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Letter to the Editor

Agonist trigger in the context of OHSS prevention: primum non nocere

Sir,

Ovarian hyperstimulation syndrome (OHSS) is a pure iatrogenic complication of assisted reproduction technique (ART), affecting young healthy women seeking fertility. According to a WHO report (Hugues, 2001) this syndrome is responsible to 1 death for every 50 000 treatment cycles, whereas the incidence of severe OHSS is 1%. I assume we all agree that we must thrive to ensure patient safety first, clinical outcome (pregnancy) later. Consequently, a reliable means for OHSS prevention is badly needed.

GnRH agonist trigger instead of HCG was introduced in the early 1990s (Itskovitz *et al*., 1991) as a means to prevent OHSS, even in extreme ovarian response. However, before the GnRH antagonist's era, agonist trigger was not a viable clinical option. Six years ago the first case-series publication brought this option back to light (Itskovitz-Eldor *et al*., 2000). Patients at extreme OHSS risk were triggered with GnRH agonist, with complete prevention of OHSS. Fauser *et al*. (2002) established the fact that the GnRH antagonist-induced competitive inhibition of the pituitary receptors is reversible with agonist trigger. However, hyper-responders were excluded from that study. Clinical outcome with agonists trigger was comparable with that after HCG trigger. These publications set the ground for adopting agonist trigger in GnRH antagonist-based stimulation protocols, if a patient hyper-responds, a move that could have eradicated clinically significant OHSS. Unfortunately, in the era of 'evidence-based medicine', the fantastic power of agonist trigger to prevent OHSS is its weakness. Can we randomize patients with extreme ovarian response to the HCG arm?

Since a prospective randomized HCG-controlled study with OHSS high-risk patients is problematic to perform, research in the field took an unexpected switch: agonist trigger in normal responders. From the practical point of view, there is really no need for an HCG-substitute in the normal responder; however, ethical review boards will not object to such study. Indeed, two additional studies were performed along this line (Humaidan *et al*., 2005; Kolibianakis *et al*., 2005), quickly followed by a 'systematic review and meta-analysis' by Griesinger *et al*. (2005). The indication for GnRH agonist trigger is indeed mentioned in the *Introduction*: '... as a measure to prevent OHSS'; however, the review itself falls short of addressing this fundamental issue. The three publications included in the meta-analysis do not touch on the subject and did not include OHSS-high-risk patients. The three papers found low-pregnancy rate following agonist trigger. Such studies, originating from opinion leaders in the field, may deter practitioners who consider using agonist trigger in the context of OHSS prevention.

Selective reporting of data put a big question mark on the objectivity of the authors as far as the crucial issue of OHSS prevention is concerned. A prominent example is the way the authors chose to cite the abstract by Bankowski *et al*. (2004). The article describes a retrospective case series of 97 very-high-risk patients [mean estradiol (E_2) = 4800 pg/ml on trigger day] triggered with agonist compared with 317 normal responders (2050 pg/ml on trigger day) triggered with HCG. The authors reported three cases of severe OHSS, surprisingly, all in the normal responders group, none in the high responders. Clearly, this remarkable result underlines the tremendous ability of agonist trigger to prevent OHSS. It also underlines the ethical problem associated with randomization of high-risk patients to the HCG arm. It takes little imagination to estimate the number of OHSS cases in a group of patients triggered with HCG when mean E_2 level is 4800 pg/ml. However, Griesinger *et al*. (2005) chose to ignore this fact, focusing on lower pregnancy rate. I cannot explain this unfortunate bias in reporting the facts as they are. The dictum 'primum non nocere' (first, do no harm) far exceeds pregnancy rate.

In the 2005 Annual ASRM meeting, Engmann *et al*. (2005) reported preliminary results of a prospective randomized controlled study of agonist versus HCG trigger in high responders. None of the 12 patients triggered with agonist developed OHSS, whereas 4 of 13 patients triggered with HCG did. Pregnancy rates were impressively high in both arms, maybe due to aggressive luteal support with exogenous E_2 and progesterone. The authors should be congratulated for their courage in conducting such a study. I hope that this study will set the stage for further practical studies along this line: using agonist trigger in the context of OHSS prevention, not in normal responders. At least two directions come to mind: fine tuning of luteal support, and per oocyte retrieval, OHSS-free, pregnancy rate (taking into account subsequent thaw cycles).

Agonist trigger is an amazing tool to prevent OHSS. It can save patients lives. Biased reviews like the one under consideration can indirectly contribute to patient morbidity and mortality.

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