hemococoncentration until then. She presented with bloating on the ninth day post-oocyte collection and there was ~600 ml ascites noted on ultrasound examination. She did not require ascites drainage and was managed with i.v. fluids and daily low-molecular-weight heparin (LMWH) injections. She had a singleton pregnancy that ended up in a miscarriage.

**Brief description of severe early OHSS cases**

The first woman with severe early OHSS was a 27-year-old oligomenorrheic PCOS patient with a BMI of 31.2 kg/m². She was on 1500 mg metformin daily. On the second day of a menstrual period following a 21 days round of combined oral contraceptive pill (Marvelon, Merck & Co., Canada), 225 IU/day rFSH was commenced. This dose was selected due to the patient’s BMI. Daily 0.25 mg GnRH antagonist injections were started on the sixth day of stimulation. On the eighth day of stimulation, the serum estradiol level was 5589 pg/ml and she had 11 follicles measuring 12–16 mm, accompanied by numerous others measuring ≤ 10 mm. The rFSH dose was decreased to 150 IU/day and she was given 1 mg buserelin acetate s.c. the next day followed by OR 36 h later; 1500 IU hCG was administered intramuscularly within 1 h of OR. A total of 65 oocytes were collected, 41 of which was at the metaphase II stage. She was simultaneously started on 0.5 mg cabergoline (Dostinex, Pfizer, Canada) once a day, orally for 7 days.
after oocyte collection, she developed vomiting, abdominal distension and pain, and subjectively reduced urinary output. Her hematocrit was 53%, her leukocyte count (white blood cell, WBC) was $21.1 \times 10^6$/ml, serum creatinine was 1.4 mg/dl, while her serum albumin level was 2.2 g/dl. An ultrasound exam revealed free fluid in the pouch of Douglas. She was admitted with the diagnosis of severe OHSS. The embryo transfer was canceled; all available embryos were cryopreserved for future transfer. She was managed with intravenous hydration and 25% albumin infusions. Daily LMWH injections were given for thromboembolic prophylaxis. Five days after OR, 2.5 l of clear ascetic fluid was drained transvaginally. She was discharged in stable condition.

The second woman with severe early OHSS was 31 years old. She had regular cycles and no evidence of hyperandrogenism. Her BMI was 29.1 kg/m². She was administered 200 IU rFSH (Puregon, Merck, Canada) daily for 7 days and the dose was decreased to 100 IU on the eighth day of ovarian stimulation. Daily 0.25 mg GnRH antagonist injections were started on the sixth day of stimulation. The starting dose was 175 IU/day and on the 11th day of stimulation her serum E2 level was 8364 pg/ml and she was given the GnRH agonist trigger. She had 26 oocytes collected, 23 of which were metaphase II. Two embryos were transferred on the third day after OR. She presented with shortness of breath, abdominal distension and reduced urinary output on the sixth day after OR; 200 cc ascites was drained and her hematocrit was 49% with a WBC of $18 \times 10^6$/ml. She was managed with i.v. fluids and LMWH injections. She did not require additional paracentesis. She did not conceive following the fresh embryo transfer.

The final case was a 30-year-old PCOS patient with a BMI of 31 kg/m². She had one previous failed IVF cycle. She was given 150 IU/day gonadotrophins and was coasted for 2 days after the eighth day of stimulation. She was given the GnRH agonist trigger on the 10th day of the ovarian stimulation cycle when her serum E2 level was 6814 pg/ml. A total of 23 oocytes, 14 of which were metaphase II, were collected. Two embryos were transferred on the third day after OR. She presented with shortness of breath, abdominal distension and decreased urinary output 4 days after OR. Her hematocrit was 46.5% and WBC was $18.9 \times 10^6$/ml; 2100 ml ascites was drained and she was given i.v. fluids and LMWH. She did not conceive.

The cases of severe early OHSS are summarized in Tables III and IV.

