Can we eliminate severe ovarian hyperstimulation syndrome?

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The desire of some couples for children is so strong that they are willing to accept a modicum of risk to treat their infertility. Ideally, assisted reproduction technology practitioners seek a balance between optimum ovarian stimulation and successful treatment outcome with minimal rate of severe ovarian hyperstimulation syndrome (OHSS) or multiple pregnancies. However, despite many years of clinical experience, there are no precise methods to completely prevent severe OHSS, except by withholding the ovulation-inducing trigger of hCG. Individualization of treatment according to the specific risk factor and the specific response in the current cycle with the option of freezing of all embryos, or replacement of only a single embryo, has the potential of reducing the risk and the severity of the syndrome in susceptible cases. We offer a triage aimed at eliminating the occurrence of severe ovarian hyperstimulation syndrome on the basis of several clinical observations, including the role of GnRH antagonist in controlled ovarian stimulation protocols, the option of freezing of all embryos, or replacement of only a single embryo in the blastocyst stage.

Key words: controlled ovarian stimulation/ovarian hyperstimulation syndrome/prevention

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovulation induction. Its cardinal features are marked ovarian enlargement and acute third-space fluid sequestration. The fluid shift from the intra- to the extravascular spaces in response to the increase in capillary permeability contributes most to the morbidity associated with OHSS (Navot et al., 1996).

The syndrome almost always presents either 3–7 days after hCG administration in susceptible patients (early onset) or during early pregnancy, 12–17 days after hCG administration (late onset). Early OHSS can to some extent be predicted by pre-ovulatory indices of ovarian response, in time to institute preventive measures such as cancellation (Hancock et al., 1970). Late OHSS does not relate strongly to pre-ovulatory ovarian response, making it difficult for clinicians to identify the cycles in which it is likely to occur (Mathur et al., 1997). In the original description of OHSS, the late form was observed only in cycles with multiple gestations (Lyons et al., 1994), with a trend toward an increase in the severity of disease with an increase in the number of gestational sacs (Mathur et al., 1995).

Several articles have reviewed the epidemiological, hormonal and ultrasonographic characteristics of patients susceptible to OHSS (Blankstein et al., 1987; Asch et al., 1991; Navot et al., 1992, 1996; Morris et al., 1995; Zalel et al., 1995; Levy et al., 1996; Delvigne and Rozenberg, 2002). Despite the many years of clinical experience, however, the pathophysiology of OHSS remains poorly understood, and there is no reliable test to predict which patients will develop severe OHSS (American Society for Reproductive Medicine Practice Committee, 2004). When all the accepted predictive variables were combined, the prevalence of severe OHSS in the ostensibly high-risk patients was only ~20% (Delvigne and Rozenberg, 2002; Orvieto and Ben-Rafael, 1998)—an extremely low value for reliable prediction.

With the introduction in 1987 of GnRH agonists to the controlled ovarian stimulation (COS) protocols, clinicians initiated treatment with higher doses of gonadotrophins for retrieval of a higher number of mature oocytes. These protocols came into widespread use because of their higher conception and lower cancellation rates (Fleming et al., 1985). Unfortunately, they were also associated with an increased occurrence of OHSS (Forman et al., 1990).

Alternatively, GnRH agonist can induce a sustained release of LH and FSH from the pituitary (‘flare effect’), which effectively triggers oocyte maturation and ovulation, making it a potential alternative to hCG. However, the use of this approach was limited by its inapplicability in GnRH agonist-induced pituitary down-regulation-based protocols. Recently, some authors have suggested that replacing hCG with GnRH agonist can reduce the occurrence of OHSS (Balasch et al., 1994, reviewed by Kol, 2004).

Morris et al. (1995) studied assisted reproduction cycles by oocyte donor and classical IVF patients, in which E₂...
(>4000 pg/ml) or oocyte number (>25) or both were elevated. While there were no cases of severe OHSS in the oocyte donor group, six cases of severe OHSS were observed in the classical IVF group. The calculated relative risk of OHSS with pregnancy was 12-fold higher. The authors concluded that the risk of OHSS even at high levels of stimulation is lower than previously believed and that donors have a very low risk of OHSS, probably because of the absence of pregnancy. As such, cryopreservation of all oocytes in IVF cycles is a reasonable alternative. Their findings were supported by Mathur et al. (1995) who observed that OHSS may be more likely if multiple pregnancy occurs following assisted conception. However, other studies showed that when there is serious risk of severe OHSS, cryopreservation of all resulting embryos may prevent pregnancy-associated late OHSS, but not early-onset OHSS, which is precipitated with the trigger hCG dose (Lyons et al., 1994; Queenan et al., 1997).

The best means of prevention is individualization. Based on the aforementioned clinical observations and our personal experience, the occurrence of severe OHSS has been eliminated by strict adherence to the following triage (Figure 1).

**Elimination of OHSS**

Severe OHSS can be almost totally prevented by withholding the ovulation-inducing trigger of hCG in patients at high risk, or by replacing hCG with GnRH agonist to trigger ovulation (Kol, 2004). We therefore believe that today, in normal and high-responder patients undergoing their first IVF attempt, it would be prudent to perform COS with a GnRH antagonist in combination with GnRH agonist to trigger ovulation. In patients in whom <20 oocytes are retrieved, and in low responders (who are expected to recruit <10 follicles) or patients ≥40 years old, the COS protocol should be individually tailored. If the combined GnRH antagonist/agonist or the tailored COS protocols yield ≥20 oocytes, or ≥10 embryos develop, the patient should be followed for 5 days after oocyte retrieval for signs of early OHSS (ultrasonographic signs of ascites, Hct levels for the degree of haemoconcentration). If signs develop, embryo transfer should be withheld and all resulting embryos cryopreserved. This will limit early OHSS, if it appears, to a milder and shorter form. If it does not appear, the transfer of one blastocyst will decrease the risk of multiple pregnancy to almost zero, thereby eliminating the risk of late OHSS.

![Figure 1. Elimination of ovarian hyperstimulation syndrome.](https://example.com/ohss_elimination_diagram.png)
In patients with <20 oocytes, the number of embryos transferred and the time of transfer should adhere to the standard practice of the specific IVF unit.

References


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Submitted on June 24, 2004; resubmitted on August 31, 2004; accepted on October 21, 2004