

Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review

Annick Delvigne¹ and Serge Rozenberg

IVF Centre, Department of Obstetrics-Gynaecology, University Hospital St Pierre (Free University of Brussels ULB), Belgium

¹To whom correspondence should be addressed at: IVF Centre, Department of Obstetrics-Gynaecology, Free University of Brussels (ULB), St Peter Hospital, rue Haute 322, B-1000 Brussels, Belgium. E-mail: annickdelvigne@swing.be

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation occurring during the luteal phase or during early pregnancy. Fortunately, the reported prevalence of the severe form of OHSS is small, ranging from 0.5 to 5%. Nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potentially fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility. The aim of this literature review was to determine whether it is possible to identify patients at risk, and which preventive method should be applied when an exaggerated ovarian response occurs. Data pertaining to the epidemiology and prevention of OHSS in women were searched using Medline, *Current Contents* and PubMed, and are summarized. Preventive strategies attempt either to limit the dose or concentration of hCG or to find a way to induce luteolysis without inducing a detrimental effect on endometrial and oocyte quality. The following particular preventive strategies were reviewed: cancelling the cycle; coasting; early unilateral ovarian follicular aspiration (EUFA); modifying the methods of ovulation triggering; administration of glucocorticoids, macromolecules and progesterone; cryopreservation of all embryos; and electrocautery or laser vaporization of one or both ovaries.

Key words: coasting/IVF/OHSS/prevention/treatment

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation that occurs during either the luteal phase or early pregnancy. The most common form occurs a few days after the induction of the follicular rupture following the administration of hCG when follicular growth has been medically induced by using either clomiphene citrate or gonadotrophins, eventually in conjunction with agonists or antagonists of the GnRH.

In the initial form of OHSS, the increase in size of the ovaries is accompanied by abdominal discomfort. In a more advanced form, the ovaries become cystic and this will often result in abdominal distension and pain, nausea, vomiting and sometimes diarrhoea. This can be followed by the formation of a small amount of ascites which is sometimes only visualized through vaginal

ultrasound, though in more severe forms ascites is clinically identifiable. This extravascular protein-rich exudate accumulates in the peritoneum, in the pleura, and even in the pericardiac space and is associated with intravascular volume depletion and haemoconcentration, activation of vasoconstrictor and anti-natriuretic factors, severe hypoalbuminaemia and sometimes hypovolaemia, oliguria and electrolyte imbalance. Liver dysfunction can also occur. Thromboembolic phenomena are the ultimate complication of OHSS, and are sometimes fatal despite appropriate treatment (Mozes *et al.*, 1965; Cluroe and Synek, 1995).

At this stage of our knowledge of the aetiology of OHSS, we have to base our decisions about preventive strategies on the identification of indirect factors that have been associated with OHSS and are thought to have predictive value, as there is currently no specific treatment for the condition.

Fortunately, the prevalence of the severe form of OHSS is small, with reported values ranging from 0.5 to 5%. Nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potential fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility, and leads to two important clinical questions:

1. Is it possible to identify patients at risk?
2. Which preventive method should be applied when an exaggerated ovarian response occurs?

The aim of this systematic review of the literature was to answer these two questions. In order to limit the length of the review, we voluntarily did not address the subject of the aetiopathology of OHSS, as this has been assessed by numerous authors and remains essentially unresolved (Elchalal and Schenker, 1997).

The medical literature was reviewed using Medline, *Current Contents* and PubMed between 1990 and 2002 using the key words: ovarian hyperstimulation syndrome (OHSS) and IVF. Articles that had been referenced were also cited.

Epidemiology

Incidence

The reported incidence of OHSS is highly variable according to different studies because various classifications are used. Furthermore, these studies relate to very different clinical situations such ovulation induction using gonadotrophins or clomiphene citrate, or ovarian stimulation during IVF, which are not comparable in terms of therapeutic goals and strategies. Before the use of IVF, the reported incidence of OHSS using gonadotrophins varied between 8.4 and 23% for the mild form of OHSS, between 0.005 and 7% for the moderate form, and between 0.008 and 10% for the severe form (Schenker and Weinstein, 1978).

