Article

How to avoid ovarian hyperstimulation syndrome: a new indication for dopamine agonists

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication associated with ovarian stimulation. Despite the numerous breakthroughs that have been made in other areas of assisted reproduction technology, it is only in recent years that the understanding of OHSS has advanced sufficiently to develop treatment options aimed at reducing the incidence and effects of OHSS. However, suitable predictors and tests with which to identify susceptible patients remain unreliable, although anti-Müllerian hormone is currently a good risk-factor candidate. More progress has been made with the prevention of OHSS, and physicians now have a wide range of treatment options, including coasting, re-initiation of gonadotrophin-releasing hormone (GnRH) antagonist and induction of a luteinizing hormone flare-up using GnRH agonist. Recently, vascular endothelial growth factor (VEGF) has been identified as a key player in the vascular permeability that is associated with OHSS. The use of the dopamine agonist cabergoline has been found to reduce the effects of VEGF-mediated vascular permeability without compromising implantation and pregnancy rates. Together, these treatments will complement the ongoing progress with other procedures such as in-vitro maturation and oocyte vitrification, and enable physicians to improve the prediction and prevention of OHSS.

Keywords: *assisted reproductive technology, ovarian hyperstimulation, ovarian hyperstimulation syndrome*

Introduction

Ovarian hyperstimulation syndrome (OHSS) remains a serious and potentially lethal complication of ovarian stimulation. Even though physicians and patients are aware of the seriousness of the syndrome and they strive to minimize it, the incidence of OHSS ranges from 1–14% of all cycles, although severe forms are less common (0.1–0.5%) (Pellicer and Garcia-Velasco, 2003). However, considering the number of assisted reproduction cycles performed worldwide, these numbers are still too high, as OHSS represents a severe complication in young, healthy females who are trying to have a child.

In brief, OHSS can be classified into an early and a late form. Early OHSS is clearly related to the ovarian response and exogenous human chorionic gonadotrophin (HCG) administration, and is detected 3–9 days after HCG administration, while late OHSS is due to the endogenous HCG that is produced by the implanting embryo, and is diagnosed 10–17 days later (Mathur *et al*., 2000). Thus, the key player in this complication is HCG, which exerts its primary function on the granulosa cells of the ovary but which also mediates effects via the lutenizing hormone (LH)/HCG receptors of the endothelium and immune cells, particularly monocytes (Bukovsky *et al*., 1995; Smith *et al*., 1996). Depending on its severity, OHSS can be categorized as mild, moderate, severe or life threatening. Patients undergoing ovarian stimulation for IVF or intracytoplasmic sperm injection routinely show mild forms or, in some cases, moderate forms of OHSS. Severe OHSS can also occur in these patients, but is less common, whereas life-threatening forms of OHSS occur

only rarely. Although mild forms are usually uneventful, more severe forms can potentially put the young, healthy patient at high risk of mortality, and should be addressed with preventive measures. Unfortunately, the lack of consensus regarding the classification criteria for OHSS makes direct comparisons between studies difficult.

Prediction

To avoid OHSS, the first issue to consider is how to identify women who are at risk. There is general agreement that these women tend to be, but not exclusively, young (<35 years old), have a low body mass index, have a history of immunoactivation or allergies, may have polycystic ovarian disease with hyperinsulinaemia or have a very high antral follicle count as determined by ultrasound (Pellicer and Garcia-Velasco, 2003). Although these characteristics may help to identify women at risk and encourage the use of milder stimulation protocols, the tests for detecting which patient will develop OHSS are currently still inadequate. Receiver–operator characteristic curve analysis of the classical parameters do not perform as well as physicians would like, and many OHSS-susceptible patients remain undetected (Papanikolaou *et al*., 2006). A recent publication evaluated the use of anti-Müllerian hormone (AMH), a predictor of OHSS, and found that values >3.36 ng/ml have a sensitivity of 90.5% and a specificity of 81.3% for the detection of OHSS (Lee *et al*., 2008).

Prevention

There are several ways to prevent the onset of OHSS. The assisted reproduction specialist might consider natural-cycle IVF (Edwards, 2007) or in-vitro oocyte maturation (Loutradis *et al*., 2006) as alternatives to ovarian stimulation. Although both of these techniques may be attractive alternatives in the future, they are currently still highly inefficient.

