Symposium: Update on prediction and management of OHSS

Prevention of OHSS

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is a major complication of ovulation induction. As the treatment of the syndrome is currently empirical, prevention is the most important aspect of its management. Identification of patients vulnerable to developing OHSS by taking a history of previous OHSS and polycystic ovarian syndrome is the first step in prevention. The use of mild stimulation protocols with small doses of gonadotrophin is also important. As gonadotrophin-releasing hormone (GnRH) antagonist protocol is associated with a lower risk of OHSS, antagonist could be the protocol of choice in high-risk patients. Withholding human chorionic gonadotrophin (HCG) and continuation of GnRH agonist will abort the syndrome but at the expense of loss of the cycle. Coasting, which involves stoppage of gonadotrophins until oestradiol drops to a low concentration before HCG injection, is an effective technique but it does not completely prevent OHSS. Intravenous albumin is useful in the prevention when given at time of oocyte retrieval. Cryopreservation of all embryos will reduce late-onset OHSS but not early-onset OHSS. In-vitro maturation of oocytes will avoid ovarian stimulation and totally prevent OHSS. Triggering ovulation with a lower dose of HCG is effective in reducing the incidence of OHSS. There are possible roles for metformin and dopamine agonist for prevention of OHSS.

Keywords: *coasting, GnRH antagonist, i.v. albumin, OHSS, prevention*

Introduction

The induction of ovulation by gonadotrophins is one of the major advances in the modern treatment of infertility (Navot *et al.*, 1992). Some degree of ovarian hyperstimulation occurs in all women who respond to ovulation induction, but this should be distinguished from the clinical entity of ovarian hyperstimulation syndrome (OHSS) (Rizk and Aboulghar, 1999).

OHSS is the most serious complication of ovulation induction (Rizk and Aboulghar, 1999). In severe forms, the syndrome is characterized by ovarian enlargement, ascites, hydrothorax, electrolyte imbalance, hypovolaemia and oliguria (Rizk and Aboulghar, 1991). Vascular complications are the most serious complications. They include cerebrovascular thrombosis and arterial thrombosis (Stewart *et al.*, 1997). Respiratory complications include, pleural effusion and adult respiratory distress syndrome (Zosmer *et al.*, 1987). Renal failure and liver dysfunction were also reported and the condition could be lethal: mortalities have been reported in rare cases (Rizk and Aboulghar, 1991).

During the past decade, there was an explosion in the number of ovarian stimulation cycles worldwide, both for IVF/intracytoplasmic sperm injection (ICSI) and ovulation induction for ovulatory infertility. In the last report of the Society for Assisted Reproductive Technology and American Society for Reproductive Medicine (2007) for results of the year 2005, 134,260 assisted cycles were started in the USA (Wright *et al.*, 2008), and in the last report of the European Society for Human Reproduction and Embryology (ESHRE)

for 2004, 367,066 assisted cycles were performed in Europe (Andersen *et al*., 2008). This tremendous increase in the number of cycles worldwide was associated with a global increase in the number of complications of ovarian stimulation and, in particular, OHSS. Searching of PubMed, EMBase and abstracts of major meetings during writing of this manuscript revealed 761 publications cited on OHSS, which emphasized the seriousness of the syndrome and its importance.

The exact aetiology of OHSS is not clearly understood. The treatment is currently empirical and that is why prevention of OHSS is the most important aspect in its management. Although no pharmacological intervention that fully prevents the development of OHSS is yet available, several measures can be adopted to limit the occurrence of this complication to a large degree, and to improve the management of patients at risk (Filicori *et al*., 1999; Homburg and Insler, 2002). Complete prevention does not seem possible without cycle cancellation and continuation of GnRH agonist in patients stimulated using a long GnRH-agonist protocol (Rizk and Aboulghar, 1991).

