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DEBATE continued

Severe OHSS

Yes, there is a strategy to prevent it!

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Effective measures to prevent ovarian hyperstimulation syndrome (OHSS) remain controversial. It became almost 'common knowledge' that there is no strategy that may completely prevent OHSS. Extensive clinical experience (albeit not derived from prospective randomized studies) clearly documents the ability of a single administration of gonadotrophin-releasing hormone (GnRH) agonist to effectively trigger ovulation, while completely eliminating any threat of clinically significant OHSS. This strategy cannot be used if the pituitary is down-regulated (as is the case in most assisted reproductive cycles today), however, the newly-introduced GnRH antagonists open new opportunities for implementing this strategy, since the pituitary preserves its responsiveness to GnRH agonists. Combining GnRH antagonist-based ovarian stimulation (particularly in 'high responders'), with GnRH agonist-driven ovulation triggering will make severe OHSS a disease of the past in assisted reproduction.

Key words: GnRH agonist/OHSS/ovulation induction

Recently, there has been a flourish of publications on the issue of ovarian hyperstimulation syndrome (OHSS). All authors agree that OHSS is the most serious complication of fertility treatment. Regrettably, most, if not all, communications state in one way or another, that there is no strategy to completely prevent severe OHSS. To quote a few typical examples: 'None of the strategies currently employed to avert severe OHSS ... completely prevents the condition' (Egbase, 2000). 'Very few medical interventions are risk-free and severe OHSS will remain a complication of IVF cycles despite all attempts at prevention' (Forman, 1999). 'While no strategy for the prevention of OHSS can be guaranteed to work, it should be made clear to the patient that there is a small, but real, risk associated with COH′ (Rimington, *et al*., 1999). And lastly: 'Since the aetiology remains unknown and the pathophysiology is poorly understood, it is not surprising that no strategy has yet been shown to completely prevent the occurrence of severe OHSS, short of cancelling the cycle' (Egbase *et al*., 1999).

These authors (as well as others) have ignored a strategy that prevents severe OHSS, i.e. triggering ovulation using gonadotrophin-releasing hormone (GnRH) agonists instead of human chorionic gonadotrophin (HCG). This strategy was first introduced by Itskovitz *et al.* (Itskovitz *et al.*, 1988, 1991), and has been used ever since with excellent results in terms of OHSS prevention. Our group has accumulated experience with this strategy with hundreds of patients (both induction of ovulation and IVF cycles), and some of this experience has been published (Itskovitz *et al*., 1991; Lewit *et al*., 1995, 1996). This strategy is not applicable in ovarian stimulation cycles before which pituitary down-regulation is induced by GnRH agonists. However, in non-down-regulated or in GnRH antagonist-based cycles this approach prevents any clinically significant OHSS.

The few cases that described possible failures of this strategy were the focus of a previous debate published 4 years ago (Kol *et al*., 1996). Of note is one paper (van der Meer *et al*., 1993), which describes three cases in which this strategy supposedly failed to prevent OHSS. While the three patients presented developed mild to moderate OHSS after receiving nasal GnRH agonist (instead of the injectable preparation), this paper is cited repeatedly, given its impressive and decisive title. This unfortunate situation undoubtedly denied a valuable treatment to many patients. We are not aware of any reports of failures during the last 4 years. On the contrary, a group from Saudi Arabia has presented its large and impressive experience with this strategy (Imoedemhe *et al*., 1999). Ovulation was effectively triggered with GnRH agonist in 682 (96%) of 708 high responder IVF patients with polycystic ovarian syndrome (mean concentration of oestradiol on the day of ovulation triggering = 7817 pg/ml). One patient (0.1%) developed severe OHSS. Significantly, this patient was treated with HCG-based luteal support, probably by mistake, as the protocol dictated progesterone-only luteal support. Also of note is that in 26 patients, the GnRH agonist-induced LH surge was judged to be 'inadequate'. In 18 of these patients, HCG was used, resulting in 11 (61%) cases of severe OHSS. This last figure may reflect the large number of severe OHSS cases in this series that were prevented by this strategy. The reason(s) for inadequate LH surge may have to do with dose (too low) or route (intranasal) of the GnRH agonist administration. A key point in this strategy is the ability of an adequate single dose of GnRH agonist to bring about an effective LH surge, and subsequently to induce early luteal phase relative pituitary down-regulation. Luteolysis could be induced by diminished early luteal phase LH pulsatility, leading

to prevention of OHSS. Our protocol calls for a single s.c. injection of 0.2 mg triptorelin (Decapeptyl®; Ferring, Malmo, Sweden). We recorded no LH surge failures with this protocol, and of course, no clinically significant OHSS thus far.

As mentioned above, in a previous debate (Kol *et al.*, 1996), we took a closer look at the reported cases where this strategy 'failed'. In short, the cases reported in the literature do not represent severe OHSS (severe ascites, hypovolaemia, electrolyte imbalance, etc.) but rather a milder condition characterized mainly by enlarged ovaries (which is an integral part of ovarian stimulation). Given the impressive observational data compiled thus far, a randomized prospective study, with comparison with HCG, would be unethical to conduct at this point.

Importantly, this strategy does not work if the GnRH agonist is used before ovarian stimulation to down-regulate the pituitary (as the pituitary will not respond to the triggering dose of GnRH agonist). This limited the application of the proposed strategy, since pituitary down-regulation is the routine approach in most IVF cycles. A major advantage of the recently introduced GnRH antagonists is that the pituitary maintains its responsiveness to GnRH agonist. Therefore, triggering ovulation using GnRH agonists in high responders is an excellent way to prevent OHSS. In fact, we have used this strategy with complete prevention of OHSS (Kol *et al*., 2000). In addition, the clinical introduction of recombinant LH (expected in the near future), may also prove beneficial in terms of curbing the occurrence of OHSS, even when pituitary down-regulation is used, although the full impact of recombinant LH must await further clinical experience.

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