Human Reproduction vol.11 no.6 pp.1143–1148, 1996

DEBATE

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

Dubourdieu, S., Charbonnel, B., D'Acremont, M.F. *et al.* (1994) Effect of administration of a gonadotropin-releasing hormone (GnRH) antagonist (Nal-Glu) during the peri-ovulatory period: the luteinizing hormone surge requires secretion of GnRH. *J. Clin. Endocrinol. Metab.*, **78,** 343–347.

Emperaire, J.C. and Ruffie, A. (1991) Triggering ovulation with endogenous luteinizing hormone may prevent the ovarian hyperstimulation syndrome. *Hum. Reprod.*, **6,** 506–510.

Gerris, J., De Vits, A., Joostens, M. and Van Royen, E. (1995) Triggering of ovulation in human menopausal gonadotropin-stimulated cycles: comparison between intravenous administered gonadotrophin-releasing hormone (100 and 500 μg), GnRH agonist (buserelin, 500 μg) and human chorionic gonadotrophin (10000 IU). *Hum. Reprod.*, **10,** 56–62.

Imoedemhe, D.A.G., Chan, R.C.W., Sigue, A.B. *et al.* (1991) A new approach to the management of patients at risk of ovarian hyperstimulation in an in-vitro fertilization programme. *Hum. Reprod.*, **6,** 1088–1091.

Itskovitz, J., Boldes, R., Barlev, A. *et al.* (1988) The induction of LH surge and oocyte maturization by GnRH analogue (buserelin) in women undergoing ovarian stimulation for *in vitro* fertilization. *Gynecol. Endocrinol.*, **2** (Suppl. 2), 165.

Itskovitz, J., Boldes, R., Levron, J. *et al.* (1991) Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. *Fertil. Steril.*, **56,** 213–220.

Itskovitz-Eldor, J., Levron, J. and Kol, S. (1993) Use of gonadotropin-releasing hormone agonist to cause ovulation and prevent the ovarian hyperstimulation syndrome. *Clin. Obstet. Gynecol.*, **36,** 701–710.

Lanzone, A., Fulghesu, A.M., Villa, P. *et al.* (1994) Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin as a trigger of ovulation in polycystic ovarian disease gonadotropin hyperstimulated cycles. *Fertil. Steril.*, **62,** 35–41.

Lewit, N., Kol, S., Manor, D. and Itskovitz-Eldor, J. (1995) The use of GnRH analogs for induction of the preovulatory gonadotropin surge in assisted reproduction and prevention of the ovarian hyperstimulation syndrome. *Gynecol. Endocrinol.*, (Suppl. 4), 13–17.

Schenker, J.G. and Weinstein, D. (1978) Ovarian hyperstimulation syndrome: a current survey. *Fertil. Steril.*, **30,** 255–268.

Segal, S. and Casper, R.F. (1992) Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in *in vitro* fertilization. *Fertil. Steril.*, **57,** 1254–1258.

Shalev, E., Geslevich, Y. and Ben-Ami, M. (1994) Induction of pre-ovulatory luteinizing hormone surge by gonadotrophin-releasing hormone agonist for women at high risk for developing the ovarian hyperstimulation syndrome. *Hum. Reprod.*, **9,** 417–419.

Shalev, E., Geslevich, Y., Matilsky, M. and Ben-Ami, M. (1995) Induction of pre-ovulatory gonadotrophin surge with gonadotrophin-releasing hormone agonist compared to pre-ovulatory injection of human chorionic gonadotrophins for ovulation induction in intrauterine insemination treatment cycles. *Hum. Reprod.*, **10,** 2244–2247.

Shoham, Z., Schachter, M., Loumaye, E. *et al.* (1995) The luteinizing hormone surge–the final stage in ovulation induction: modern aspects of ovulation triggering. *Fertil. Steril.*, **64,** 237–251.

van der Meer, S., Gerris, J., Joostens, M. and Tas, B. (1993) Triggering of ovulation using a gonadotropin-releasing hormone agonist does not prevent ovarian hyperstimulation syndrome. *Hum. Reprod.*, **8,** 1628–1631.

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% (Smitz *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 chorionic 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-trp^6, Pro^9 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).