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Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures

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The aim of this review was to summarize previously published classifications for ovarian hyperstimulation syndrome (OHSS), as well as to analyse the available methods for preventing OHSS. Withholding hCG and cycle cancellation—once the main methods of preventing OHSS—are now seldom used. There is a growing body of evidence to support the use of coasting to prevent OHSS, without cycle cancellation. However, most studies on coasting are retrospective, and well-designed prospective randomized studies are lacking. There is no current consensus as to how coasting should be carried out. A serum estradiol level of 3000 pg/ml is generally considered optimum for administration of hCG. It appears that intravenous albumin or hydroxyethyl starch at the time of oocyte retrieval is beneficial in preventing OHSS, but does not offer complete protection. There is insufficient evidence to support routine cryopreservation of all embryos for the later transfer of frozen–thawed embryos in high-risk patients. Several uncontrolled studies have reported the protective effect of GnRH agonist to trigger ovulation in preventing OHSS, though the method is applicable solely for gonadotrophin-only or GnRH antagonist cycles. A single dose of recombinant LH to trigger ovulation significantly reduced OHSS as compared with hCG. The possible role of GnRH antagonist protocols in reducing the incidence of OHSS is debatable. The above measures to prevent OHSS were successful in reducing the incidence of the syndrome, but complete prevention is not as yet possible.

Keywords: classification/coasting/intravenous 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). While mild OHSS is of no clinical relevance, severe OHSS—characterized by massive ovarian enlargement, ascites, pleural effusion, oliguria, haemoconcentration and thromboembolic phenomena—is a life-threatening complication (Schenker and Weinstein, 1978; Navot *et al*., 1992; Aboulghar *et al*., 1993; Schenker and Ezra, 1994; Serour *et al*., 1998; Hock and Seifer, 2000). The clinical course and treatment of OHSS was recently reviewed (Delvigne and Rozenberg, 2003).

The aim of this review was to detail the different classifications of OHSS, in addition to critically appraising the different strategies used to prevent this serious iatrogenic complication. The medical literature was reviewed using Medline and Pubmed, using the keywords: ovarian hyperstimulation syndrome (OHSS), IVF and classification. Articles were all hand-searched and reviewed. Recent books published between 1990 and 2002 were also hand-scanned.

Classifications of OHSS

The first classification of OHSS, which was prepared in 1967 (Rabau *et al*., 1967), combined both laboratory and clinical findings, but others (Schenker and Weinstein, 1978) later reorganized and modified the classification into three main clinical categories and six grades according to the severity of symptoms and signs and laboratory findings. In 1989, a new classification of three categories and five grades was introduced (Golan *et al*., 1989), and this was later modified by further dividing the severe form into two subgroups (Navot *et al*., 1992). The most recent classification with further modifications was introduced in 1999 (Rizk and Aboulghar, 1999). All five classifications with different grades are listed in Table I.

The objectives of all classifications were two-fold. The first objective was to compare the incidence of OHSS in different

Table I. Classification of ovarian hyperstimulation syndrome (OHSS)

Study	Mild	Moderate	Severe		
Rabau *et al.* (1967)	Grade 1: estrogen >150 μg and pregnanediol >10 mg 24 h Grade 2: + enlarged ovaries and possibly palpable cysts Grade 1 and 2 were not included under the title of mild OHSS	Grade 3: grade 2 + confirmed palpable cysts and distended abdomen Grade 4: grade 3 + vomiting and possibly diarrhoea	Grade 5: grade 4 + ascites and possibly hydrothorax	Grade 6: grade 5 + changes in blood volume, viscosity and coagulation, time	
Schenker and Weinstein (1978)	Grade 1: estrogen >150 μg/24 h and pregnanediol >10 mg 24 h Grade 2: grade 1+ enlarged ovaries, sometimes small cysts	Grade 3: grade 2 + abdominal distension Grade 4: grade 3 + nausea, vomiting and/or diarrhoea	Grade 5: grade 4 + large ovarian cysts, ascites and/or hydrothorax	Grade 6: marked haemoconcentration + increased blood viscosity and possibly coagulation abnormalities	
Golan *et al.* (1989)	Grade 1: abdominal distension and discomfort Grade 2: grade 1 + nausea, vomiting and/or diarrhoea, enlarged ovaries 5–12 cm	Grade 3: grade 2 + ultrasound evidence of ascites	Grade 4: grade 3 + clinical evidence of ascites and/or hydrothorax and breathing difficulties	Grade 5: grade 4 + haemoconcentration, increase blood viscosity, coagulation abnormality and diminished renal perfusion	
Navot *et al.* (1992)			Severe OHSS: variable enlarged ovary; massive ascites ± hydrothorax; Hct >45%; WBC >15 000; oliguria; creatinine 1.0–1.5; creatinine clearance ≥50 ml/min; liver dysfunction; anasarca	Critical OHSS: variable enlarged ovary; tense ascites ± hydrothorax; Hct >55%; WBC ⩾25 000; oliguria; creatinine ⩾1.6; creatinine clearance <50 ml/min; renal failure; thromboembolic phenomena; ARDS	
Rizk and Aboulghar (1999)		Discomfort, pain, nausea, distension, ultrasonic evidence of ascites and enlarged ovaries, normal haematological and biological profiles	Grade A: Dyspnoea, oliguria, nausea, vomiting, diarrhoea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, US showing large ovaries and marked ascites, normal biochemical profile	Grade B: Grade A plus massive tension ascites, markedly enlarged ovaries, severe dyspnoea and marked oliguria, increased haematocrit, elevated serum creatinine and liver dysfunction	Grade C: Complications as respiratory distress syndrome, renal shut-down or venous thrombosis

ARDS = acute respiratory distress syndrome; Hct = haematocrit; US = ultrasound; WBC = white blood cells.

grades, and this is essential for the evaluation and comparison of the efficacy of different preventive measures for OHSS. The second objective was to plan and standardize an outline for the management of each grade of OHSS.

It was first suggested in 1967 (Rabau *et al*., 1967) that grade 1 and 2 were not considered as adverse reactions. The objective of the classification was that grade 1 and 2 required no treatment, grades 3 and 4 needed observation for prevention of possible future complications, and grades 5 and 6 required hospitalization.

Others (Schenker and Weinstein, 1978) subsequently modified the classification such that grades 1 and 2 were grouped together as mild OHSS which was not clearly defined in Rabau's 1967 classification; however, the general outline and objectives of the classification were similar.

One drawback of these two classifications was that 24 h urine collection for hormonal assays complicated the classification. On the other hand, severe OHSS, which is the most important category, was well defined in these classifications.