When using clomiphene citrate, the same authors reported an occurrence of 13.5% of mild forms of OHSS in 8029 cycles, while moderate and severe OHSS forms were described only sporadically. When considering IVF cases, the reported incidence of OHSS is 3–6% for the moderate form, and 0.1–2% for severe forms (Golan *et al.*, 1989; Schenker and Ezra, 1994; Brinsden *et al.*, 1995; Serour *et al.*, 1998). The mild forms of OHSS, which have little clinical relevance, constitute about 20–33% of the IVF cycles (Golan *et al.*, 1989; Morris *et al.*, 1995). It has been estimated (Schenker and Ezra, 1994) that world-wide, at least 100–200 women suffer annually from severe OHSS out of 100 000 cycles of ART that occurred during that time.

In the largest cohort reported in Israel (Abramov *et al.*, 1999), an increase in incidence of severe forms of OHSS was observed due to IVF. Indeed, while the number of severe OHSS cases following ovarian induction remained unchanged, the number of cases following IVF increased from an estimated 0.06% in 1987 to 0.24%. The increase in the incidence of severe OHSS surpassed the total IVF activity (20-fold versus six-fold respectively), hence entailing a substantial rise in the severe form (Abramov *et al.*, 1999). In summary, although the incidence of severe forms is about 1%, one should be aware of its recent, progressive increase.

Factors influencing the incidence of OHSS

Age

It has been reported in most studies that women suffering from OHSS were significantly younger than those who did not (Golan *et al.*, 1988; Navot *et al.*, 1988). For instance, in the latter study the mean age of the 54 OHSS patients was 27.8 ± 3.6 versus 31.5 ± 5.7 years in the 54 control cycles. In another study (Lyons *et al.*, 1994), the age distributions were 29.7 ± 1.8 years for OHSS versus 33.9 ± 0.15 years for controls, while in a large Belgian

population of 128 cases of OHSS (Delvigne *et al.*, 1993a) the mean age was 30.2 ± 3.5 years for OHSS versus 32.0 ± 4.5 years for 256 controls. The difference was also significant in a prospective study (Enskog *et al.*, 1999) including 49 cases of OHSS. A plausible explanation is that the ovaries of younger women are more responsive to gonadotrophins because they possess a higher density of gonadotrophin receptors or a larger number of follicles that are able to respond to gonadotrophins.

Body mass index (BMI)

Only one group (Navot *et al.*, 1988), with 54 OHSS cycles, has described a positive correlation between lean body mass and OHSS. No significant difference was observed in this respect in a large Belgian series of 85 OHSS versus 88 controls (Delvigne *et al.*, 1993a), while others (Lewis *et al.*, 1990; Enskog *et al.*, 1999) also failed to find a correlation between either BMI or body weight and propensity for OHSS. BMI does not appear to be a useful marker of increased risk for OHSS.

Allergies

Because the pathophysiological changes that occur in the ovaries during OHSS closely resemble an overactive inflammatory response with participation of immunomodulatory cytokines, it has been hypothesized (Enskog *et al.*, 1999) that differences in the immunological sensitivity of patients may be a predictive sign of OHSS. Indeed, in a prospective study recording 18 severe OHSS cases (Enskog *et al.*, 1999), a significant increase was observed in the prevalence of allergies (50 versus 21% in the control group); however, this observation should be studied through biological assessment on a larger cohort.

Aetiology of infertility

Although OHSS has been found as often in primary as in secondary infertility, its duration seems not to influence its incidence, as was shown in a study of these parameters and performance of logistic regression analyses of 54 OHSS cases and 54 controls (Navot *et al.*, 1988). Moreover, women who are at increased risk are those who have previously developed OHSS (Delvigne *et al.*, 1993b).

Polycystic ovary syndrome (PCOS): Oligomenorrhoea is thought to be a risk factor for OHSS patients, and patients belonging to oligomenorrhoeic anovulation group II according to the World Health Organization (WHO) classification were reported to suffer more often from OHSS after ovarian induction than patients diagnosed as the hypogonadotrophic amenorrhoea group I (Schenker and Weinstein, 1978; Navot *et al.*, 1988). The basal hormonal profile of OHSS patients usually revealed hyperandrogenism, and the ovaries showed PCOS characteristics at echography (Adams *et al.*, 1985) or at laparoscopic examination. Similarly, OHSS incidence was observed to be higher among patients who bled after a progestagen test (Tulandi *et al.*, 1984), which means that these patients had high levels of estrogen. Indeed, even in IVF cycles, PCOS appeared to be the major predisposing factor for OHSS in a large number of studies (Amso *et al.*, 1990; Smitz *et al.*, 1990; Asch *et al.*, 1991; Rizk *et al.*, 1992; Delvigne *et al.*, 1993a; MacDougall *et al.*, 1993; Todorow *et al.*, 1993). For example, in one series (MacDougall *et al.*, 1992), 63% of severe OHSS patients showed ultrasonically diagnosed PCOS, while in another study of 128 Belgian OHSS

patients, 37% suffered from PCOS compared with 15% among the 256 controls (Delvigne *et al.*, 1993a).

