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GnRHa trigger and modified luteal support with one bolus of hCG should be used with caution in extreme responder patients

Dear Sir,

We read with interest the retrospective report by Seyhan *et al.* (2013) presenting five cases of early ovarian hyperstimulation syndrome (OHSS) in OHSS high-risk patients, following GnRHa trigger and modified luteal phase support with one bolus of 1500 IU hCG. As we have performed the majority of randomized controlled trials (RCTs) in this field, we feel an urge to further comment on the paper, although the report was previously accompanied by an editorial (Bodri, 2013).

Seyhan *et al.* (2013) in their two-centre retrospective analysis included 23 patients at risk of developing OHSS, defined as 'a high number of follicles ≥12 mm during the late follicular phase'. Patients received a GnRHa trigger followed by a bolus of 1500 IU hCG on the day of oocyte retrieval (Humaidan *et al.*, 2005; Humaidan, 2009; Humaidan *et al.*, 2010). If a decision was made to go ahead with an embryo transfer a standard luteal phase support was added to the protocol. A total of six patients (26%) developed severe OHSS of whom five patients developed early onset OHSS (22%). Of these patients three had their embryo transfer cancelled and two received a dual embryo transfer. The authors analyzed possible risk factors of OHSS and concluded that the only significant parameter was the number of follicles measuring 10–14 mm on the day of trigger, being significantly higher in the patients who developed severe early OHSS. This made the authors conclude that it would be prudent to avoid hCG luteal rescue and instead freeze all embryos in women with a total of ≥18 follicles with 10–14 mm diameters.

GnRHa trigger followed by a modified luteal phase support with one bolus of 1500 IU hCG was developed by our group through a series of trials (Humaidan *et al.*, 2005; Humaidan *et al.*, 2010) mainly involving normal responder patients. However, in our RCT from 2010, including 302 patients (Humaidan *et al.*, 2010), more than one-third of the patients in the GnRHa triggered as well as the hCG triggered groups had >14 follicles ≥11 mm on the day of trigger, a level previously suggested to distinguish between the OHSS risk patient and the patient at low risk of OHSS (Papanikolaou *et al.*, 2006). No patient developed OHSS in the GnRHa triggered group versus 2% after hCG trigger.

In our latest RCT including a total of 384 patients (Humaidan *et al.*, 2013) we randomized 118 patients considered at risk of OHSS to either GnRHa trigger followed by the previously described modified luteal phase support or trigger with 5000 IU hCG. Risk of OHSS was *a priori* determined as the presence of 15–25 follicles ≥11 mm on the day of triggering final oocyte maturation. Importantly, patients with >25 follicles were excluded from this study based on the results of a previous pilot study in OHSS risk patients (Humaidan, 2009).

In this new large RCT, no OHSS case was seen after GnRHa trigger and modified luteal phase support when compared with two moderate late-onset OHSS cases (3.4%) after hCG trigger. Reassuringly, no statistical difference in ongoing clinical pregnancy rates between the two trigger concepts was observed. Thus, in patients with up to 25 follicles, we feel quite confident with the use of GnRHa trigger followed by a modified luteal phase support with one bolus of 1500 IU hCG. Above 25 follicles we recommend a 'freeze all' policy. If for some reason a decision to perform a fresh transfer is made in this type of OHSS high-risk patient, it is our clinical experience that luteal supplementation with hCG post-GnRHa trigger should only be performed in the well-informed patient with great caution and employing a lower dose of hCG.

Regarding the Seyhan *et al.* paper (2013) our main concern and utter surprise is the fact that the authors still decided to proceed with a bolus of 1500 IU hCG in patients who had as many as 50–65 oocytes retrieved. This conduct seems to us unethical, jeopardizing the health of the patient when it would have been more prudent to 'freeze all' after GnRHa trigger without any risk whatsoever of OHSS development in the patient. Although GnRHa trigger and modified luteal phase support has allowed fresh transfer in OHSS risk patients, there is clearly an upper biological limit above which it would be unrealistic to believe that all OHSS cases could be avoided. In these cases we call upon the sound clinical judgment of the treating clinician.

We also question the upper cut-off value of ≥18 follicles measuring 10–14 mm suggested by Seyhan *et al.* (2013), as these results derive from a retrospective analysis including 23 OHSS risk patients only. Moreover, in their paper, this cut-off value is severely jeopardized by the discrepancy between the follicular count on the day of trigger and the actual number of oocytes retrieved in several of their patients.