Cycle cancellation is obviously a choice worth considering because it balances the benefits of avoiding severe OHSS with economic costs, as well as the patient's quality of life.

Coasting, the withholding of gonadotrophins while maintaining the gonadotrophin-releasing hormone (GnRH) analogue until oestradiol concentrations drop to a safe value, is still the most widely used approach for avoiding severe OHSS (Garcia-Velasco *et al*., 2006). **Table 1** summarizes the criteria for performing coasting, which does not completely avoid severe OHSS but which significantly reduces the incidence and severity of this condition. The main problem with coasting is that some oocytes may be lost during the procedure, especially if it takes >4 days, which could also affect the endometrial maturation status and thus reduce the chances of achieving a pregnancy. To reduce the time required for coasting, Aboulghar *et al*. (2007) recently evaluated, in a randomized controlled trial, classical coasting in patients at very high risk of developing OHSS, by changing from agonist to GnRH antagonist. They found that the group receiving the antagonist obtained more eggs and, perhaps more importantly, almost 80% of these individuals could undergo egg retrieval after 2 days of coasting, whereas >60% of the patients in the group undergoing classical coasting required 3 days of the procedure before oocyte retrieval.

Another new approach recently described in a case report is the reintroduction of the GnRH antagonist after embryo freezing, in patients with established severe OHSS (Lainas *et al*., 2007). In three patients undergoing ovarian stimulation using GnRH antagonist and who underwent HCG administration and egg retrieval, GnRH antagonists were reintroduced on day 3 after oocyte retrieval following signs and symptoms of OHSS. Ovarian volume, haematocrit and urea improved significantly, meaning that hospitalization was avoided for all three patients. Although HCG had already been given and, thus, early OHSS initiated, this simple approach enabled ambulatory management, a finding that has been validated in a more recent case series by Lainas *et al*. (2008) and others (Giles *et al*., 2008). However, this procedure should be evaluated in larger trials.

If the reason for HCG being the key player in OHSS is because of its long half-life, clinicians may wish to reduce the dose of HCG used for triggering ovulation. In a study of patients with polycystic ovarian syndrome undergoing IVF, a reduction of HCG from 10,000 to 2500 IU did not adversely affect the probability of pregnancy (Kolibianakis *et al*., 2007). Similarly, Nargund *et al*. (2007) confirmed these findings. Another very attractive option for preventing OHSS is the use of endogenous LH, instead of exogenous HCG, to trigger final oocyte maturation; this can be achieved in patients undergoing ovarian stimulation with GnRH antagonists by inducing a flare-up with the agonist (Beckers *et al*., 2003). Since endogenous LH has a very short half-life, this approach allows the retrieval of a similar number of eggs to that recovered using HCG, with the benefit that there is no risk of moderate/severe OHSS. The main obstacle with this method is that the corpus luteum appears to be highly deficient and, regardless of different luteal phase supplementation protocols, implantation and clinical pregnancy rates are clearly diminished (Beckers *et al*., 2003; Griesinger *et al*., 2006). However, a more recent trial showed similar clinical outcomes (i.e., implantation, clinical pregnancy and ongoing pregnancy rates) between these two approaches (Engmann *et al*., 2008), which is in contrast to previous studies. Clearly, further research is needed in this area because, if a good luteal phase supplementation protocol could be found, it would provide an attractive method to reduce the risk of OHSS. Today, inducing a flare-up with GnRH agonists, instead of using HCG, is the preferred choice for those patients who are not undergoing embryo transfer, such as egg donors or fertility preservation patients (Bodri *et al*., 2008; Cerrillo *et al*., 2008).

A recent technological and methodological advance that may profoundly affect the way physicians practise in the near future is oocyte vitrification, especially using the Cryotop device (Cobo *et al*., 2007). Until recently, slow cooling enabled egg freezing with variable results and achieving pregnancies but with a very low efficiency. Ultra-rapid freezing, without the formation of water crystals, has been a tremendous advance in egg-freezing procedures. Cryotop, which is a device that permits oocyte vitrification to be performed in very small volumes, has provided 97% oocyte survival rates after thawing. Consequently, similar fertilization and implantation rates between freeze–thawed and fresh oocytes have been achieved; an outcome never obtained with previous freezing techniques. By contrast, oocyte vitrification needs to be placed into context with the general approach to cryopreservation and prevention of moderate/severe OHSS, when combined with other treatment methods, as described in this article. Recent evidence shows