

Low-dose hCG supplementation after GnRH agonist triggering: don't be too quick on the trigger

Daniel Bodri*

Fertility Center Mallorca, Palma de Mallorca, Spain

*Corresponding author: Fax: +34-871-964-970 E-mail: bodridaniel@gmail.com

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Induction of final oocyte maturation using a GnRH agonist was first described in the early nineties, though with the advent of the GnRH antagonist era it has gained ever increasing attention some two decades later (Humaidan *et al.*, 2011). The primary motive for substituting the 'classical' hCG trigger is the complete elimination of clinically significant ovarian hyperstimulation syndrome (OHSS). When used alone (or with steroid-only luteal support) GnRH agonist triggering is undoubtedly the most efficient and powerful way of (secondary) OHSS prevention. So far there is no confirmed OHSS case in the literature that proves the opposite (Kol and Humaidan, 2012). This prevention occurs due to a massive, rapid and irreversible luteolysis leading to a practical, total elimination of clinically significant moderate/severe OHSS (Kol, 2004). Consequently when fresh embryo transfer is not planned this strategy has established itself as the first choice option in oocyte donor/fertility preservation cycles and before total freezing of oocytes or embryos (Bodri *et al.*, 2010; Griesinger *et al.*, 2011).

However, if the primary goal is performing fresh embryo transfer then the challenge is to save the severely impaired luteal phase without increasing the risk of early/late-onset OHSS. After the discouraging results of initial trials only a few dedicated research groups have made further efforts to undertake research in this area (Humaidan *et al.*, 2006; Engmann *et al.*, 2008; Castillo *et al.*, 2010; Papanikolaou *et al.*, 2011b). Humaidan *et al.* developed the concept of a modified luteal support aimed at rescuing the impaired luteal phase by administering small boluses of luteotropic substances. This hypothesis was first tested in pilot studies, both in normal and high responders (Humaidan *et al.*, 2006 Humaidan, 2009) and later in a randomized clinical trial (Humaidan *et al.*, 2010). The first randomized trial (mainly involving normal responders) suggested that the reproductive outcome can be improved to the level of control patients with a single, low-dose (1500 IU) hCG bolus administered at the time of oocyte retrieval, without increasing the risk of OHSS (Humaidan *et al.*, 2010). These encouraging results were also reproduced in a retrospective study by an Australian group (Radesic and Tremellen, 2011). Although Radesic and Tremellen used the aforementioned strategy with a fairly high OHSS

risk population (without a pre-established upper limit of ovarian response) they were cautious enough to only perform mandatory single embryo transfer to reduce the risk of any late-onset OHSS.

In the current issue of Human Reproduction the case series by Seyhan *et al.*, report the combined experience from two geographically distant centres in Canada and Turkey with IVF patients at high risk of OHSS, who received the low-dose hCG rescue protocol. Despite using co-interventions (such as coasting and cabergoline administration) the authors reported a worryingly high rate (22%) of early onset severe OHSS requiring hospitalization. Although the presented retrospective case series is fairly small, the authors felt that it was important to highlight that early onset OHSS can still occur after applying the low-dose hCG rescue protocol. At first sight their findings are in blunt disagreement with most previously published studies that have also used low-dose hCG luteal support (single or multiple-bolus) following GnRH agonist trigger (Table 1). However, at closer look notable differences can be observed. Among the four studies that were conducted in high OHSS risk patients Seyhan *et al.*'s 23 patients represent the highest ovarian response category with extremes of 49 and 65 oocytes retrieved. Moreover, although in one of the participating centres total freeze was considered in 33% of the cases, in the other fresh transfer was performed only transferring two to three embryos. Taken altogether these factors considerably influence the risk of early and late-onset OHSS. Although it was based on a very limited number of cases (5 versus 18) Seyhan *et al.* also suggested a threshold (≥ 18 follicles) based on the number of intermediate-sized (10–14 mm) follicles above which embryo/oocyte freezing is strongly recommended. This threshold (which was the only significant finding in this series) was based on the number of intermediate follicles and might be less practical for everyday clinical use than the total follicular count (Papanikolaou *et al.*, 2006). Interestingly, in the design of a more recent randomized trial by Humaidan *et al.* on low-dose hCG support, patients with >25 follicles >11 mm were judged to be at too high risk and excluded from participation (www.clinicaltrials.gov: NCT00627406).