Later, a new classification was proposed (Golan *et al*., 1989) in which 24-h urinary assays of hormones became obsolete, and subsequently estrogen and pregnanediol assays were also excluded. Nausea, vomiting and diarrhoea and abdominal distension were moved from moderate OHSS to mild OHSS. Ultrasound examination of the ovaries (5–12 cm) was also included in mild OHSS. Moderate OHSS was not divided into two grades as in the previous classifications, and it mainly added ultrasound evidence of ascites to grade 2 OHSS. Severe OHSS was classified into two grades which were similar to those in previous classifications.

The incorporation of ultrasound into the OHSS classification was an important addition as the technique became a routine tool for monitoring ovulation induction and follow-up of OHSS.

During the early 1990s, a modification was introduced into the previous classifications which did not allow any distinction to be made between severe and life-threatening forms of OHSS (Navot *et al*., 1992). This distinction was created by dividing severe OHSS into severe and critical subgroups. Furthermore, generalized

oedema (anasarca) and liver dysfunction were also considered to be signs of severe OHSS. These authors considered ovarian size to be the most important factor when ovulation induction was the sole technique, but when controlled ovarian stimulation is used for assisted reproduction, massive ascites frequently coexist with relatively minor ovarian enlargement (<10 cm). Thus, the classification of OHSS for these patients should rely more on the general clinical picture and laboratory parameters than on ovarian enlargement. This subdivision of severe OHSS is important from clinical and prognostic aspects, as the critical OHSS is that grade which results in most of the serious complications and which should be treated carefully under close supervision in an intensive care unit.

The later classification (Rizk and Aboulghar, 1999) differed from previous systems in several aspects. A mild degree of OHSS was omitted from the classification, as mild forms can occur in most patients after ovarian stimulation; moreover, the condition had no complications and did not require special treatment. Severe OHSS was further classified into three grades with distinct definitions: grades A and B were similar to the two subgroups of Navot's classification. A new subgroup (Grade C) was then introduced which included OHSS complicated by severe complications such as venous thrombosis and respiratory distress syndrome. Serious complications of OHSS usually occur in severe forms of the syndrome, though some (e.g. venous thrombosis) may occur even with moderate OHSS. Complications of OHSS were not included in any of the previous classifications. It was suggested that moderate OHSS would require observation and follow-up by regular visits, severe OHSS group A would require outpatient treatment and possibly short-term hospitalization, group B would require intensive care admission, and group C would require, in addition, treatment of the complications.

Prevention of OHSS

Currently, the condition of OHSS is incompletely understood and its pathogenesis remains an area of controversy (Balasch *et al*., 1991; Yarali *et al*., 1993). 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). As there is at present no completely curative therapy for OHSS (Pride *et al*., 1986; Abramov *et al*., 1999), the most effective treatment is prevention. However, 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). There is nonetheless an increasing awareness among physicians regarding the different measures to prevent OHSS which, in careful hands, will reduce its incidence to a minimum (Aboulghar *et al*., 1996a; Delvigne and Rozenberg, 2002; Homburg and Insler, 2002).

Identification of patients at risk before ovarian stimulation

History of OHSS

Those patients who developed OHSS in a previous cycle are prone to develop the condition in any subsequent stimulated cycle (Aboulghar *et al*., 1996a). In future IVF cycles, extreme caution should be taken and it is suggested that the lowest possible dose of FSH should be given as a starting point (El-Sheikh *et al*., 2001). In addition, patients should be closely monitored using ultrasound and serial serum estradiol (E_2) measurements made as a preventive measure in patients at risk of developing OHSS (Homburg and Insler, 2002). The use of recombinant FSH (rFSH) in a low-dose protocol was effective in achieving a 20% pregnancy rate without OHSS in non-IVF cycles (Aboulghar *et al*., 1996b).

Identification of polycystic ovary disease

It is well established that OHSS is more frequent in patients with polycystic ovary disease (PCOD) (Schenker and Weinstein, 1978; Bider *et al*., 1989; Aboulghar *et al*., 1992; Navot *et al*., 1992; Rizk and Smitz, 1992).

Women with PCOD appear to have a greater sensitivity to gonadotrophins (Raj *et al*., 1977; Schenker and Ezra, 1994), and this effect may be secondary to the increased recruitment of follicles of varying maturational phase owing to pathological endogenous gonadotrophin and steroid hormone responses to exogenous stimulation (Surrey *et al*., 1989). 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). Recently, it was demonstrated that hyperinsulinaemic PCOD patients are exposed to a greater risk than are normoinsulinaemic patients (Fulghesu *et al*., 1997).

Baseline ovarian ultrasonography and endocrine assessments during the early follicular phase are needed to identify the presence of polycystic ovaries (Navot *et al*., 1988). The dimensions and number of antral follicles on each ovary should be noted. Increased ovarian volume (Lass *et al*., 2002), 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 was a significant correlation between the baseline ovarian volume and subsequent occurrence of OHSS (Danning *et al*., 1996). Young age (<35 years) has also been identified as a risk factor (Golan *et al*., 1988), though the contribution of patient characteristics such as a younger age and a lean body habitus has been debated (Asch *et al*., 1991; Ayhan *et al*., 1996).

Stimulation protocols and OHSS

For non-IVF cycles

The low-dose, step-up protocol to achieve successful unifollicular ovulation will minimize—if not completely prevent—the development of OHSS (Homburg and Howles, 1999). However, even after increasing the gonadotrophin dose a total lack of ovarian response may occur (particularly in obese women) as the threshold for ovarian follicular development is not exceeded, and in these cases the starting dose in future cycles could be increased (Homburg and Insler, 2002). The step-down protocol is also associated with a low risk of OHSS (Macklon and Fauser, 2000).

Although one group (White *et al*., 1996) reported no cases of severe OHSS in almost 1000 treatment cycles performed with low-dose gonadotrophins, the major limitation of these regimens is that they cannot be used to induce multifolliculogenesis for assisted reproduction technology (ART) procedures (Homburg and Insler, 2002).

For IVF cycles

Lower doses of gonadotrophins: The risk of OHSS is particularly evident when controlled ovarian stimulation for ART procedures is performed with elevated gonadotrophin dosages (Golan *et al*., 1988; Homburg and Insler, 2002). It is advisable to use a low starting dose of 150 IU for all patients at possible risk of OHSS, irrespective of their age (Homburg and Insler, 2002). Limited ovarian stimulation helped to prevent OHSS in PCOD patients with a history of severe OHSS (El-Sheikh *et al*., 2001). With the 'step-down' protocol (van Santbrink *et al*., 1995), an initial starting dose is derived from prior cycle reviews in combination with the patient's age and body weight.

GnRH agonist protocols: Use of the long GnRH agonist protocol of ovarian stimulation with the objective of pituitary down-regulation was originally introduced aiming at a reduction in the incidence of OHSS (Salat-Baroux *et al*., 1988; Moreau *et al*., 1989). However, it was confirmed by several studies that the use of a long GnRH agonist protocol increases the incidence of OHSS, possibly because of the stimulation of a large cohort of follicles and the associated high serum E_2 levels (Charbonnel *et al*., 1987; Golan *et al*., 1988; Forman *et al*., 1990; Smitz *et al*., 1990).