In conclusion, GnRHa trigger followed by a modified low-dose early luteal hCG support will provide patients who on the day of trigger have developed up to 25 follicles >11 mm with the opportunity to proceed to fresh embryo transfer with good ongoing pregnancy rates and no OHSS according to the results of our latest RCT. However, until ongoing studies have defined the minimal hCG activity needed in patients with >25 follicles ≥11 mm, we firmly recommend GnRHa trigger followed by a 'freeze all' policy to avoid any risk of OHSS development.

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Reply: GnRHa trigger and modified luteal support with one bolus of hCG should be used with caution in extreme responder patients

Dear Sir,

We read Dr Humaidan's letter with great interest. We are pleased to see that our report of five cases of severe early ovarian hyperstimulation syndrome (OHSS) following the agonist trigger + 1500 IU hCG luteal support protocol draws attention and stimulates further debate. There is no doubt that debate benefits science and patient care.

In response to Dr Humaidan's comments, we have several questions, which we wish to pose as well as reply to several issues that arose. First, we are surprised to learn that Dr Humaidan *et al*. have excluded women who had >25 follicles of ≥11 mm on the day of trigger from their subsequent trial. They state that this was decided 'based on the results of a previous pilot study in OHSS risk patients' (Humaidan, 2009) Although we find this a sound decision based on our own experience (Seyhan *et al*., 2013), we fail to see how Dr Humaidan arrived at this decision based on his former publication. Dr Humaidan's former study included exactly the same population as the women who were excluded from the subsequent trial (>25 follicles of ≥11 mm on the day of trigger) and he has reported not having a single case of severe early or late OHSS despite the mean estradiol level of 5066 pg/ml on the day of trigger and a mean number of 21.5 oocytes collected. Moreover, the live birth rate was excellent at 50% after fresh transfer of an average 1.7 embryos. Indeed, his conclusion was 'The advantages of the present procedure compared with a total freeze are the avoidance of the psychological distress of a cancelled transfer, the avoidance of embryo loss due to the freezing and thawing procedure and lower pregnancy rates in thaw cycles'. He called for 'more and larger studies to confirm the present report . . .'. It is now surprising to see that he calls a similar study using the same protocol in a similar group of patients 'unethical'. We would like to note that our patients were given this treatment because we thought they would benefit from it, based on the published literature (Humaidan, 2009). They were not given this treatment for the purpose of a prospective study. In his 2009 paper, Dr Humaidan also heralded obtaining ethics committee approval for an upcoming trial, which would compare 1500 hCG with a lower dose in the high responder patients. No change in the study population was mentioned. We are curious to learn what has changed Dr Humaidan's mind even before the publication of our report, as there were only a few late onset OHSS cases following this protocol published in the literature and no cases of early OHSS.

Dr Humadian also questions a discrepancy between the follicular count and the actual number of oocytes collected in our series. The follicular counts reported in our study reflected only follicles >12 mm on the day of trigger. We are unaware of Dr Humaidan's oocyte collection technique, but it is possible to collect mature oocytes even from follicles that are <10 mm on the day of collection (Salha *et al*., 1998; Triwitayakorn *et al*., 2003). Thanks to our vast experience from IVM oocyte collection procedures, we are often able to collect more oocytes than the number of follicles >12 mm on the day of trigger. This is indeed apparent in our data; patients from McGill had similar number of oocytes collected when compared with patients from Anatolia IVF, despite the latter having significantly higher serum estradiol (E2) levels and significantly more follicles of >12 mm (Table 2 of the original paper). Moreover, all four women with >40 oocytes collected in our series were from McGill and they had serum E2 levels of 2563, 2779.9, 4958 and 5588.94 pg/ml and they had 9, 15, 17 and 30 follicles ≥12 mm. Apparently, three of these four women would not be excluded from the recent, yet unpublished trial by Humaidan *et al*. and would have received 1500 IU hCG or the comparator, which also involved some hCG following the agonist trigger.

Although Humaidan *et al*. did not mention in their letter, they could be critical about the accuracy of ultrasound monitoring or the quality of our ultrasound equipment used in our study. In order to save from limited space we would like to refer them to our paper on ultrasound monitoring of stimulated IVF cycles, which specifies the equipment used in our center (GE Voluson E8 Expert) and our method of follicle measurements (Ata *et al*., 2011).

We admire Dr Humaidan's work in improving the agonist trigger + 1500 IU hCG luteal rescue protocol, which benefits most patients at risk and we are happy to see that he agrees with us in recommending avoiding any hCG injections to women under high risk and offering complete cryopreservation.

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