

coasting' in patients with polycystic ovarian syndrome is consistent with good clinical outcome. *Hum Reprod* 2002; 17(5):1212-6.

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Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic life-threatening complication of ovarian stimulation in Assisted Reproductive Techniques. In spite of the extensive researches and articles published upon the preventive measures for the syndrome, there is a feeling that we are still faraway from an effective and completely safe preventive strategy for the syndrome, which at the same time will not jeopardize the oocytes and embryos quality as well as the pregnancy rate. In the literature the authors gave an outstanding different opinions on the same preventive option. In the following we try to summarize the value of each preventive option and the different opinions on each option.

**Defining patients at risk and adjusting the stimulation protocol**

The first important step of prevention is the identification of risk factors, in order to individualize the patient's stimulation regimen. PCOS patients are the most vulnerable group for the development of the syndrome. While it is believed that both E2 and ultrasound monitoring is necessary, it is insufficient as most IVF centers still report the occurrence of severe forms of OHSS, even though such monitoring is practiced (1). A serum E2 level of 12,315 pmol/ L (3,354 pg/ml) on day 11 of ovarian stimulation gives a sensitivity and specificity of 85% for the detection of women at risk for OHSS (2). Strict monitoring

does however allow the application of a number of preventive measures when ovarian response is exaggerated.

**Canceling the cycle**

Canceling the cycle and withholding HCG is the only method which totally avoids the risk of OHSS in ovarian induction cycle or in IVF. All other procedures usually succeed in decreasing either the risk or the severity of OHSS rather than totally preventing it (3). When GnRH agonists or antagonists are not used, one should remain vigilant, since a spontaneous LH peak may still occur, resulting in a pregnancy that is sometimes associated with OHSS complications (4).

**Intravenous albumin**

The suggestion that i.v. albumin might prevent the development of severe OHSS was first made in 1993 (5). In the literature, the dose of i.v. albumin varies between 20-50 g and the time of its administration was either; before, during or immediately after oocyte retrieval. This dose was not adjusted according to the serum albumin level. A Cochrane Review on the use of i.v. albumin to prevent severe OHSS, included five randomized controlled trials that enrolled 378 women (193 in the albumin - treated group and 185 in the control group). A meta-analysis of the five included trials showed a significant reduction in severe OHSS by administration of human albumin, but it did not lead to complete prevention. No second dose was given later on except in one study (6). Kamel in 2003 adjusted the dose according to the drop of serum albumin level (7).

**Other volume expanders such as hydroxyethyl starch**

As an alternative to human albumin, 1000 ml 6% hydroxyethyl starch solution may be infused at the time of oocyte collection, followed by another 500 ml 48 h later (8). Although there was no significant reduction in the severe OHSS cases, but there was a high significant decrease in moderate OHSS in the i.v. starch group. In a prospective randomized, double -blind, placebo - controlled

study hydroxyethyl starch significantly reduced the incidence of OHSS (9).

### **Coasting**

In a Cochrane review D' Angelo and Amso assess the effect of "Coasting" (Withholding gonadotrophins) as a preventive strategy in the management of OHSS in comparison with "early unilateral follicular aspiration (EUFA)" or other interventions. Out of thirteen studies surveyed, only one trial met the inclusion criteria. Their conclusion was that there is a lack of randomized controlled trials for where coasting is compared with no coasting or other interventions such as embryo freezing or i.v. albumin infusion for prevention of OHSS. There is insufficient evidence to determine if coasting is an effective strategy for preventing OHSS (10). Another systematic review of coasting as a procedure to avoid OHSS in IVF patients was done by Delvinge and Rosenberg in 2002. They concluded that, while coasting does not avoid totally the risk of OHSS, it decreases its incidence in high- risk patients (11). Coasting was applied up to 12% of all cycles. This means that some cycles were coasted unnecessarily. If coasting is prolonged for >4 days there is a significant decrease in both implantation and pregnancy rates (12).

### **Intravenous albumin versus coasting**

There is lack of prospective randomized controlled trials comparing coasting with i.v. albumin in preventing OHSS. Chen et al., 2003 in a retrospective comparative study found no statistically significant difference in the entire outcome examined. Coasting was as effective as i.v. albumin in preventing OHSS in high-risk patients but yields inferior pregnancy rates (13).