Table 1 Studies using low-dose hCG (single or multiple-bolus) luteal support following GnRH agonist triggering.

Author, year	Design	Period	Patients with hCG suppl. protocol	Inclusion criteria	Follicles	Peak E2 pg/ml	COC	Clinical pregnancy rate/ Embryos transferred	Early/late-onset OHSS
Humaidan <i>et al.</i> (2006)	Pilot, randomized	December 2004–May 2005	13 (+35 h: 1500 IU hCG)	Normo-responder	NA	2392 ± 978	12.5 ± 4	46 (6/13) 1.8	0
Humaidan (2009)	Pilot, observational	May 2006–August 2007	12 (+35 h: 1500 IU hCG)	High responder (≥25 follicles ≥ 11 mm)	NA	5067 ± 2860	21.5 ± 6	50 (6/12) 1.7	Early: 0 Late: 1
Castillo <i>et al.</i> (2010)	Retrospective	2002–2006	192 (OPU + D1, +D4, +D7: 1000/500/250 IU)	High responder (≥ 15 follicles ≥ 14 mm)	NA	2531 ± 1366	14.8 ± 7.2	43.2 (83/192) 2.1	15 ^b
Humaidan <i>et al.</i> (2010)	Randomized clinical trial	January 2006–January 2007	152 (+35 h: 1500 IU hCG)	Normo-responder, but 1/3: ≥ 13 follicles ≥ 11 mm	NA	2165 ± 1762	8.9 ± 5.4	33 (50/152) 2	0
Radesic and Tremellen (2011)	Retrospective	January 2010–April 2011	71 (+35 h: 1500 IU hCG)	High responder (≥ 14 follicles ≥ 12 mm, no upper limit)	18.4 ± 0.87	3356 ± 150 ^a	16.8 ± 0.8	52.1 (37/71) 1	Early: 0 Late: 1
Seyhan <i>et al.</i> (2013)	Retrospective	December 2008–August 2012	23 (+35 h: 1500 IU hCG)	Very high responder	20.3 ± 6.3	4892 ± 2213	27.4 ± 13.9	NA 0.7 and 2.1	Early: 5 Late: 1

NA, not available; E2, estradiol; COC, cumulus–oocyte complex.

^aSerum E2 on stimulation Day 9.^bDistinction between early and late-onset OHSS is not available.

In retrospect, most of the Seyhan series of patients were clearly not suitable candidates for the Humaidan protocol. In a similar manner caution is recommended when low-dose hCG luteal support is used at shorter intervals. As shown previously, the preventive effect of the agonist trigger was greatly reduced, and an OHSS rate as high as 7.8% was observed, when low-dose hCG was administered every three days during the luteal phase (Castillo *et al.*, 2010). In the setting of the classical hCG trigger the risks of hCG-based luteal support were already demonstrated by earlier studies performed several years ago (van der Linden *et al.*, 2011).

Despite the efforts of a few dedicated research groups, GnRH agonist triggering with modified luteal support still remains a relatively new concept that is in continuous development (Humaidan *et al.*, 2011). One must also take into account that if fresh embryo transfer is the goal compared with innovative approaches involving GnRH agonist triggering, the classical hCG trigger as an 'alternative' simply cannot get us closer to the goal of an OHSS-free clinic. As recently reviewed by Papanikolaou *et al.* there are currently well-defined time points at each step of an IVF cycle (end of diagnostic workup, triggering day, OPU day and afterwards on post-oocyte retrieval Day 1, 3 or 5) where clinicians have to make decisions influencing the overall OHSS risk (Papanikolaou *et al.*, 2011a).

In conclusion, currently available data suggest that in normo-responders and in moderate-high OHSS risk patients the low-dose hCG supplementation protocol after agonist triggering is effective in reducing (though not completely eliminating) the OHSS incidence and also assure good reproductive outcome. In contrast, patients at a much higher OHSS risk would currently benefit more from a freeze-all strategy. Further research in better defining OHSS risk groups and fine-tuning low-dose hCG supplementation protocols is still necessary.

Potential conflict of interest

The author is a member of the Copenhagen Agonist Trigger Workshop Group which was founded by Peter Humaidan and others in November 2009.

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