The explanation might be that PCOS cases are known to produce three times more follicles and oocytes than normo-ovulatory patients when stimulated according to similar protocols (Dor *et al.*, 1990; Buyalos and Lee, 1996; Shulman and Dor, 1997). An increased expression of vascular endothelial growth factor (VEGF) mRNA within the hyperthecal stroma of women with PCO has been reported, and this may be responsible for their higher risk of OHSS (Kamat *et al.*, 1995).

A higher incidence of OHSS is also observed in patients who suffer from certain isolated characteristics (such as PCOS-like ultrasonographic images) of PCOS, but not from a 'complete' form which fulfils clinical, echographical and biological criteria. One group (Tibi *et al.*, 1989) showed that in normo-ovulatory patients, the presence (at ultrasound) of 10 follicles or more which measured 4–8 mm in at least one ovary, was predictive of an exaggerated ovarian response and should be considered a risk factor for OHSS. This concept has been further described as the 'necklace sign' (Navot *et al.*, 1992), and suggests an increased incidence of OHSS risk even in the absence of other clinical or biological signs of PCOS (Brinsden *et al.*, 1995). Similarly, others (Levy *et al.*, 1996) reported a severe case of OHSS in a patient who was considered to be at very low risk for the condition as she suffered from hypogonadotrophic hypogonadism and had low serum estradiol (E_2) levels, but in whom this PCOS-like echographical image was the only recorded sign.

Using ovarian volumetry, one group (Danninger *et al.*, 1996) found a significant correlation between baseline ovarian volume (measured by 3-D ultrasonography) and the development of OHSS in 101 patients who underwent IVF. In addition, a significant correlation was found between the baseline number of follicles, the number of oocytes retrieved, and OHSS.

Some investigators evaluated intra-ovarian blood flow and identified a close correlation between OHSS severity and lowered resistance to blood flow in the stimulated ovaries (Moohan *et al.*, 1997). However, the predictive value of these data should be validated in larger series.

An LH:FSH ratio >2 has also been considered as a risk factor for OHSS, even in the absence of other signs of PCOS. This is one of the significant parameters which appeared in a discriminant analysis conducted to predict OHSS in a series of 128 cases (Delvigne *et al.*, 1993b). Others (Bodis *et al.*, 1997) also confirmed the importance of an increased LH:FSH ratio in 12 OHSS patients, and suggested that LH dominance leads to disturbed androgen-oestrogen conversion and to a higher propensity for OHSS. Likewise, a lower basal FSH was also observed in normo-ovulatory patients who developed OHSS (Tibi *et al.*, 1989).

Hyperandrogenism is the final example of 'isolated characteristics of PCOS', since women with an increased ovarian contribution to circulating androstenedione also constitute a group at risk for OHSS (Gustafson *et al.*, 1992; Bodis *et al.*, 1997). In cases of hyperandrogenism, some authors have suggested inhibiting androgen secretion by using small corticoid doses (Bettendorf and Lindner, 1987)

Hypogonadotrophic hypogonadism: Generally, this type of anovulation necessitates prolonged stimulation using higher doses of gonadotrophins, because lower E_2 levels than usual are

reached. Nevertheless, among these patients it is important to distinguish the primary from the secondary forms, as the latter may be associated with a shorter follicular phase, multiple folliculogenesis and a higher multiple pregnancy rate. It is possible that cases of OHSS may occur in this latter group of patients (Filicori *et al.*, 1991). Some authors have also observed high basal levels of prolactin in the group of OHSS patients (Navot *et al.*, 1988; Tibi *et al.*, 1989).

Types of stimulatory drugs

There is no doubt that the incidence of OHSS is related to the stimulation regimens used.