### **Intravenous albumin versus no treatment**

Although i.v. albumin administration in different studies as well as in a Cochrane review showed a protective value against OHSS, one recent study showed different opinion. Bellver et al., 2003 in a study that included 976 women comparing 40 g albumin at the time of oocyte

retrieval with no treatment showed that, i.v. albumin on the day of oocyte retrieval is not a useful means of preventing the development of moderate- severe OHSS. This study included only 154 (15.6 %) PCOS patients out of the 988 included patients. At the same time coasting was done in 11 patients (14). There is no standardization of the protocol of induction either with the down regulation or type of gonadotropins used. The starting dose of gonadotropins is high. There was a mix between minority of PCOS patients in a majority of non- PCOS patients, who are not at risk of OHSS, but pushed for the syndrome by the aggressive induction protocol.

### **Embryo freezing**

In a Cochrane review D' Angelo and Amso evaluated the effectiveness of cryopreservation (embryo freezing) for the prevention of OHSS. Out of 17 studies included only two of which met the inclusion criteria. When cryopreservation was compared with i.v. albumin no difference was found in all the outcomes examined. When elective cryopreservation of all embryos was compared with fresh embryo transfer no difference was found in all the outcomes examined. It seems that cryopreservation of all embryos has no value for preventing the early type of the syndrome and it may of value in preventing its late type if pregnancy will occur. The conclusion was that there is insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of i.v. albumin versus cryopreservation (15).

### **Luteolysis induced by a gonadotropin- releasing hormone agonist**

Kol in 2004 revised the studies published over the past 15 years on the use GnRH agonist for ovulation triggering as a means to prevent OHSS. The conclusion was that; controlled ovarian stimulation protocols based on GnRH antagonist to prevent premature LH rise and GnRH agonist for ovulation triggering provide a safe and OHSS - free clinical environment. The mechanism of action involves complete, quick, and irreversible luteolysis. Adequate luteal support compensates

for leuteolysis. It is clear that in this regimen, no HCG was used. It should be emphasized that the clinical findings attributable to mild OHSS are an integral part of most cases of ovulation induction in IVF. Yet some reports of moderate cases were also described. A practical major limitation of Gn RHa- induced ovulation is that it is not applicable in IVF stimulated cycles during which pituitary down -regulation with a GnRH agonist is used, which is used routinely by most IVF programs until recently (16).

### **Follicular aspiration**

Early unilateral follicular aspiration (EUFA) 10-12 h after hCG administration was compared with coasting in a prospective randomized study. Fewer oocytes were recovered in the coasting group, but fertilization, embryonic cleavage and pregnancy rates were similar. Neither method completely prevented the occurrence of severe OHSS. As the method is not completely preventive for the syndrome as well as its invasive nature, necessitating two oocyte retrievals, explain why it has been attempted less often than coasting.

### **Oral hydration with increased protein intake**

An advice to increase oral hydration and protein intake should be given to all women at risk to develop OHSS. This may prevent haemoconcentration and increase urinary excretion of vasoactive mediators responsible for the syndrome (17).

### **In- vitro maturation (IVM) of oocytes**

IVM is one of the new assisted reproductive technologies for the infertile women with PCOS, especially those with history of OHSS. This may eliminate the risk of the syndrome for this group of patients (18).

## **CONCLUSION**

We see from the previous review of the available preventive options for OHSS, that there is no agreement on each preventive strategy. This

may be due -at least in part- to the lack of well designed prospective randomized controlled clinical trials with sufficient number of cases. The sample should be uniform in each study with no mix between PCOS patients and other risk groups. The end point in each study, as well as the points of comparison should be clear. Until this I feel that clinical judgement and dose adjustment should be the first line of prevention. There should be a reassessment of i.v. albumin administration with dose adjustment according to the serum albumin level against coasting. Luteolysis with GnRH- a after antagonist will have a limited role until the clinical experience with the antagonist will build - up. Oral hydration with increased protein intake starting from day 8 of the stimulation cycle may be of help with other preventive measures. Other measures as EUFA and cryopreservation have limited practical preventive value. IVM may be of help in PCOS patients in the future.

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Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of controlled ovarian hyperstimulation (COH) for assisted reproduction technologies (ART). It is characterized by a broad spectrum of signs and symptoms that includes abdominal distention and discomfort, enlarged ovaries, ascites, and other complications of enhanced vascular permeability. The syndrome can be strictly defined as the shift of serum from the intravascular space to the third space, mainly to the abdominal cavity, in the context of enlarged ovaries due to follicular stimulation. In its very severe form, OHSS