We are surprised to learn that Dr Humaidan has decided against administering GnRH agonist with GnRH antagonist, a treatment protocol we have successfully employed in our clinic. We find this a sound decision based on our own experience. In 2009, Humaidan et al. (Hum Reprod 2013; 28:2511–2521) described the use of GnRH agonist with GnRH antagonist in 100 high-risk OHSS patients, resulting in a live birth rate of 50% and avoiding the risk of severe OHSS. The authors noted that this protocol was associated with a lower number of follicles and oocytes compared with a total freeze protocol. However, we are critical about the accuracy of ultrasound monitoring or the quality of our published literature (Humaidan, 2009). They were not given this treatment because we thought they would benefit from it, based on the published literature (Humaidan, 2009). Our patients were given this treatment in the high responder patients. No change in the study population was mentioned. We would like to note that our patients were 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 Humaidan 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., 1999; Triwitayakorn et al., 2003). Thanks to our vast experience from IVF 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.

References


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doi:10.1093/humrep/det287

Advanced Access publication on July 9, 2013

Reply: GnRH agonist 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 not 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 for 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.

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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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doi:10.1093/humrep/det288
Advanced Access publication on July 9, 2013

**Risk factors for ovarian hyperstimulation syndrome: relevance of the number of follicles, serum estradiol levels and the number of oocytes collected**

Dear Sir,

We read with interest Dr Bodri’s editorial on our recent report ‘Severe early ovarian hyperstimulation syndrome (OHSS) following GnRH agonist trigger with the addition of 1500 IU hCG’ (Bodri, 2013; Seyhan et al., 2013). However, we did question some of his comments.

While Dr Bodri describes all other studies evaluating OHSS risks using this protocol as containing ‘normo-responders’ or just ‘high responders’ he calls our patients ‘very high responders’ and ‘not suitable candidates for the Humaidan protocol (Bodri, 2013). Dr Bodri’s opinion seems to be solely based on our collecting a higher number of oocytes compared with the study of Humaidan (2009). Although the number of oocytes collected is a well-known risk factor for OHSS, there are other risk indicators including serum estradiol levels and the number of growing follicles (Papanikolaou et al., 2006). While serum estradiol levels are determined using standardized techniques around the world, and even physicians and technicians with limited experience can count follicles, the number of oocytes collected depends on the experience of both the physician and the embryologist. Experience in aspiration of small follicles and in identifying oocytes surrounded with sparse cumulus cells is especially important for oocyte collection from women with polycystic ovaries, which contains numerous small follicles besides larger ones. We think the number of collected oocytes is more likely to vary between clinics and is a less reliable indicator of ovarian response than serum estradiol levels or the number of growing follicles in this context.

We believe the higher number of oocytes collected in our series is simply due to McGill team’s extensive experience of oocyte collections during in vitro maturation cycles. Moreover, an overall mean serum estradiol level in our series (4891 pg/ml) was not higher than that reported in Dr Humaidan’s series (5066.7 pg/ml) (Humaidan, 2009). In Dr Humaidan’s study, 12 women were recruited based on having ≥25 follicles of ≥11 mm (Humaidan, 2009). To the contrary, in our series only 5 women had ≥25 follicles of ≥12 mm. Dr Humaidan did not report either the maximum serum estradiol levels or the maximum number of oocytes collected in his series. This prevents a more detailed comparison of the two study populations. We would also like to highlight that of the five patients in our study who developed severe early OHSS, one had 23 oocytes collected and a second had 26 oocytes collected. Therefore, we disagree with Dr Bodri’s categorization of our series as ‘very high responders’ while Dr Humaidan’s series with higher number of follicles and apparently similar serum estradiol levels were defined as ‘high responders’.

**References**


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doi:10.1093/humrep/det289
Advanced Access publication on July 9, 2013

**Raman microspectroscopy: a method with great promise but which also needs circumspection**

Sir,

Although the excitement surrounding the potential of a new analytical technique can be heady, this must be tempered by the necessities of validation, verification and the establishment of its veracity through the...