Clomiphene citrate: This is only rarely associated with severe forms of OHSS, although a moderate form of OHSS is encountered in about 8% of stimulation cycles when this drug is used (Kistner, 1965; Hammerstein, 1967).

HMG or purified FSH: A much higher incidence has been observed when using urinary gonadotrophins such as hMG or purified FSH. One group (Schenker and Weinstein, 1978) reported several studies which showed that the LH:FSH ratio in gonadotrophin preparations had only a moderate effect on the stimulation success rate and on the incidence of OHSS stimulation. Only in clomiphene-resistant PCOS was it demonstrated (using a meta-analysis of the Cochrane database) that there was an advantage in using purified forms of urinary FSH (Hughes *et al.*, 2000). Several studies have shown that, when using recombinant FSH (rFSH), the incidence of OHSS in women is comparable with that of women treated with urinary gonadotrophin, whether purified or not (Check *et al.*, 1985a; Hedon *et al.*, 1995; Aboulghar *et al.*, 1998). Finally, a systematic review and meta-analysis of 18 randomized, controlled trials, comparing recombinant (r)FSH and urinary FSH confirmed that there was no difference in the incidence of OHSS induced with these regimens (Daya, 2002).

Use of GnRH agonists: GnRH agonists have the effect of artificially bringing all patients, and even those with oligomenorrhoeic anovulation (group II, WHO classification), to a state of hypogonadotrophic anovulation (group I, WHO). A reduction in the number of OHSS cases would thus have been expected with this treatment. However, some authors showed that the increased ovarian sensitivity to gonadotrophins in women with PCOS is not affected by achieving preliminary pituitary desensitization with GnRH agonists (Walmer *et al.*, 1989). Since the introduction of GnRH agonists in 1986, a six-fold increase in the incidence of severe forms of OHSS has been observed as compared to the incidence among IVF cycles stimulated by clomiphene/hMG (Neveu *et al.*, 1987; Rabinovici *et al.*, 1987; Golan *et al.*, 1988; Caspi *et al.*, 1989; Forman *et al.*, 1990; Asch *et al.*, 1991; Hampton *et al.*, 1991; FIVNAT statistics of 1996). This unfavourable effect of GnRH agonists may be due to the abolition of the spontaneous luteinization process which is associated with the LH peak, and may be a mechanism preventing excessive follicular growth. Using GnRH agonists, the number of retrieved oocytes, the attained E_2 level and the number of corpora lutea each increased, as did eventually the incidence of OHSS (MacDougall *et al.*, 1992; Rizk *et al.*, 1992; Mordel and Schenker, 1993). Furthermore, GnRH agonist suppression confers a risk for OHSS on the patient, regardless of its being used in either short or long protocols (Whelan and Vlahos, 2000).

GnRH antagonists: In some controlled clinical trials the reported OHSS complication was lower using GnRH antagonists than with agonists (Olivennes *et al.*, 2002). A systematic review (Al-Inany and Aboulghar, 2002) selected five randomized trials of which the meta-analysis showed there to be no statistically significant reduction in the incidence of severe OHSS (Relative Risk: 0.51; 95% CI 0.22–1.18) using antagonist regimens as compared with the long GnRH agonist protocols. However, it should be borne in mind that if antagonists do not seem to reduce the incidence of OHSS, they still provide the opportunity to trigger ovulation using agonists instead of using hCG, and this may reduce the incidence of OHSS (Devroey, 2000), though the latter treatment regimen has not been tested in a randomized trial.

Medication to reduce insulin-resistance: A much higher OHSS risk has been seen in patients with PCOS in whom hyperinsulinaemia had been documented (Fulghesu *et al.*, 1997). Certain medications (metformin and octreotide) have been used to reduce insulin resistance in PCOS patients (Dunaif *et al.*, 1996), and the number of mature follicles and E₂ levels were significantly lower with these treatments (Morris *et al.*, 1999), although no reduction has been reported in the incidence of OHSS in either ovulation induction or IVF. One group (Fedorcsak *et al.*, 2001) found similar incidences of OHSS in insulin-resistant ($n=26$) and non-insulin-resistant ($n=30$) PCOS women during 100 IVF cycles, while others (Delvigne *et al.*, 2002a) investigated whether a higher incidence of hyperinsulinism was to be found in 25 matched IVF women who had suffered from OHSS. The latter study did not provide any evidence for an increased prevalence in hyperinsulinism among women who had developed OHSS in the past and who did not suffer from PCOS.