### Analysis of risk factors

In order to determine which characteristics can be useful to identify women who will develop severe early OHSS following the GnRH

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**Table III  Patient and COS cycle characteristics of severe early OHSS cases.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>PCOS</th>
<th>GnRH agonist starting dosage (IU/day)</th>
<th>Co-treatment</th>
<th>Number of follicles ≥ 12 mm</th>
<th>Peak E2 in pg/ml</th>
<th>Number of oocytes collected (metaphase 2 oocytes)</th>
<th>Number of transferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (McGill)</td>
<td>27</td>
<td>31.2</td>
<td>Yes</td>
<td>225</td>
<td>Metformin</td>
<td>11</td>
<td>5589</td>
<td>65 (41)</td>
<td>Freeze all</td>
</tr>
<tr>
<td>2 (McGill)</td>
<td>30</td>
<td>29.1</td>
<td>No</td>
<td>200</td>
<td>Cabergoline</td>
<td>15</td>
<td>2563</td>
<td>49 (32)</td>
<td>Freeze all</td>
</tr>
<tr>
<td>3 (McGill)</td>
<td>33</td>
<td>22.0</td>
<td>No</td>
<td>100</td>
<td>Cabergoline</td>
<td>34</td>
<td>3011</td>
<td>33 (18)</td>
<td>Freeze all</td>
</tr>
<tr>
<td>4 (Anatolia)</td>
<td>31</td>
<td>32.6</td>
<td>Yes</td>
<td>175</td>
<td>Coasting</td>
<td>25</td>
<td>8364</td>
<td>26 (23)</td>
<td>2</td>
</tr>
<tr>
<td>5 (Anatolia)</td>
<td>30</td>
<td>31.0</td>
<td>Yes</td>
<td>150</td>
<td>Coasting</td>
<td>24</td>
<td>6814</td>
<td>23 (14)</td>
<td>2</td>
</tr>
</tbody>
</table>
agonist trigger + hCG support protocol, we compared female age, BMI, AFC, numbers of follicles > 12 mm, number of follicles measuring 10–14 mm on the day of trigger and peak serum E2 levels between the 5 women who had severe early OHSS and the 18 women who did not develop the syndrome in our series. The only variable that was significantly different between these two groups was the number of follicles measuring 10–14 mm on the day of agonist trigger, as presented in Table V. Interestingly, the BMI tended to be higher in those who developed severe early OHSS than in those subjects who did not (P = 0.07). Possibly, these patients were placed on higher doses of gonadotrophins to compensate for their high BMIs, on average 31.0 kg/m².

**Discussion**

Two recent reviews on triggering of final oocyte maturation with hCG or a GnRH agonist clearly noted that the use of GnRH agonist was associated with a statistically significantly reduction the incidence of OHSS (Humaidan et al., 2011; Youssef et al., 2011). Strikingly there was not a single case of moderate or severe OHSS among the 437 women who were randomized to GnRH agonist trigger, including 182 women who also received a single 1500 IU dose of hCG after the GnRH agonist trigger in two trials by Humaidan et al. (2006, 2010) (Youssef et al., 2011). Although women at high risk of OHSS were not included in the two trials by Humaidan et al. (2006, 2010), two case series exclusively including women at high risk of OHSS also reported complete prevention of early OHSS when the GnRH agonist trigger + hCG support protocol was employed (Humaidan, 2009; Radesic and Tremellen, 2011).

The first series included 12 women who had ≥ 25 follicles of ≥ 11 mm on the day of the triggering oocyte maturation with a 0.5 mg buserelin injection. Women were given 1500 IU hCG 35 h after the GnRH agonist trigger. The average number of oocytes collected was 21.5 ± 6.0, and mean serum estradiol level on the day of trigger was 5066 ± 2860 pg/ml. Luteal phase was supported with vaginal micronized progesterone and oral estradiol valerate tablets. All 12 women underwent fresh embryo transfer. While there were no cases of early onset OHSS of any degree, one woman developed late OHSS that did not require hospitalization (Humaidan, 2009). In the latter publication, Radesic and Tremellen reported their experience of 71 women receiving the GnRH agonist trigger + hCG support protocol (Radesic and Tremellen, 2011). Their series included women who had ≥ 14 follicles of ≥ 12 mm on Day 8/9 of the ovarian stimulation cycle. The mean serum estradiol level on the ninth day of stimulation was 3356 ± 150 pg/ml and oocyte maturation was triggered with 2 mg leuprolide acetate followed by 1500 IU hCG 37 h later. The average number of oocytes collected was 16.8 ± 0.8. Luteal phase support was given with vaginal micronized progesterone and oral estradiol valerate similar to the former