The objective of this review is to present the different strategies used in prevention of OHSS, with stress on the most effective policies and the newly introduced methods within the frame of evidence-based medicine. These strategies are summarized in **Figure 1**.

Identification of high-risk patients for OHSS before treatment

Two types of patients are at extreme risk for the development of OHSS.

Patients who developed OHSS in a previous stimulation cycle

This group is vulnerable to develop OHSS once more (Aboulghar *et al*., 1996). These patients should be handled very carefully and counselled thoroughly about the risks. If these patients are to undergo ovulation induction for non-IVF treatment, the low-dose step-up protocol should be used very carefully (Homburg and Howels, 1999), and if the patient is to undergo IVF, they should be started on the lowest possible dose of FSH and close monitoring during stimulation is very important (El-Sheikh *et al*., 2001).

Patients with polycystic ovarian syndrome

It is well established that OHSS is more frequent in patients with polycystic ovarian syndrome (PCOS) (Schenker and Weinstein, 1978; Bider *et al*., 1989; Aboulghar *et al*., 1992; Navot *et al*., 1992; Rizk and Smitz, 1992). Multiple immature and intermediate follicles have been associated with an increase in OHSS risk (Asch *et al*., 1991; Dale *et al*., 1991; MacDougall *et al*., 1993). It has been demonstrated that hyperinsulinaemic PCOS patients are exposed to a greater risk than are normoinsulinaemic patients (Fulghesu *et al*., 1997). The diagnosis of PCOS should be based on the Rotterdam criteria (Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004). Increased number of antral follicles and the 'necklace' or 'ring of pearls' appearance of the ovaries should alert the clinician to a heightened sensitivity to gonadotrophins (Navot *et al*., 1992). There has been a significant correlation between the baseline ovarian volume and subsequent occurrence of OHSS (Danning *et al*., 1996; Lass *et al*., 2002).

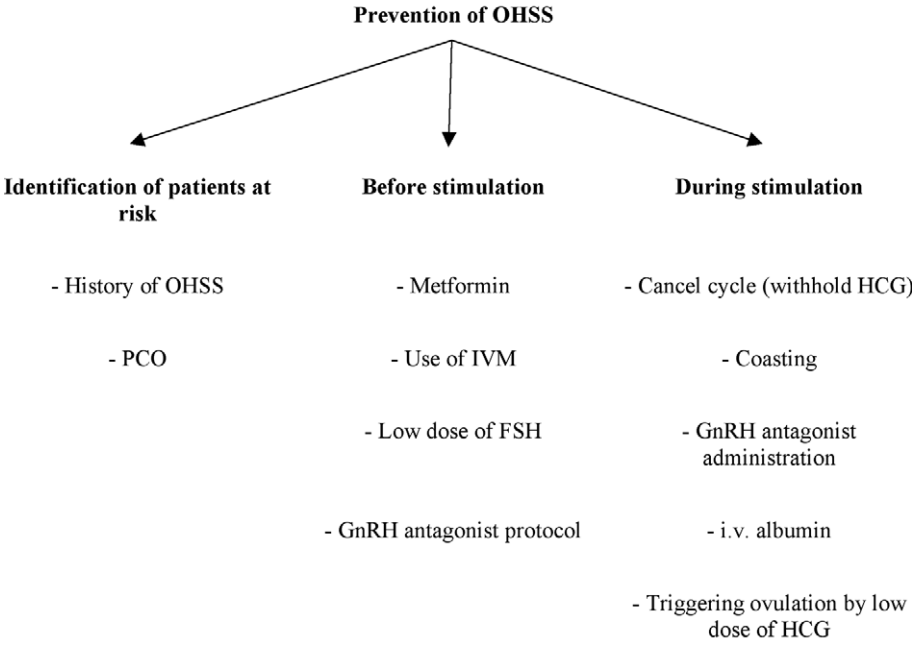

Figure 1. Strategies used in the prevention of ovarian hyperstimulation syndrome (OHSS).