GnRH antagonist protocols: There was no significant difference in the incidence of OHSS between agonist and antagonist protocols in the five large phase III multicentre randomized studies (Albano *et al*., 2000; European Orgalutran Study Group, 2000; Olivennes *et al*., 2000; European-Middle East Orgalutran Study Group, 2001; Fluker *et al*., 2001). In a Cochrane review, one group (Al-Inany and Aboulghar, 2002) reported that there was no significant difference between the incidence of OHSS in GnRH agonist/FSH or GnRH antagonist/FSH protocols. By contrast, in a prospective randomized study, another group (Ludwig *et al*., 2000) compared the long GnRH agonist luteal phase with the multiple dose antagonist (cetrorelix), and showed there to be no significant difference in pregnancy rate but a significantly greater chance of OHSS developing in the long agonist protocol. In a meta-analysis on the use of GnRH antagonists in ovarian stimulation for ART compared with the long GnRH agonist protocol (Ludwig *et al*., 2001), the authors demonstrated a significant reduction in the number of OHSS cases in the cetrorelix studies [Odds Ratio (OR) 0.3, 95% CI 0.10–0.84], but no reduction for ganirelix (OR 1.13; 95% CI 0.24–5.31). The authors claimed that this difference might be due to the use of hMG which contained an LH component in some of the cetrorelix studies, whereas rec-FSH only was used in the ganirelix studies. It was also suggested that there might have been a difference between the two drugs.

Identification of patients at risk of OHSS during ovarian stimulation

Adequate monitoring of ovulation induction is a key prerequisite for limiting OHSS. Traditionally, ultrasound and serum E_2 assays have been used in differing combinations and frequencies for monitoring the programme of ovarian stimulation.

Endocrine monitoring

The association between high serum E_2 levels and the slope of log E_2 increment and OHSS has been known for more than 30 years. Serum E_2 was seen to be the best predictor of the hyperstimulation score (Haning *et al*., 1983).

A large multicentre Belgian study used multiple discriminate analysis to predict OHSS (Delvigne *et al*., 1993). The best prediction (78.5%) was obtained in 128 cases using log E_2, slope of log E_2 increment, hMG dosage, number of oocytes retrieved and LH/FSH ratio. However, the use of logE_2 and slope of log E_2 increments had not been translated widely into clinical practice.

Follicular monitoring by ultrasound

It has been stated that a decrease in the fraction of the mature follicles and an increase in the fraction of the very small follicles correlated with an augmented risk for the development of severe OHSS (Blankstein *et al*., 1987). Others (Golan *et al*., 1989) stated that the combination of E_2 and ultrasonography offers the best chance for the prediction of OHSS.

In a review of 538 consecutive IVF cycles conducted to ascertain whether routine serum E_2 monitoring was of help in preventing OHSS, the authors concluded that serum E_2 assays were necessary only for patients in whom >20 follicles were detected on ultrasound (Thomas *et al*., 2002).

Preventive measures in high-risk patients during ovarian stimulation

Withholding hCG and cycle cancellation

Withholding hCG was the most commonly used method of preventing OHSS in patients predicted to be at high risk of developing the syndrome. This approach will lower the incidence of OHSS, but at the expense of losing the cycle, thereby placing heavy psychological and financial burdens onto the patient. Prevention was seen to be complete if the pituitary was down-regulated and GnRH agonist administration continued. However, in gonadotrophin-only stimulated cycles, there is no guarantee of complete prevention of OHSS. The serum E_2 levels above which hCG should be withheld varied widely among different centres. One group (Schenker, 1993) withheld hCG if the serum E_2 level exceeded 1500 pg/ml in ovulation induction and 2500 pg/ml in IVF. Others (Blankstein *et al*., 1987) suggested a serum level of 1700 pg/ml, whilst another group (Haning *et al*., 1983) accepted 4000 pg/ml as the upper limit. It is believed that when guidelines for withholding hCG are suggested, more than one parameter should be considered, namely the presence of polycystic ovary on ultrasound, the occurrence of OHSS in previous cycles, a

serum E_2 level ⩾3500 pg/ml, the slope of E_2 rise and presence of 25 or more follicles, particularly of small and intermediate sizes (Rizk and Aboulghar, 1991).

Following the introduction of different modalities to prevent OHSS in high-risk patients—and in particular coasting—withholding hCG with cyclic cancellation is seldom used. One group (Dhont *et al*., 1998) performed almost 2000 IVF cycles and used coasting as the only measure to prevent OHSS, with no cycles being cancelled.

Triggering ovulation and OHSS

Reducing the hCG trigger dose: In a comparison of single doses of 2000, 5000 and 10 000 IU hCG to trigger ovulation, a significantly lower successful oocyte recovery was found in patients who received 2000 IU hCG as in those who received either 5000 or 10 000 IU (Abdalla *et al*., 1987). Hence, it would be reasonable to consider reducing the hCG dose to 5000 IU in high-risk patients.

Use of recombinant hCG to trigger ovulation: In a randomized study using the long GnRH protocol, a low dose of recombinant hCG (250 μg) was found to be as effective as 10 000 IU urinary hCG in triggering ovulation; moreover, the pregnancy rate, implantation rate and OHSS rate were similar (Driscoll *et al*., 2000; The European Recombinant Human Chorionic Gonadotrophin Study Group, 2000; Chang *et al*., 2001). Induction of ovulation in WHO group II anovulatory women undergoing follicular stimulation with rFSH showed that 250 μg rhCG and 5000 IU hCG produced comparable results (International Recombinant Human Chorionic Gonadotrophin Study Group, 2001).

Recombinant LH for triggering ovulation: In using the long GnRH protocol, moderate OHSS was reported in 12.4% of patients who received urinary hCG and in 12.0% of patients who received two injections of recombinant hLH (rhLH) (The European Recombinant LH Study Group, 2001). Neither moderate nor severe OHSS was reported in patients who received a single dose of rhLH up to 30 000 IU. These results showed that a single dose of rhLH was effective in inducing final follicular maturation and early luteinization in IVF patients, and was comparable with 5000 IU urinary hCG. A single dose of rhLH resulted in a highly significant reduction in OHSS compared with hCG.

GnRH agonist for triggering ovulation: In *gonadotrophin-only stimulated cycles*, although similar in action to LH, hCG does not provide a physiological stimulation that is identical to the endogenous LH surge (Hoff *et al*., 1983; Itskovitz *et al*., 1991). Furthermore, hCG therapy, because of its longer half-life compared with LH, is associated with a sustained luteotrophic effect, multiple corpora lutea development, and supraphysiological serum levels of estradiol and progesterone throughout the luteal phase (Itskovitz *et al*., 1991). Some authors have suggested that these differences are responsible for the development of OHSS (Haning *et al*., 1985).