<table>
<thead>
<tr>
<th>Time of diagnosis (days after OR)</th>
<th>Presenting symptoms</th>
<th>Hematocrit</th>
<th>Ascites drainage (amount drained)</th>
<th>Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 3</td>
<td>Abdominal distention</td>
<td>0.53</td>
<td>Yes (2.5 l)</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 2 3</td>
<td>Abdominal distention</td>
<td>0.51</td>
<td>Yes (3.3 l)</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 3 4</td>
<td>Abdominal pain</td>
<td>0.54</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 4 6</td>
<td>Abdominal distention</td>
<td>0.49</td>
<td>Yes (0.2 l)</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 5 4</td>
<td>Abdominal distention</td>
<td>0.47</td>
<td>Yes (2.1 l)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Table V** Comparison of women who did and did not develop severe early OHSS following the GnRH agonist plus 1500 IU hCG protocol.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Severe early OHSS (n = 5)</th>
<th>Not severe early OHSS (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 (29.5–32.0)</td>
<td>32 (29.8–35.3)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>31.0 (25.6–31.9)</td>
<td>25.6 (20.9–27.2)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>35.0 (26.5–49.0)</td>
<td>26.0 (22.5–47.0)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>15.0 (11.5–24.5)</td>
<td>20 (16.8–24.5)</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of follicles</th>
<th>Severe early OHSS (n = 5)</th>
<th>Not severe early OHSS (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 12 mm on the day of trigger</td>
<td>34.0 (17.0–49.0)</td>
<td>12 (9–18.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>5589 (2787–7589)</td>
<td>4156 (3212–5507)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Coasting (%)</td>
<td>2 (40)</td>
<td>3 (16.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Cabergoline given (%)</td>
<td>3 (69)</td>
<td>4 (22.2)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

All values are median (interquartile range) unless otherwise stated. AFC, antral follicle count.

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publication. Similarly, all women underwent fresh embryo transfer and there was not a single case of early OHSS (Radesic and Tremellen, 2011). It is noteworthy that no other measures to prevent OHSS such as ‘coasting’ or co-administration of dopamine agonists were taken in either study (Humaidan, 2009; Radesic and Tremellen, 2011).

Despite the above studies, direct evidence suggesting that low-dose hCG prevents early OHSS is limited and it is known that even small doses of hCG such as 2500 or 3300 IU can lead to early OHSS (Nargund et al., 2007; Kashyap et al., 2010). However, some infertility specialists hold the view that 1500 IU hCG is too low a dose to cause OHSS. Indeed, Radesic and Tremellen report employing no upper limit of ovarian response to preclude 1500 IU hCG luteal support following the agonist trigger in their series (Radesic and Tremellen, 2011). Our experience has been different from both of these groups. The main difference between our results and the prior reports is the occurrence of severe early OHSS in our series. Although some women had embryo transfer canceled due to early OHSS, late onset OHSS occurred in only one of the 18 women who underwent a fresh embryo transfer, which is similar to previous reports. Given their mean values with relatively small standard deviations, Radesic and Tremellen’s data seem to have a normal distribution and ~96% of their observations should be below mean plus 2 standard deviations. Therefore, the vast majority of their patients should have had an E2 level of <3656 pg/ml and <19 oocytes collected. Probably their series included only about 5 women exceeding any of these values, compared with 13 women with E2 ≥ 3656 pg/ml and 14 women with ≥20 oocytes collected in our series. However, similar statistical inference is not possible for Humaidan et al.’s smaller series of 12 high-risk patients as the estradiol values do not seem to be normally distributed given the high standard deviation relative to the mean value. Regardless, the mean estradiol value of 5066 pg/ml and the mean number of oocytes collected of 21 suggest their series is more similar to our series than they are to that of Radesic and Tremellen.

