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 strive 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 even in extreme ovarian response. However, before the GnRH agonist 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.

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 (E2) = 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 E2 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 E2 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.

References


Engmann L, Dihlberg A, Schmidt D, Nulsen J, Maier D and Benadiva C (2005) Prevention of ovarian hyperstimulation syndrome (OHSS) with the use of gonadotropin releasing hormone (GnRH) agonist to trigger final oocyte maturation after cotreatment with GnRH antagonist in patients with polycystic ovarian syndrome (PCOS) or previous high response undergoing IVF treatment – a prospective randomized clinical trial. Fertil Steril 84 (Suppl. 1), S96 [abstract O-233].


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Letters to the Editor


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

Sir,

We thank Dr Kol for his interest in our recent systematic review (Griesinger et al., 2005) on GnRH agonist usage for triggering final oocyte maturation in IVF patients.

In his letter, Dr Kol scrutinizes the necessity to test GnRH agonist triggering in normal responders at all, although he acknowledges that a randomized controlled trial (RCT) in ovarian hyperstimulation syndrome (OHSS)-risk patients is unethical. Still, Dr Kol states that exploring GnRH agonist triggering in normal responder patients came unexpectedly to him. How-ever, in an article Dr Kol co-authored, it is suggested that ‘the introduction of the GnRH agonist-induced triggering of ovulation in GnRH antagonist protocols would offer additional benefits to all patients, i.e. both high and normal responders, though the efficacy and safety of such new treatment regimen needs to be established in comparative, randomized studies’ (Itskovitz-Eldor et al., 2000). We certainly agree with Dr Kol on the latter, and we like to add that a protocol should have proven safe and efficacious, before it can be recommended for wider spread clinical use.

Following the proposals of Kol (Kol, 2003, 2004; Kol and Muchtar, 2005), GnRH agonist triggering could eradicate clinically significant OHSS. To put this broad claim into practice, however, also implies that a significant proportion of patients will have to be exposed to GnRH agonist triggering, simply because no reliable text exists to predict patients who will develop OHSS. In line with this, it was recently proposed (Orvieto, 2005) in Human Reproduction, based on Kol’s (2004) ideas, to trigger virtually all patients (‘normal’ and ‘high’ responders) with GnRH agonist in a first IVF cycle. This example vividly illustrates the necessity to review and evaluate the data on the clinical efficacy of GnRH agonist-triggering protocols from RCTs conducted in (assumable) normal responder populations. Besides that, a scientific and clinical interest into the effects of GnRH agonist triggering on other outcome parameters than OHSS incidence and clinical pregnancy justifies such an evaluation.

Next, Kol expresses concerns about selective reporting and possible bias in our review, which might deter practitioners to use GnRH agonist in the context of OHSS prevention. The review was conducted with the aim of collating evidence on the clinical efficacy of GnRH agonist agonist triggering—as explicitly stated. Because OHSS (which also occurs in assumable normal responder populations) was either not reported or did not occur in the available studies, no conclusion on OHSS incidence in normal responder populations can be drawn from comparative studies assessed—as explicitly stated. However, the review indicated that a decreased likelihood of pregnancy achievement can be expected after GnRH agonist triggering in current protocols in (assumable) normal responders. Whether this is also the case in OHSS patients is unclear, but at least possible. To illustrate this, we cite clinical outcome from observational studies (such as the study by Bankowski et al., 2004, entitled ‘Triggering ovulation with leuprolide acetate is associated with lower pregnancy rates’) on GnRH agonist triggering in OHSS risk patients.

As we strived to keep the article unbiased by our personal opinion, we had to refrain from expressing an opinion, let alone give a recommendation for clinical practice, whether the protocol as suggested by Kol and Muchtar (2005), or the protocol evaluated by Bankowski et al. (2004), or the protocols evaluated by the studies summarized in the systematic review (Griesinger et al., 2005) are useful for clinical use in OHSS risk patients, when risks, financial, physical and psychological burden of overall treatment have to be balanced with the chance of success.

We are aware of two publications of Kol containing original data on the use of GnRH agonist for prevention of OHSS: in the paper by Itskovitz-Eldor et al., 2000, eight patients considered at OHSS risk were triggered with 0.2 mg Triptorelin subcutaneously and received luteal phase support with daily injections of 50 mg progesterone in oil and 2 mg estradiol orally. No patient conceived. In another article (Kol and Muchtar, 2005), six patients considered at OHSS risk were triggered with 0.2 mg Triptorelin subcutaneously and received luteal phase support with 600 mg micronized vaginal progesterone and 4 mg vaginal estradiol. One patient conceived.

This, together with the evidence summarized in our review (Griesinger et al., 2005) is, at least for us, suggestive of the fact that the current GnRH agonist-triggering protocols might need optimization for possible use in both normal responders and patients considered at risk of OHSS. At no point did we suggest that the concept of GnRH agonist triggering should be abandoned. Instead, suggestions are made in the article, how the existing GnRH agonist-triggering protocols could possibly be modified for future use. The claim of Kol that our review could indirectly contribute to patient morbidity and mortality seems to arise mostly from the authors’ misunderstanding of our article.