Serum hCG concentrations are detectable up to 6 days following intramuscular (i.m.) injection of 5000 IU hCG, whereas a single GnRH agonist injection (500 μg leuprolide acetate s.c.) resulted in a combined LH and FSH surges lasting 34 h (Gonen *et al*., 1990). Therefore, the shorter duration of LH-like activity after GnRH agonist compared with hCG administration may indeed reduce stimulation of the ovary in the luteal phase (Segal and Casper, 1992).

Several articles have described the application of the flare-up effect of GnRH agonist on the pituitary gland for induction of an endogenous pre-ovulatory LH and FSH surge (Bentick *et al*., 1988; Emperaire and Ruffie, 1991). One or two doses of buserelin acetate 250–500 μg were administered to six patients with moderate response and eight patients with exaggerated response to gonadotrophin stimulation (Itskovitz *et al*., 1991). GnRH agonist effectively triggered the LH/FSH surge, and mature oocytes were recovered from all patients. Luteal E_2 and progesterone levels were lower than in patients injected with hCG, and no signs of OHSS were observed. Similar results were achieved by other investigators (Imoedemhe *et al*., 1991; Van der Meer, 1993; Balasch *et al*., 1994; Shalev *et al*., 1994).

Most of the studies reporting the protective effect of GnRH agonist administration in preventing severe OHSS have been uncontrolled. One group (Segal and Casper, 1992) randomized 179 women to receive either hCG (5000 IU i.m.) or leuprolide acetate (500 μg s.c.) to trigger follicular maturation in IVF. Estradiol concentrations were comparable, and no case of OHSS was seen in either group.

In *GnRH antagonist cycles*: the major limitation against the routine use of GnRH agonists to trigger ovulation was that the majority of IVF cycles worldwide were down-regulated by GnRH agonist, thereby rendering their use unsuitable. The introduction of GnRH antagonists has led to a renewed interest in the use of GnRH agonists to induce final oocyte maturation.

One group (Itskovitz-Eldor *et al*., 2000) used a single bolus of 0.2 mg triptorelin to trigger ovulation in eight patients at risk of OHSS who underwent ovarian stimulation for IVF with FSH and GnRH antagonist. The mean number of oocytes obtained was 23.4 ± 15.4, none of the patients developed OHSS, and four clinical pregnancies were achieved.

It was also reported (Tay, 2002) that an international multicentre randomized controlled trial has recently been completed which compared the efficacy of GnRH agonist with hCG for triggering ovulation in GnRH antagonist cycles, though the results have not yet been published.

Coasting

Coasting is a technique which involves withdrawing exogenous gonadotrophins and withholding hCG until the patient's serum E_2 level decreases to a safer level. The technique of coasting appeals to both physicians and their patients, and it also allows for the timely transfer of fresh embryos.

Coasting for non-IVF cycles: Many studies have been published on the effect of coasting in the prevention of OHSS. These studies are highly heterogeneous in nature, with differing thresholds to initiate coasting or to trigger hCG and numbers of embryos transferred, all of which factors affect the outcome. Coasting was introduced for the

prevention of OHSS in stimulated non-IVF cycles, long before it was introduced in IVF. The technique was exactly the same as coasting for IVF. Initial experiences related to the rescue of 12 gonadotrophin-induced cycles that were liable to develop hyperstimulation (Rabinovici *et al*., 1987). Treatment with hMG was stopped for 2 to 10 days, and pregnancies occurred in three patients whose serum E_2 levels continued to rise until the day of hCG.

Another group (Urman *et al*., 1992), in an attempt to avoid cancellation of 40 cycles which had been overstimulated with exogenous gonadotrophins in patients with PCOD, withheld the gonadotrophins and continued to monitor by daily assays for E_2 and frequent ultrasound examinations. hCG was administered after a mean 2.8 days drift period. The clinical pregnancy rate per cycle was 25%, only one patient (2.5%) developed severe OHSS, and five patients developed twins (50% multiple pregnancy rate).

Coasting for IVF cycles

It has been suggested that prolonged coasting in GnRH agonist/hMG/FSH cycles might prevent life-threatening complications of OHSS (Sher *et al*., 1993). These authors withheld menotrophins in 17 patients whose serum E_2 levels exceeded 6000 pg/ml, and continued daily GnRH agonist treatment until serum E_2 levels had fallen below 3000 pg/ml. hCG was then administered to trigger ovulation. The coasting period lasted between 4 and 9 days, after which six of the 17 cycles (35%) produced viable pregnancies. All 17 patients developed signs of grade 2 or 3 OHSS, but none developed severe OHSS. In another trial, the same group (Sher *et al*., 1995) treated 51 women at great risk of developing OHSS by coasting until the plasma E_2 level fell to <3000 pg/ml. The mean number of embryos transferred per procedure was 5.4, and there were 21 clinical pregnancies (41% per oocyte retrieval), but none of the women developed severe OHSS.

In a pilot study, 66 at-risk patients were coasted and hCG was given when the serum E_2 level reached 2500 pg/ml, but four patients developed OHSS (Ben-Nun *et al*., 1993).

A retrospective study of 120 women considered to be at risk of OHSS (Dhont *et al*., 1998) were coasted when serum E_2 levels exceeded 2500 pg/ml, and hCG was delayed until E_2 levels fell below 2500 pg/ml. Outcomes were compared with those from 120 matched OHSS high-risk patients, but without coasting. Coasting was found significantly to decrease the incidence of both moderate and severe OHSS.

In a multicentre trial (Waldenstrom *et al*., 1999), 65 IVF cycles were severely hyperstimulated, and 'coasting' was carried out until the serum E_2 level fell below 10 000 pmol/l (mean 4.3 days). Four cycles were cancelled, and a pregnancy rate of 42% per started cycle, with an implantation rate of 31%, was achieved. Only one patient developed severe OHSS.

In another study (Lee *et al*., 1998), four out of 20 patients developed severe OHSS despite coasting. The mean duration of coasting was 3 days and hCG was administered on the day that serum E_2 levels began to fall. The conclusion of the authors was that this was too early to administer hCG.

A prospective randomized study was conducted to evaluate the incidence of OHSS and the cycle cancellation rate in 49 high-risk patients using a reduced hMG dose in one arm and continuation of the same dose in the other arm before coasting (Aboulghar *et al*., 2000). The duration of coasting was significantly reduced when the hMG dose was reduced, but there were no cases of severe OHSS reported in either group after coasting.