The apparent discrepancy between the number of follicles measuring ≥ 12 mm and the number of oocytes collected in Cases 1 and 2 is possibly due to McGill team’s extensive experience with oocyte collection for in vitro maturation cycles. Both patients had very high AFCs and despite that a small proportion of these follicles had reached a diameter >12 mm. We aspirated all follicles including those as small as 4–5 mm and our embryologists are used to identifying oocytes with a small amount of cumulus cells retrieved from follicles <12 mm.

Readers can be critical about administration of any hCG at all to some of the patients presented in this report. However, when these patients were treated, there was not a single case of severe early OHSS reported following the GnRH agonist trigger plus hCG support protocol, even in high-risk patients. Indeed, the only publication about high-risk patients that was available at the time of our treatment reported that 12 women with a mean E2 level of 5066 ± 2860 pg/ml were given the GnRH agonist trigger + 1500 hCG support. These figures suggested there were some women with similarly high E2 levels and none had severe early OHSS following the GnRH agonist trigger + 1500 hCG support. We also took additional preventive measures, including the use of metformin, coasting, dopamine agonist and postponing fresh embryo transfer until Day 5 in order to see whether the patients would develop early OHSS. It is also noteworthy that two of the women who developed severe early OHSS had E2 levels of 2563 and 3011 pg/ml and the former had only 15 follicles measuring ≥12 mm.

It may be argued that the rate of severe early OHSS is excessively high. However, this is a select group of high-risk patients. Had hCG triggering been used it is likely that a large percent of patients would have developed severe early OHSS, a greater number than those in which it occurred.

While it sounds prudent to totally avoid hCG injections for patients at high risk of OHSS, to the best of our knowledge, published literature lacks a single case of severe early OHSS following the GnRH agonist trigger plus hCG support protocol. Apparently this can lead to the thinking that this protocol has no risk of OHSS and is applicable to any patient regardless of the extent of ovarian response to ovarian stimulation. Our current report presents five cases of severe early OHSS following the GnRH agonist trigger plus hCG support protocol. The occurrence of severe OHSS in a patient with serum E2 level <3500 pg/ml and only 15 follicles ≥12 mm on the day of trigger such as in Case 2 clearly demonstrates and re-confirms that severe OHSS can even occur in patients who are not deemed to be at high risk on the day of triggering. Furthermore, it can even occur after the GnRH agonist trigger plus hCG support protocol. Reporting the occurrence of severe early OHSS following GnRH agonist trigger plus hCG luteal support, despite co-employment of other evidence-based preventive methods including coasting and the use of metformin and dopamine agonist, is another important aspect of the current manuscript.

In conclusion, the available evidence strongly suggests that GnRH agonist triggering of ovarian stimulation cycles down-regulated with GnRH antagonists significantly decreases the risk of OHSS. However, when a single 1500 IU hCG injection is used to rescue the luteal phase following GnRH agonist triggering severe early OHSS can still develop in some patients. Clearly it would be prudent to avoid hCG injection in patients deemed to be at very high risk. Based on our data we suggest to avoid hCG rescue for women who have ≥18 follicles measuring 10–14 mm in diameter on the day of agonist trigger, even if the number of larger follicles is limited. This threshold is based on the 25th percentile value of the women with severe early OHSS and the 75th percentile value of the women without severe early OHSS in our series. These women can be offered cryopreservation of all embryos for later transfer in a non-stimulated cycle. This should also be noted that the limited sample size could have prevented identification of other significant risk factors.

Authors’ roles
A.S.: conception of study, acquisition of data, revising the manuscript for intellectual content, approval of the final version. B.A.: conception of the study, data analysis and interpretation, drafting the manuscript, approval of final version. M.P., W.Y.S.: data acquisition, revising the manuscript for intellectual content, approval of the final version. H.Y.: revising the manuscript for intellectual content, approval of the final version. M.H.D.: conception of the study, revising the manuscript for intellectual content, approval of the final version.

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Conflict of interest
None declared.
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