Symposium: Update on prediction and management of OHSS – Opinion

Prevention of OHSS: GnRH agonist versus HCG to trigger ovulation

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Abstract

Ovarian hyperstimulation syndrome (OHSS) remains a major complication of IVF. Triggering ovulation with human chorionic gonadotrophin (HCG) (as a surrogate to LH) is a major factor in the initiation of OHSS. The pathological process usually intensifies if pregnancy is achieved, as the rising endogenous HCG overstimulates the corpora lutea. Decreasing HCG trigger dose does not prevent OHSS. Gonadotrophin-releasing hormone agonists (GnRHa) induce endogenous LH and FSH surges that reliably trigger ovulation, even if a GnRH antagonist is used during ovarian stimulation. Moreover, such a trigger quickly and irreversibly induces luteolysis, thereby preventing OHSS. Contrasting reports regarding clinical outcome probably reflect different approaches to luteal phase support. Zygotes or embryos frozen post GnRHa trigger give excellent clinical outcome post thaw. In summary, GnRHa trigger is the key for complete OHSS prevention.

Keywords: *GnRH agonists, HCG, ovarian hyperstimulation syndrome, ovarian stimulation*

Ovulation triggering with HCG

Human chorionic gonadotrophin (HCG) is routinely used to trigger ovulation in ovarian stimulation cycles. Given its long half-life and luteotrophic activity, it is blamed for the initiation of the OHSS process. If pregnancy is achieved, endogenous HCG production replaces and augments the trigger dose, leading to enhancement of the OHSS pathology. The extent of ovarian stimulation invariably correlates with the degree of OHSS, although variation between patients is large. For the purpose of minimizing OHSS risk, however, available data suggest that reducing the dose of HCG does not eliminate the risk of OHSS in a high-risk group.

While long GnRH agonist-based protocols are associated with increased incidence of OHSS, reflecting the recruitment of a large number of follicles, it was suggested that GnRH antagonist-based protocols may reduce the incidence of OHSS. However, the available publications suggest that the difference, if it exists, is minimal. The significant advantage of GnRH antagonist-based protocols, as discussed herein, lies in the flexibility to trigger ovulation with a GnRH agonist, induce luteolysis and prevent OHSS altogether.

Ovulation triggering with GnRH agonists

The injection of GnRHa results in an acute release of LH and FSH. The amplitude of the surge is similar to that seen in the normal menstrual cycle, and was shown to reliably trigger final oocyte maturation and its release from the ovary.

The introduction of GnRH antagonists in ovarian stimulation protocols has opened new opportunities in the context of OHSS prevention. The quick reversibility of the antagonist-induced

pituitary suppression can be of advantage by allowing the use of GnRHa for the purpose of ovulation triggering. This possibility was first assessed in a randomized prospective multicentre study by Fauser *et al*. (2002), although not in the context of OHSS prevention. LH dynamics post trigger was similar to that reported without GnRH antagonist pretreatment, in other words, the routine daily dose of a GnRH antagonist does not blunt the effect of an agonist at the pituitary level.

To further characterize the presumed luteolytic process induced by mid-cycle injection of GnRHa, and to avoid confusion between endogenous biosynthesis and exogenous luteal support, Nevo *et al*. (2003) measured non-steroidal luteal function markers, inhibin A and pro-alphaC. Agonist trigger caused a sharp decrease in these markers compared with patients who were treated with HCG. Pregnancy was not associated with a rise in the concentrations of the luteal markers. GnRH agonist trigger resulted in complete and quick luteolysis. By the time endogenous HCG appeared (if pregnancy was achieved) the corpora lutea were beyond the point of resuscitation, therefore endogenous sex steroid production did not resume, together with the long list of mediators responsible for OHSS.

Two groups performed randomized controlled studies with patients at high risk of OHSS (Babayof *et al*. 2006, Engmann *et al*. 2008). A third group (Acevedo *et al*. 2006) used the donor-recipient model to elucidate the role of agonist trigger in terms of OHSS incidence and pregnancy rate, while neutralizing the endometrial factor. Taking the three studies together, remarkably, none of the 78 patients in the agonist groups developed OHSS. Of the 75 patients triggered with HCG, 19 (25%) developed OHSS. No statistically significant difference in clinical pregnancy rate between HCG and agonist trigger was observed in any of the individual studies, though the numbers are too low for firm conclusions in that aspect. Furthermore, live birth rates were not available.

Since agonist trigger should be used when there is a high risk of OHSS, a large number of oocytes is expected, leading to a large number of embryos to be cryopreserved. A proof-of-concept study by Griesinger *et al*. (2007) produced very promising results. Twenty patients at high risk of OHSS (≥20 follicles or oestradiol ≥4000 pg/ml on trigger day) were triggered with agonist, and all 2 pronucleate (2PN) oocytes were cryopreserved. None of the patients developed OHSS. Subsequent thaw cycles (mean of 2.3 embryos transferred) resulted in 29.2% ongoing pregnancy rate. Each patient had an average of 7.4 2PN cryopreserved, allowing for an average of three subsequent thaw cycles. With a 29.2% ongoing pregnancy rate per thaw cycle, each patient has an excellent chance of achieving ongoing pregnancy from single oocyte retrieval, with complete safety as far as OHSS is concerned. Indeed, this is great news to high-responder patients.

Conclusion

A GnRH agonist trigger effectively prevents OHSS. This conclusion is based now on randomized prospective studies. Further studies must concentrate on luteal phase support following agonist trigger, and on per retrieval pregnancy rate, taking into account subsequent thaw cycles.

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