In another study, 112 severely over-stimulated IVF/ICSI patients were treated with coasting when the serum E_2 level was >3000 pg/ml and the leading follicles had attained a diameter of ⩾18 mm (Grochowski *et al*., 2001). Fertilization failure was noted in six couples, and in another 10 cases it was decided to freeze all of the embryos. A pregnancy rate per patient of 30.4%, with an implantation rate of 18.1%, was reported, while six patients developed moderate and two severe OHSS.

Three groups of IVF-embryo transfer patients—namely, a group of highly responsive coasted patients, a group of equally responsive non-coasted patients, and an age-matched normally responsive control group—were also studied (Tortoriello *et al*., 1998a). Two groups of coasted patients were also compared to assess the effect of E_2 levels at the time that they met the follicular criteria for hCG administration. Lastly, the effect of varying coasting duration was examined by regression analysis. Coasting had no detrimental effect on cycle outcome in the subset studied. Regression analysis, however, suggested an inverse relationship between coasting duration and the number of mature oocytes retrieved as well as the clinical pregnancy rate.

The same group also observed patients who developed severe OHSS (despite coasting) as gonadotrophins were withheld when serum E_2 levels were 14 700 pmol/l (Tortoriello *et al*., 1998b). Similarly, a higher than expected incidence of severe OHSS (33%) was encountered when coasting was started with serum E_2 levels >29 400 pmol/l and a large number of follicles with diameter >18 mm.

Coasting was effective in preventing OHSS in five patients with PCOD who had developed severe OHSS in a previous stimulation cycle (Ohata *et al*., 2000).

Gonadotrophin administration was withheld in 22 patients at risk of OHSS and hCG was administered when serum E_2 levels fell to ⩽3000 pg/ml (Benadiva *et al*., 1997). Outcomes were compared with 26 patients in whom embryo transfer was cancelled and all embryos cryopreserved for transfer during a subsequent unstimulated cycle. The authors commented that the fertilization rates, delivery rates and incidence of OHSS did not differ significantly between the two groups. Their conclusion was that coasting could provide a high pregnancy rate, without the need to repeat multiple frozen–thawed cycles.

A modified coasting protocol was developed in which identification of patients at risk of severe OHSS was based on ultrasound monitoring (Al-Shawaf *et al*., 2001). Serum E_2 levels were measured only in patients with >20 follicles on ultrasound. Overall, moderate OHSS occurred in three patients (0.7%) and severe OHSS in one patient (0.2%). The pregnancy

rate in the cycles where the gonadotrophin dose was reduced or withheld was 39.6 and 40% per cycle respectively.

Others (Al-Shawaf *et al*., 2002) also determined that measuring serum FSH in addition to E_2 during coasting in patients at high risk of developing OHSS can assist in predicting the point at which the serum E_2 level had declined to a sufficiently safe point to administer hCG in order to trigger ovulation.

The results of a pilot study suggested that withholding gonadotrophins at an earlier stage in patients at risk of developing OHSS was consistent with good clinical outcome (Egbase *et al*., 2002).

It is also possible to use coasting in GnRH antagonist cycles. In one case report, a GnRH antagonist was used to stop the LH surge in a patient who had been stimulated using the FSH/GnRH antagonist protocol, and who was at risk of OHSS (De Jonge *et al*., 1998). hCG was withheld and antagonist continued, whereupon the serum E_2 levels fell and OHSS was prevented. Coasting was also effective in preventing OHSS in two high-risk patients receiving a GnRH antagonist/FSH protocol (Delvigne *et al*., 2001). One pregnancy was obtained, but there was no effect on oocyte retrieval, fertilization or cleavage rate.

In a Cochrane review on coasting for the prevention of OHSS, 13 studies were identified but only one trial met the inclusion criteria (D'Angelo and Amso, 2002). It was concluded that insufficient evidence was available to determine whether coasting was an effective strategy to prevent OHSS. However, only one prospective study with 15 patients was included in each study arm comparing coasting with unilateral follicular aspiration, a technique that is seldom used. The Cochrane review stressed the absence of high-quality studies, and this limited to a great extent the conclusions that could be drawn.

Another group (Delvigne and Rozenberg, 2001) assessed whether physicians modify their preventive attitude in relation to clinical factors and to the E_2 response chart. Three case scenarios with three levels of risk factors for OHSS were constructed. At random, three out of the 12 artificially constructed case scenarios were sent to 573 physicians who are members of the ESHRE. Among the selected preventive measures, coasting was by far the most popular choice (60%), followed by the use of i.v. albumin or hydroxyethyl starch solution (36%) and cryopreservation of all embryos (33%).

The limitations of conducting a survey across a large number of countries where the availability of facilities in each unit, the statutory regulations in any particular country and the clinicians' preferences would ultimately have restricted the results obtained, which may not have reflected evidence-based best practice.

In a retrospective study, an attempt was made to define the optimal interval of coasting in patients at risk of developing OHSS (Ulug *et al*., 2002). Patients were grouped according to the number of days elapsed between cessation of gonadotrophins and administration of hCG. Patients in whom coasting lasted $\geqslant$4 days had significantly reduced implantation compared with patients with a shorter coasting interval. Others (Tortoriello *et al*., 1998a) reported that coasting for >3 days did not have any adverse effect on oocyte quality and subsequent fertilization.

The reasons why coasting is effective in preventing OHSS are speculative. Although high E_2 levels are associated with OHSS, it is unlikely that they are causally involved in its development. Hence, reduction of E_2 levels in itself is not the main goal of coasting (Dhont *et al*., 1998). It has been hypothesized (Tortoriello *et al*., 1998a) that coasting may diminish the functional granulosa cell cohort, resulting in the gradual decline in circulating levels of E_2 and, perhaps more importantly, in a reduction of the chemical mediators or precursors that augment fluid extravasation. During coasting, E_2 levels initially increased before falling, illustrating that at least dominant follicles can continue their growth in the face of a virtually absent stimulus, whereas intermediate follicles will undergo atresia. This, presumably, is one reason for the efficacy of coasting in preventing OHSS. Most studies on coasting have presented encouraging results, and have suggested that the chances of pregnancy remain unaffected while the risk of severe OHSS is diminished. However, all except one of these studies were retrospective in nature and used a variety of protocols. No current consensus exists as to how such a study should be carried out. Most of those physicians surveyed who would use coasting selected an E_2 level of 3000 pg/ml as a safe value for the administration of hCG (Sher *et al*., 1995; Benadiva *et al*., 1997; Tortoriello *et al*., 1998a; Egbase *et al*., 1999; Fluker *et al*., 2000; Ohata *et al*., 2000). It has been noted that prematurely reducing or withholding gonadotrophins prior to follicular maturation may lead to arrest of follicular growth (Ben-Nun *et al*., 1993; Sher *et al*., 1995; Benadiva *et al*., 1997; Dhont *et al*., 1998; Waldenstrom *et al*., 1999).

