Ovarian hyperstimulation: effects of GnRH analogues

Ovarian hyperstimulation syndrome after using gonadotrophin-releasing hormone analogue as a trigger of ovulation: causes and implications

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Exogenous gonadotrophin administration, the mainstay of ovarian hyperstimulation, is associated with increased risk of ovarian hyperstimulation syndrome (OHSS). The possibility of developing this syndrome often leads to cycle cancellation, with the inevitable patient discomfort and disappointment. It is now well established that the use of human chorionic gonadotrophin (HCG) for ovulation induction is all but in line with ovarian physiology. Specifically, the resultant luteinizing hormone (LH)-like activity spans several days, given HCG carbohydrate content and longer half-life, compared with the endogenous LH surge. Although the exact pathophysiological mechanism underlying OHSS has not been fully elucidated, the role of protracted LH-like activity rendered by HCG with prolonged stimulation of the corpora lutea in the development of this syndrome is strongly suggested.

The use of gonadotrophin-releasing hormone analogue (GnRHa) in the context of triggering ovulation has been suggested several years ago (Itskovitz et al., 1988). The combination of initial gonadotrophin ‘flare-up’ followed by pituitary down-regulation offers a unique advantage in the effort to minimize this risk of OHSS. Specifically, the nearly physiological LH and follicle stimulating hormone (FSH) surges are followed by timely ovulation. However, as the young corpora lutea are devoid of the necessary gonadotrophin support, their demise is reflected in a fall in progesterone concentrations (Itskovitz et al., 1991, 1993) and elimination of the risk for OHSS. In addition, the possibility that endogenous LH surge triggers the ovulation of fewer follicles (compared with HCG under similar conditions) cannot be ruled out. Luteal support (with progesterone not HCG) is therefore suggested for achieving pregnancy in these cases. Theoretically, therefore, a complete elimination of OHSS is projected according to these considerations. The reported experience with this approach is very encouraging (Itskovitz et al., 1988, 1991, 1993; Imoedemhe et al., 1991; Emperaire and Ruffie 1991; Segal and Casper 1992; Lanzone et al., 1994) in different clinical settings [in-vitro fertilization (IVF) with embryo transfer, ovulation induction] and different stimulation protocols.

As a rule, ovulation is induced, while OHSS is prevented, even in very high risk patients as judged by extremely high concentrations of oestradiol just prior to ovulation induction (Lewit et al., 1995).

We have used GnRH agonist as an ovulation trigger in over 80 high risk IVF patients, and have not observed a single case of severe OHSS induction (Lewit et al., 1995). It should be emphasized that the clinical findings attributable to mild OHSS (Schenker and Weinstein, 1978; e.g. ovarian enlargement, abdominal discomfort, excessive steroid production) are an integral part of most cases of ovulation induction in IVF, and so are meaningless in this context.

The purpose of this short communication is to take a closer look at those cases where this approach has failed. A literature search was initiated for reports detailing cases in which OHSS developed despite the use of GnRH agonist to induce ovulation. Three cases of OHSS were reported by van der Meer et al. (1993). The clinical details of the three cases are in line with a mild to moderate OHSS. Severe ascites, hypovolaemia or electrolyte imbalance did not occur, nor were the patients hospitalized. Note was made of the fact that the three patients received nasal GnRHa preparations (buserelin, Suprefact; Hoechst, Frankfurt, Germany). In one of them, a very weak response to GnRHa was noted, with an LH surge peak of 15.9 mIU/ml, suggesting that the dosage used or the route of administration was less than optimal. Clearly, the possibility of incomplete absorption using nasal administration cannot be ignored. Of note is the fact that the three patients were stimulated in preparation for intrauterine insemination (IUI). Gerris et al. (1995) have also reported OHSS following this approach; however, in this case, use was made of native GnRH (and not GnRHa), resulting in successful ovulation triggering, but without the critical gonadotrophin suppression which is the key element in preventing OHSS. Lastly, Shoham et al. (1995) reported a personal communication in which two cases of OHSS were described; however, the complete details of the treatment protocols, symptoms and signs leading to the diagnosis of OHSS, severity of the syndrome and clinical outcome were not available.

