Can we eliminate severe ovarian hyperstimulation syndrome? Comment I

Sir,

We read with interest the article by Orvieto (2005) ‘Can we eliminate severe ovarian hyperstimulation syndrome?’ recently published in Human Reproduction. In this paper the author suggests a practical behaviour to avoid the occurrence of ovarian hyperstimulation syndrome (OHSS) by delaying embryo transfer with embryo cryopreservation if early signs of OHSS develop, or decreasing the risk of multiple pregnancy by transferring only one blastocyst. However, we think that these suggestions may be useful to prevent late but, not early OHSS. In the light of current knowledge, in fact, the last is due to ovarian/endothelial production of vascular endothelial growth factor (VEGF) after ovulation induction by exogenous hCG administration (Wang et al., 2002).

On the contrary we think that we already have effective pharmacologic tools which have been used for several years by many authors for the treatment of this complication in assisted reproductive technology, without complete awareness of their mechanisms of action. These drugs, in the light of the new pathogenic and pharmacological evidence, should be reconsidered for prevention of both early and late OHSS.

In fact, both dopamine and heparin were used in the past to treat OHSS (Ferraretti et al., 1992; Al Shawaf and Grudzinskas, 2003). In these studies, the D_1 receptor-mediated diuretic effect of dopamine and the heparin anti-thrombotic effect were emphasized. However, recent studies suggest that VEGF plays a pivotal role in OHSS development by an effect on the microvascular system with increased vascular permeability and third space fluid shift (McClure, 1994); moreover, both dopamine agonists and heparin demonstrated a substantial anti-VEGF action.

Basu et al. (2001) showed that dopamine is able to prevent a VEGF effect on vascular system, i.e. reducing VEGF receptor 2 expression/phosphorylation by a D_2 receptor receptor-mediated mechanism. So dopamine and particularly D_2 dopamine agonists may be effective, safe, unexpensive anti-angiogenic drugs worthy further consideration for OHSS prevention. Previous works suggested that D_2 dopamine agonist may reduce OHSS occurrence during controlled ovarian stimulation for intrauterine insemination (Papaleo et al., 2001) and may impair ovarian response and oocyte maturation if administered before oocyte retrieval during ICSI cycles (Doldi et al., 2000) due to VEGF’s essential role in follicular growth and oocyte maturation. Moreover, substantial toxic and teratogenic effects of dopamine agonists, during early pregnancy, were excluded by several years of bromocriptine or cabergoline hyperprolactinaemia treatment (Verhelst et al., 1999).

Due to the above observations, after informed consent, we used the D_2 dopamine agonist cabergoline from 2002 in OHSS treatment with exciting results showing a prompt haematocrit decrease, increased urine output and body weight reduction (Manno et al., 2005). So we were induced by our own and others’ previous observations to try cabergoline in OHSS prevention, administering the drug immediately after pickup and thus avoiding a possible detrimental effect on follicular growth and oocyte maturation due to VEGF system block (Doldi et al., 2000; Zimmermann, 2003). None of the high-risk patients treated [peak estradiol (E_2) level between 3000 and 7000 pg/ml] developed OHSS and preliminary data on pregnancy rates were at least comparable and implantation rates significantly higher (12/52, 23% versus 62/592, 10%; P = 0.003, Fisher’s test for unpaired data) than those observed in historical untreated high-responder controls. If cabergoline effectiveness in OHSS prevention is confirmed in a large study in the near future, early OHSS-related abortions would be prevented, also yielding further improvement of assisted reproductive in high-responder patients.

Low molecular weight heparin, used in the past to prevent OHSS thrombotic complications, may also prevent OHSS occurrence independently by its anti-thrombotic effect, interfering with VEGF binding to its VEGF receptor 2 (Castelli et al., 2004).

So, due to the safety of these drugs during the first trimester of pregnancy, we should consider their use not only for treatment but also for an effective pharmacological OHSS prevention in high-risk patients (3rd day FSH level <8 ng/ml, E_2 3rd day level <50 pg/ml, female age ≤35 years, polycystic ovarian syndrome, previous OHSS, E_2 peak levels >3000 pg/ml or >20 oocytes retrieved). The effectiveness of cabergoline, at least, has already been demonstrated in animals by Basu et al. (2001) and preliminary studies and our observations show that it may also be effective in humans.

This pharmacological approach may be a small contribution toward preserving patients’ health, notwithstanding...
the legislation recently approved by the Italian Parliament designed to protect embryos burdening women.

References

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Can we eliminate severe ovarian hyperstimulation syndrome? Comment 2

Sir,

We read with great interest the opinion paper by Orvieto (2005) which addresses the question of the possibility to eliminate severe ovarian hyperstimulation syndrome (OHSS). A patient-tailored flow chart is proposed because previously described risk factors such as serum estradiol levels and number of follicles appear insufficient to predict occurrence of severe OHSS. In this flow chart, however, single blastocyst transfer is proposed as a method to decrease multiple pregnancy and the authors conclude that the risk of late OHSS can be eliminated. It is correct that with postponement of transfer, the patient can be evaluated and transfer considered or postponed. However, to our knowledge it has never been published that avoidance of multiple pregnancy is sufficient to reduce the risk of OHSS. In the literature, an association between multiple pregnancies and the late form of OHSS is given (Lyons et al., 1994; Papanikolaou et al., 2005). We recently found that, unfortunately, singleton pregnancies are affected by OHSS as frequently as twin pregnancies (De Neubourg et al., 2004). This is probably because the patients at risk for OHSS are the same but receive only one embryo for transfer. The risk for OHSS seems to be more related to a threshold value of hCG in patients at risk rather than to the number of embryos transferred.

References

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Replies: Can we eliminate severe ovarian hyperstimulation syndrome. Comments 1 and 2

Sir,

I thank Dr Manno for his interest in our view (Orvieto, 2005). We offered a patient-tailored flow chart, which includes several clinically applicable and universally acceptable measures in the attempt to eliminate severe OHSS.

Unfortunately, Dr Manno’s suggestion is based on his own study, not yet published (Manno et al., 2005) and which probably awaits further verification. Concerning the numerous preventative measures previously suggested to prevent OHSS, I shall be pleased to add his suggestion to a subsequent flow chart, in the hope that it will achieve validation.

I also thank Drs de Neubourg and Gerris for their interest in our view (Orvieto, 2005). Our patient-tailored flow chart includes several measures among which was the single embryo transfer. We did not claim that merely the avoidance of multiple pregnancy would eliminate OHSS, but that the adherence to the offered stepwise comprehensive approach