There is a need for excessive caution in interpreting the results of coasting studies. It is recommended that well-designed, large prospective randomized studies should be performed to compare and evaluate different modalities for prevention of OHSS. Correctly handled, this is believed to be a major advance in the search for improved stimulation policies for high-responders and an effective method for the prevention of OHSS (Table II). In conclusion, there is a need to exercise caution in interpreting the coasting studies.

Intravenous albumin for prevention of OHSS

The suggestion that i.v. albumin might prevent the development of severe OHSS was first made in 1993 (Asch *et al*., 1993). These authors administered 50 g human albumin intravenously to 36 women who were considered at risk for the development of severe OHSS during and immediately after oocyte retrieval, and in no case did severe OHSS develop. Subsequently, the results of the study were questioned (Morris and Paulson, 1994), the claim being that the study was not controlled, the sample size was small, the embryo transfer rate was low (15/36), and patients were followed for only 5 days

Table II. Coasting studies for prevention of ovarian hyperstimulation syndrome (OHSS) in IVF cycles

Study	Type	No. of patients	Days of coasting	Serum E_2 level on day of hCG (pg/ml)	Pregnancy (*n*)	Patients with severe OHSS (*n*)
Sher *et al*. (1993)	Pilot	17	4.8	3000	6 (35)	0
Ben-Nun *et al*. (1993)	Pilot	66	NS	2500	17 (26)	4
Sher *et al*. (1995)	Pilot	51	6.1	3000	21 (41)	0
Benadiva *et al*. (1997)	Retrospective	22	1.9	2206	14 (64)	0
Dhont *et al*. (1998)	Controlled	120	1.9	2348	45 (37.5)	1
Tortoriello *et al*. (1998a)	Controlled	22	>2	2282	12 (57)	2
Lee *et al*. (1998)	Pilot	20	3	3000	8 (40)	4
Waldenstrom *et al*. (1999)	Multicenter	65	4.3	2724[a]	27 (42)	1
Aboulghar *et al*. (2000)	Controlled	49	2.35	4500	15 (31)	0
Grochowski *et al*. (2001)	Pilot	112	3.5	3000	31(30.4)	2
Al-Shawaf *et al*. (2001)	Prospective	50	3.4	2724[a]	20 (40)	1
Egbase *et al*. (2002)	Pilot	102	3	2169	46 (45)	0

Values in parentheses are percentages.
[a]E_2 converted to pg/ml.
NS = not stated.

post-oocyte retrieval. However, several studies were later published which supported the proposal that i.v. albumin is effective in the prevention of OHSS.

Another group (Shoham *et al*., 1994) performed a prospective, randomized, placebo-controlled study on 31 patients who had a mean serum E_2 level of 1906 pg/ml and multiple follicular development on the day of hCG administration. After hCG administration, 31 patients were randomized to receive i.v., either 50 g human albumin diluted in 500 ml sodium chloride 0.9% or saline alone, at the time of oocyte retrieval. No patient who had received human albumin solution developed severe OHSS. There were four cases of OHSS in the control group, and all four were hospitalized with marked ascites and ovarian enlargement. Moreover, there were no differences in all parameters between both groups, including pregnancy rate.

Next, the effectiveness of a single dose of human serum albumin (20 g) administered i.v. immediately after oocyte retrieval was investigated in a prospective, randomized study (Shalev *et al*., 1995). There was a significantly higher number of severe OHSS cases in the control group ($n = 4$) than in the treatment group ($n = 0$) ($P = 0.035$).

Intravenous albumin was given to 30 consecutive patients with serum E_2 levels $\geqslant$3600 pg/ml on the day of hCG and/or $\geqslant$20 oocytes retrieved, and the effects compared with 42 consecutive patients with the same criteria but not receiving i.v. albumin (Chen *et al*., 1997). None of the patients in the treatment group in non-conception cycles developed OHSS, compared with 21.7% in the control group. In conception cycles, 28.6% in the treatment group developed severe OHSS, as compared with 47.4% of in the control group. All four patients with multiple pregnancies in the treatment group developed severe OHSS, compared with three of five in the control group. The authors commented that i.v. albumin seemed to prevent severe OHSS in high-risk patients who did not conceive or who carried singleton pregnancies, but not in the patients with high-order pregnancies. One problem with this study was that the luteal phase was supported with hCG and progesterone, when it is well documented that luteal phase supplementation with hCG increases the risk of OHSS (Araujo *et al*., 1994).

In a prospective randomized study, patients with E_2 levels $\geqslant$3000 pg/ml on the day of hCG were assigned to one group, which received 50 ml of 20% human albumin infusion (= 10 g albumin) before oocyte retrieval, or to another (control) group which received no medication. No OHSS developed in the i.v. albumin group, whereas one severe and four moderate OHSS cases developed in the control group. The difference was significant in favour of albumin treatment (Isik *et al*., 1996).

By contrast, several reports have shown that i.v. albumin does not prevent OHSS. For example, two patients developed severe OHSS despite the i.v. administration of 50 g albumin at the time of oocyte retrieval (Mukherjee *et al*., 1995).

A case was also reported of severe early OHSS which developed despite the administration of i.v. human albumin in an attempt to prevent severe OHSS (Orvieto *et al*., 1995). Others (Ng *et al*., 1995) performed a cohort study to compare the effect of i.v. administration of either 1000 ml lactated Ringer's solution or two doses of 50 g human albumin on patients at risk of OHSS. Severe OHSS developed in two patients who received human albumin, and in 10 women who did not receive albumin. A report was also made of five women who received i.v. albumin and two patients developed severe OHSS despite withholding embryo transfer (Lewit *et al*., 1996).

Among 60 women who were at high risk of developing severe OHSS and who were given 45 g i.v. albumin during and immediately after oocyte retrieval, five (8%; including three who were pregnant) developed severe OHSS which led to hospitalization. The mean serum E_2 level was 5052 pg/ml on the day of hCG administration (Ndukwe *et al*., 1997).

In a prospective, randomized, placebo-controlled, double-blind study, 98 women were consecutively assigned to either an i.v. albumin (n = 46) or a control (n = 41) group (Ben-Chetrit *et al*., 2001). Four patients in the i.v. albumin group developed severe OHSS and five developed moderate OHSS. In the control group, one patient developed severe OHSS and five patients developed moderate OHSS. The difference in OHSS incidence rates between the two groups was not statistically significant. The authors commented that albumin appears to have no positive effect on OHSS or conception rates, while its use carries the risk of undesirable side effects, including exacerbation of ascites in OHSS, nausea, vomiting, febrile reaction, allergic reaction, anaphylactic shock and risk of virus and prion transmission.