Shalev et al. (1994) used GnRHa (0.5 mg Decapeptyl; Ferring, Malmo, Sweden) as a trigger of ovulation in 12 non-IVF patients, who were at high risk of developing OHSS, as determined by oestradiol concentrations and number of follicles. Progesterone was given for luteal phase support, six pregnancies were achieved, yet none of the patients developed OHSS. In a subsequent publication, the same group (Shalev et al., 1995) made use of a lower dose of the same GnRHa preparation (0.1 mg Decapeptyl), in a comparable clinical setting. Importantly, in this study patients at high risk of developing OHSS were excluded, although grade 3–4 OHSS was observed in two of the 24 patients. Severe ascites,
hypovolaemia or electrolyte imbalance were not observed. Taken together, these studies strongly suggest that while the lower dose of GnRHa is highly effective in inducing ovulation, it might fall short of preventing OHSS.

Pituitary down-regulation with GnRHa prior to ovarian stimulation, eliminates the possibility of using it to trigger ovulation. We expect that this limitation will be circumvented with the introduction of GnRH antagonists. GnRH antagonist may be used to achieve pituitary down-regulation, while maintaining the ability of the gonadotrophs to react to GnRH with gonadotrophin secretion (Dubourdieu et al., 1994). The introduction of recombinant human LH may serve as an attractive alternative for precise induction of ovulation when it becomes available.

In summary, the use of GnRHa as an ovulation trigger reliably eliminates the risk of clinically significant OHSS. To ensure its action, we suggest that GnRHa should be given s.c. so the full required dose is securely delivered. Since the dose required for achieving ovulation is probably lower than that required for preventing OHSS, the doses of newly introduced GnRHa preparations should be carefully determined. Lastly, native GnRH [luteinizing hormone releasing hormone (LHRH)] should not be used in that context as it offers no protection against OHSS.

References


Does triggering ovulation with gonadotrophin-releasing hormone analogue prevent severe ovarian hyperstimulation syndrome?

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Severe ovarian hyperstimulation syndrome (OHSS) is associated with massive ovarian enlargement, ascites, haemoconcentration, peripheral oedema and oliguria (Navot et al., 1992). This iatrogenic condition has been reported to occur in from 0.5% (Medical Research International, 1992) to 2% (Smits et al., 1990) of in-vitro fertilization (IVF) treatment cycles. Kol et al. (1996) have proposed that the use of gonadotrophin-releasing hormone analogue (GnRHa) to trigger ovulation, or the final stage of follicle maturation in IVF, reliably eliminates the risk of severe OHSS. The hypothesis for this protective effect is based on the pharmacodynamics of GnRHa-induced luteinizing hormone (LH) release which, in comparison with human choriionic gonadotrophin (HCG) administration, is of short duration. We have demonstrated that serum HCG concentrations are detectable up to 6 days following 5000 IU of HCG injected i.m. and that a single GnRHa injection (500 μg leuprolide acetate s.c.) resulted in a combined LH and follicle stimulating hormone (FSH) surge lasting 34 h (Gonen et al., 1990). Therefore, the shorter duration of LH-like activity following GnRHa compared with HCG administration may indeed reduce the stimulation of the luteal phase ovary. In addition, Kol et al. (1996) postulate that a period of down-regulation of GnRH receptors in the pituitary occurs after the mid-cycle use of GnRHa for ovulation induction, further reducing endogenous LH stimulation of the corpora lutea. It is certainly possible that short-term desensitization of the pituitary occurs, even after a single administration of GnRHa as we have previously demonstrated (Casper and Yen, 1979). Injection of only 50 μg of D-trp⁶, Pro⁹ NET in the midluteal phase resulted in complete refractoriness of LH and FSH secretion to a second dose 24 h later (Casper and Yen, 1979).