GnRH agonist for triggering final oocyte maturation: time for a critical evaluation of data

Sirs,

We read with great interest the manuscript by Humaidan et al. (2011). In this review, the authors summarize the published evidence regarding the use of GnRH agonist for triggering final oocyte maturation in patients undergoing IVF.

By combining the results of six recently published randomized controlled trials (RCTs), the authors suggest that when a modified luteal phase support (LPS) is employed, following GnRH agonist triggering, pregnancy rates are comparable with those achieved after hCG triggering and standard LPS. Moreover, they suggest that GnRH agonist triggering combined with a modified LPS results in elimination of ovarian hyperstimulation syndrome (OHSS). These findings are very interesting, since they support the notion that GnRH agonist triggering when combined with a modified LPS is both an effective and safe treatment. We would like to elaborate on the data presented by the authors and extend the implications of the available evidence on the efficacy and safety of GnRH agonist triggering.

The RCTs that have been performed so far in which a modified LPS is employed, when GnRH agonist triggering is used, include two distinct patient populations: (i) normo-ovulatory patients, at a normal risk for OHSS (Humaidan et al., 2006, 2010; Pirard et al., 2006; Papanikolaou et al., 2011) and (ii) patients with polycystic ovary syndrome (PCOS) at a high risk for OHSS (Babayof et al., 2006; Engmann et al., 2008). In addition, two distinct strategies for a modified LPS are used in these two populations.

In normo-ovulatory patients, a modified LPS involves LH activity by administration of (i) low-dose bolus hCG (Humaidan et al., 2006, 2010), (ii) multiple doses of rLH (Papanikolaou et al., 2011) and (iii) multiple doses of GnRH agonist (Pirard et al., 2006). The rationale of this approach is mild stimulation of the existing corpora lutea.

On the other hand, in PCOS patients, a modified LPS involves intensified support, devoid of LH activity, with the use of intramuscular progesterone and estradiol in the form of oral tablets or transdermal patches (Babayof et al., 2006; Engmann et al., 2008). Apparently, the rationale for the latter approach is to provide adequate luteal support, without, however, stimulating the numerous existing corpora lutea in the high risk for OHSS patients, by providing LH activity.

Based on the data presented by Humaidan et al. (2011), if the six aforementioned studies are combined, a significantly lower occurrence of OHSS by 7% (95% confidence interval (CI): −11 to −4) and a nonsignificantly lower delivery rate by 6% (95% CI: −14 to +2) is observed. An alternative approach to the analysis of these data, however, reveals a different picture that might have significant clinical implications.

By pooling the data from the four studies (Humaidan et al., 2006, 2010; Pirard et al., 2006; Papanikolaou et al., 2011) comparing normo-ovulatory patients, who were either triggered by GnRH agonist and received LH activity supplementation during the LP or triggered by hCG and received standard LPS, the significantly lower incidence of OHSS is no longer present [rate difference (RD): −2%, 95% CI: −4 to +1]. At the same time, a non-significant decrease in delivery rates (−7%, 95% CI: −16 to +2) is detected in the patients who received LH activity supplementation after GnRH agonist triggering when compared with those triggered by hCG receiving standard LPS. Thus, in normo-ovulatory patients, considered to be at a normal risk for OHSS, GnRH agonist triggering combined with LH activity supplementation during the luteal phase does not significantly decrease the incidence of OHSS.

On the other hand, in PCOS patients, when GnRH agonist triggering combined with intensified luteal support, devoid of LH activity, is compared with hCG triggering followed by a standard LPS, a significantly lower OHSS rate is present in the GnRH agonist group (RD: −31%, 95% CI: −46 to −17). At the same time, delivery rates between the two groups compared are not significantly different (RD: +1%, 95% CI: −18 to +19). Thus, it seems that in women at a high risk for OHSS, such as those with PCOS, GnRH agonist combined with a modified LPS devoid of LH activity significantly decreases the incidence of OHSS.

Based on the above analysis, it cannot yet be concluded that ‘GnRH agonist triggering is a valid alternative to hCG triggering’ (Humaidan et al., 2011), although it is apparent that GnRH agonist administration when combined with modified LPS activity does achieve OHSS prevention in high-risk women.

References


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Reply: GnRH agonist for triggering final oocyte maturation: time for a critical evaluation of data

Sir,
We read with interest the letter by Kolibianakis et al., concerning our consensus paper by The Copenhagen GnRH agonist Triggering Workshop Group (Humaidan et al., 2011). In their letter, the authors conclude that ovarian hyperstimulation syndrome (OHSS) is reduced only in the OHSS-high-risk patient and not in the normal OHSS-risk patient, by further subdividing the population of six recently published studies into normo-ovulatory (normal OHSS-risk patients) (Humaidan et al., 2006, 2010; Pirard et al., 2006; Papanikolaou et al., 2011) and high-risk OHSS patients—mainly polycystic ovary syndrome patients (Babayof et al., 2006; Engmann et al., 2008), using a modified luteal phase support after GnRHa trigger.

Clearly, the authors of the current letter focus on statistical significance when analyzing the results of the four trials in the normal OHSS-risk patient, using a modified luteal phase support; however, still not 1 patient of a total of 188 patients triggered with GnRHa developed OHSS, compared with 3 of 189 patients (2%) triggered with hCG.

Moreover, the findings of the four studies performed in a donor oocyte population are completely ignored (Acevedo et al., 2006; Galindo et al., 2009; Melo et al., 2009; Sismanoglu et al., 2009). When analyzing the data from these studies, the OHSS incidence is 0% (0/230) after GnRHa trigger versus 8% (19/230) after hCG trigger. Importantly, the oocyte donor is a normo-ovulatory patient as well as eliminate the risk of OHSS. On this basis, we founded The Copenhagen GnRH Agonist Triggering Workshop Group—an international network of clinical scientists with a specific interest in GnRHa triggering.

Based on our present knowledge, we disagree with the authors’ statement that after further subdividing the data, ‘the picture is significantly different’. Although low-risk patients by definition will have a lower risk of developing OHSS, when hCG is used for triggering final oocyte maturation, only the use of a GnRHa trigger will completely eliminate that risk. Considering the medical, social and economical consequences of even one single case of OHSS, the clinical implications are not insignificant.

Although we understand that hCG triggering still remains the standard of care for triggering final oocyte maturation for the OHSS low-risk patient, we maintain that based on the available data, GnRHa triggering is a valid alternative to hCG triggering for both the low-risk and the high-risk patients.

Finally, we certainly agree that the time has come for a ‘critical evaluation of data’ as the health and well-being of a patient undergoing controlled ovarian stimulation is beyond the confidence interval of statistical significance.

References