In a prospective randomized study, i.v. albumin and transfer of fresh embryos was compared with cryopreservation of OHSS in 26 patients considered to be at high risk of developing severe OHSS (Shaker *et al*., 1996). None of the patients in either arm of the study developed severe OHSS. The pregnancy rate was 38.5% in the cryopreservation group, compared with 0% in the i.v. albumin and fresh embryo transfer group. The authors were unable to provide an adequate explanation as to why none of the 13 patients in the group receiving i.v. albumin became pregnant.

Recently, in an updated Cochrane Review on the use of i.v. albumin to prevent severe OHSS (Aboulghar *et al*., 2002), seven randomized controlled trials were identified, five of which met the inclusion criteria and 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 (OR 0.28; 95% CI 0.11–0.73). The relative risk was 0.35 (0.14–0.87) and the absolute risk reduction was 5.5. For every 18 women at risk of severe OHSS, albumin infusion will save one more case of OHSS. The reviewers' conclusion was that i.v. albumin shows a clear benefit in the prevention of severe OHSS. However, whether the number needed to treat (NNT) would justify the routine use of albumin in high-risk patients must be judged by the clinical decision makers and future large randomized trials.

Details of the controlled studies using i.v. albumin versus placebo for prevention of OHSS are listed in Table III.

The use of i.v. albumin as prophylaxis against OHSS was based on past experience with albumin in other forms of third-space fluid accumulation, which showed its efficacy in preventing and correcting hemodynamic instability (Tullis, 1977a). The exact mechanism by which treatment with human albumin may prevent the development of severe OHSS remains unknown. Albumin has a low molecular weight, and its average normal half-life is 17–20 days; it also has both osmotic and transport functions (Shoham *et al*., 1994) and it contributes approximately 75% of the plasma oncotic pressure (Tullis, 1977b).

Human albumin is non-toxic and safe from viral contamination (McClelland, 1990; Erstand, 1991), and it is convenient to use as no cross-matching is required. However, it should be administered with caution to patients with diminished cardiac reserve because a rapid increase in plasma volume may cause circulatory embarrassment and pulmonary oedema (McClelland, 1990; Erstand, 1991). A slow rate of administration is always desired.

By contrast, it has been reported that i.v. albumin administration is not without its own dangers (Ndukwe *et al*., 1997). These authors believe that, under circumstances of volume depletion (as in OHSS), the oncotic action of albumin lasts for <36 h (Rackow *et al*., 1983), after which the albumin leaves the intravascular space and moves into the interstitium where it can draw fluid from the intravascular space. This has the potential of actually worsening OHSS. In addition, if derangement of capillary permeability is the basic pathology, it is questionable whether the duration of the oncotic effect of albumin would be sufficient to prevent OHSS. The authors also added that albumin is a human product, and the manufacturers state that the risk of transmitting infection by blood-borne viruses (including HIV and hepatitis virus) cannot be excluded entirely.

As an alternative to human albumin, 1000 ml 6% hydroxyethyl starch solution was infused at the time of oocyte collection, followed by another 500 ml 48 h later, in 100 IVF patients considered to be at risk of developing OHSS (Graf *et al*., 1997). Two patients developed severe OHSS, compared with seven patients in a matched group of 82 who did not receive i.v. starch. The difference was not statistically significant, but there was a highly 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 (Konig *et al*., 1998).

A prospective randomized, placebo-controlled clinical trial was carried out in 250 patients considered at risk of developing OHSS (Gokmen *et al*., 2001). Patients were randomized to receive either 50 ml of 20% human albumin:6% hydroxyethyl starch (HES) (n = 82) or a placebo during oocyte collection. There was no severe OHSS in patients who received albumin and HES, while four patients who received placebo developed severe OHSS. From the available data, it seems that HES is a cheap and safe alternative to human albumin in the prevention of OHSS. Both HES and albumin significantly reduced the overall incidence of moderate and severe OHSS, but neither completely prevented occurrence of the syndrome.

Cryopreservation of all embryos for future transfer

In one of the first reports on patients at risk of developing OHSS, four women underwent oocyte retrieval but not embryo replacement (Amso *et al*., 1990). The embryos were cryopreserved for future transfer, and three of the women conceived after thawed embryo replacement.

Among 33 high-risk patients monitored for the development of OHSS (Salat-Baroux *et al*., 1990), fresh embryo transfer was deferred; embryo transfer was subsequently performed artificially in 87% of the deferred cycles. Only one severe case of

Table III. Intravenous albumin for prevention of ovarian hyperstimulation syndrome (OHSS): controlled studies versus placebo

Study	Type	No. of patients			Albumin dose	E_2 level on day of hCG (pg/ml)	No. OHSS (albumin)	No. OHSS (control)
		Total	Albumin (i.v.)	Control				
Shoham *et al*. (1994)	Prospective randomized	31	16	15	50 g	1906	0	4
Shalev *et al*. (1995)	Prospective randomized	40	22	18	20 g	>2500	0	4
Isik *et al*. (1996)	Prospective randomized	55	27	28	10 mg	⩾3000	0	4
Ben Chetrit *et al*. (2001)	Prospective randomized	87	46	41	50 g	2724	4	1
Ng *et al*. (1995)	Cohort controlled	207	49	158	50 g	2724	2	10
Chen *et al*. (1997)	Prospective historical control	72	30	42	According to BMI	⩾3600	4	14

Odds Ratio = 0.42; 95% CI 0.21–0.88 ($P = 0.012$).
BMI = body mass index.

Table IV. Cryopreservation for prevention of ovarian hyperstimulation syndrome (OHSS): controlled studies

Study	Type	Total	Cryo	Control	E_2 level day of hCG in study group (pg/ml)	Pregnancy		Severe OHSS	
						Cryo	Control	Study	Control
Awonuga *et al.* (1996)	Retrospective controlled	117	52	65 (fresh ET)	2724 and or >15 oocytes	18 (35)	11 (17)	2 (3.1)	0
Shaker *et al*. (1996)	Prospective randomized	26	13	16 (i.v. albumin)	5060	5 (38.5)	0	0	0
Benavida *et al.* (1997)	Retrospective controlled	48	26	22 (coasting)	4390	13 (50)	14 (63.6)	2 (7.7)	1 (4.54)
Ferraretti *et al.* (1999)	Prospective randomized	125	58	67 (fresh ET)	2498	28 (48.3)	31 (46.5)	0	4 (5.97)
Endo *et al.* (2002)	Prospective randomized	138	68	70 (cryo + continue GnRH agonist)	5817	22 (20)	20 (29)	7 (10.3)	0

Odds Ratio = 2.43; 95% CI 0.83–7.11 ($P = 0.08$).
Values in parentheses are percentages.
ET = embryo transfer.

OHSS occurred, thereby emphasizing the caution needed, even with this technique.

Another group (Wada *et al*., 1993) electively cryopreserved all the embryos from women with a serum E_2 level >3500 pg/ml on the day of hCG. This approach reduced the severity, but not the incidence, of OHSS.

In a retrospective study of 69 patients at risk of OHSS, cryopreservation of all embryos and delayed embryo transfer resulted in a low incidence of severe OHSS (1.8%), and thawed embryo replacements resulted in 25.2% pregnancy rate per treatment (Pattinson *et al*., 1994).

Others (Tiitinen *et al*., 1995) cryopreserved all embryos in 23 patients at risk of OHSS; subsequently, one patient developed moderate OHSS, and frozen–thawed embryo transfer achieved a pregnancy rate of 32.6%. Pregnancy outcome was also shown to be successful after cryopreservation of all fresh embryos with subsequent transfer into an unstimulated cycle (Fredrick *et al*., 1995).

In 15 patients at risk of OHSS, cryopreservation of all fertilized oocytes was carried out at the pronuclear stage (Queenan *et al*., 1997). Two patients (13%) developed OHSS, and two others (13%) developed moderate OHSS. Subsequent transfer of cryopreserved–thawed embryos yielded a clinical pregnancy rate of 58% per transfer. It was concluded that OHSS was reduced, but not eliminated in patients at risk.

The details of five controlled trials (two retrospective and three prospective) are listed in Table IV. In a prospective randomized study of patients at risk of OHSS, fresh embryo transfer was carried out in 67 patients, and all embryos were cryopreserved in 58 patients (Ferraretti *et al*., 1999). No cases of OHSS occurred in the cryopreservation group, compared with four cases in the fresh group.

Others (Endo *et al*., 2002) conducted a controlled study (n = 138) to compare the elective cryopreservation of all embryos versus elective cryopreservation of embryos followed by continuation of GnRH agonist administration for 1 week. Continuation of GnRH agonist prevented OHSS, while severe OHSS occurred in 10% of patients who had elective cryopreservation alone.

In a Cochrane Review (D'Angelo and Amso, 2002), 17 studies were identified, two of which met the inclusion criteria. One study was included where cryopreservation was compared with i.v. albumin administration (Shaker *et al*., 1996), and one study was included where elective cryopreservation of all embryos was compared with fresh embryo transfer (Ferraretti *et al*., 1999). Intravenous albumin was administered to all

patients in the latter (1999) study. This may possibly have affected the incidence of severe OHSS, since when cryopreservation was compared with i.v. human albumin administration no difference was found in all the outcomes examined between the two groups. When elective cryopreservation of all embryos was compared with fresh embryo transfer, no difference was found in all the outcomes examined between the two groups. This review showed that, at present, there is insufficient evidence to support routine cryopreservation, and also insufficient evidence for to determine the relative merits of i.v. albumin versus cryopreservation.

Other measures for prevention of OHSS

Follicular aspiration: Various studies have demonstrated a protective value of follicular aspiration at the time of oocyte retrieval on OHSS outcome (Hazout *et al*., 1984; Laufer *et al*., 1990).

By contrast, many authors have claimed that follicular aspiration for IVF does not prevent OHSS (Friedman *et al*., 1984; Golan *et al*., 1988; Aboulghar *et al*., 1992). Selective oocyte retrieval by puncturing most of the follicles 35 h after hCG, leaving few follicles for spontaneous pregnancy, was successfully tried (Belaisch-Allart *et al*., 1988).

Early follicular aspiration of one ovary at 10–12 h after administration of hCG was considered to be an effective method of preventing OHSS (Tomazevic and Meden-Vrtovec, 1996).

One group (Egbase *et al*., 1997) performed a prospective randomized study in which unilateral ovarian follicular aspiration was either performed or omitted (controls) at 6–8 h before hCG injection in 31 patients who were at serious risk of OHSS. These authors concluded that unilateral ovarian early follicular aspiration prior to hCG trigger administration does not reduce the occurrence of severe OHSS in women at risk.

In another prospective randomized study (Egbase *et al*., 1999), early unilateral follicular aspiration was compared to coasting in 30 patients at high risk of developing OHSS. Four women in the first group, compared with three women in the second group, developed OHSS. Both lines were equally ineffective in the prevention of OHSS.

Ovarian cauterization for prevention of OHSS: One group (Fukaya *et al*., 1995) performed laser vaporization for 26 PCOD patients with a history of OHSS. Later, ovarian stimulation with gonadotrophins was carried out in 17 patients, but severe OHSS did not develop in any patient.

Fifty women with PCOD considered to be at high risk of OHSS following ovarian stimulation with a GnRH agonist long protocol, were randomized into two groups: laparoscopic ovarian cauterization versus no cauterization after pituitary down-regulation. In the no-cauterization group, five patients developed severe OHSS as compared with none in the control group (Rimington *et al*., 1997). These authors suggested that the technique might be useful in the prevention of OHSS.

Corticosteroids for prevention of OHSS: In a prospective randomized study, it was found that administration of glucocorticoids in high-risk patients did not reduce the rate of OHSS (Tan *et al*., 1992). By contrast, others (Lainas *et al*., 2002) reported that methylprednisolone 16 mg per day, starting on day 6 of the stimulation and tapered to day 13 after embryo transfer, was effective in significantly reducing the OHSS rate (10%) as compared with 43.9% in the control group.

Concluding remarks

Based on the findings of the present review, it be concluded that:

- Ovarian hyperstimulation syndrome is a serious complication of ovarian stimulation, which could be life-threatening.
- The identification of high-risk patients, and in particular PCOD patients and the use of low-dose protocols of ovarian stimulation, have an important role in the prevention of OHSS.
- To date, no methods are available to completely prevent this complication, except for withholding hCG and gonadotrophins and continuing GnRH agonist in down-regulated cycles. In gonadotrophin-only-stimulated cycles, even withholding hCG does not completely prevent the development of OHSS.
- Despite the increasing literature that proposes the use of coasting to prevent OHSS, there are as yet no well-designed randomized studies which provide the highest level of evidence to suggest the use of coasting in preference to other strategies. Equally, there is no evidence not to support its use. Attempts should be made to standardize the criteria used to initiate coasting and the administration of hCG.
- It appears that i.v. albumin administered at the time of oocyte retrieval may help in the prevention of OHSS, though the degree of protection offered is not complete.
- At present, there is insufficient evidence available either for or against the routine use of cryopreservation in the prevention of OHSS. Elective cryopreservation was as effective as i.v. albumin in reducing the incidence of moderate/severe OHSS.
- GnRH agonist treatment to trigger ovulation in gonadotrophin-only cycles or GnRH antagonist cycles may have a protective effect, as well as the use of single-dose recombinant LH to trigger ovulation.
- There is a clear need for large randomized studies to be conducted that would compare different modalities in women at high risk of OHSS, thus providing evidence-based practice.

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