In conclusion, no stimulation regimen can (as yet) claim to avoid all risk of OHSS. A correct evaluation of the patient's clinical profile may allow the clinician to individualize the stimulation regimen in order to minimize the risk of OHSS. Close monitoring will be more effective in detecting risk situations and preventing OHSS, rather than simply relying on a particular medication regimen (Whelan and Vlahos, 2000).

Gonadotrophin dosage

There appears to be no linear positive relationship between hMG quantity and OHSS incidence. On the contrary, patients suffering from OHSS often receive much less hMG than others (Navot *et al.*, 1988; Smitz *et al.*, 1990; MacDougall *et al.*, 1992; Delvigne *et al.*, 1993a; Enskog *et al.*, 1999). Ovarian hypersensitivity to hMG, as reflected by higher E₂ peak concentrations in response to low dosages of hMG and by a steeper slope of E₂ increment during stimulation, has been reported in two large cohorts (Delvigne *et al.*, 1993a; MacDougall *et al.*, 1993), where $n=128$ and 76 respectively.

Consequently, in patients at risk of developing OHSS (e.g. PCOS patients), the dosage regimens of hMG should be well controlled. For example, the low step-up regimen in ovarian induction or the low-dose stimulation protocol (LDS) in IVF allows the incidences of both multiple pregnancy and OHSS to be reduced (MacDougall *et al.*, 1992; Shoham *et al.*, 1993; Marci *et al.*, 2001). Likewise, others (Forman *et al.*, 1990) halved the initial dosage of gonadotrophins when risk factors of developing OHSS were present, and none of their 10 patients developed

OHSS when using a dose of hMG which had been reduced by half.

In a prospective study of 'limited ovarian stimulation' (LOS) in an IVF programme dealing with patients affected by PCOS who had developed severe OHSS in the past (El-Sheikh *et al.*, 2001), hCG was administered when the leading follicles reached a mean diameter of only 12 mm. Among these patients no recurrence of OHSS was observed, despite a pregnancy rate of 40% being reached. It seems thus that a logical prevention strategy consists of adapting the ovulation stimulation scheme in patients at risk for OHSS in order to decrease its incidence, rather than applying a systematic decrease of the stimulation doses in all patients (Seibel *et al.*, 1985; Buvat *et al.*, 1989).

The effect of renal impairment on the metabolism of FSH should also be considered as 10% of rFSH is excreted into the urine, and renal metabolism of human FSH may occur (Ben-Rafael *et al.*, 1995). The delayed clearance of FSH from the circulation may enhance the stimulatory effect of normal daily doses (Hampton *et al.*, 1991; Khalaf *et al.*, 2000). It was therefore suggested that dosages of gonadotrophins be adapted in relation to renal function.

Exogenous hCG to induce ovulation

In most stimulation schemes for fertility treatment, ovulation is induced using hCG of urinary origin, and this has been chosen for its LH-like effect. hCG is characterized by a longer half-life than LH (>24 h versus 60 min for LH), a higher receptor affinity, and a longer duration of intracellular effect compared with endogenous LH. Consequently, the duration of hCG activity lasts for up to 6 days (Casper, 1996). Urinary hCG is not only able to separate the cumulus-oophorus complex from the follicular wall and induce final maturation of the oocytes, but also has a certain FSH-like effect which contributes to ovarian stimulation. This has been shown in a study of peri-ovulatory and luteal phase endocrinological characteristics following LH induction by the flare-up of GnRH and its agonists as compared with hCG administration (Gerris *et al.*, 1995). Indeed, after hCG administration these authors identified similar pre-ovulatory levels of E₂, but superior levels of post-ovulatory E₂ and progesterone. hCG is a well-known promoter of OHSS and appears to initiate the complex cascade that leads to the development of symptomatic hyperstimulation, whereas an endogenous LH surge rarely causes OHSS.

Normal doses of hCG are 10 000 IU, but doses ranging from 2000 to 25 000 IU have been used. The pregnancy rate seems not to vary for doses >5000 IU (Thompson *et al.*, 1970; Abdalla *et al.*, 1987). One group (Schenker and Weinstein, 1978) reported fewer cases of OHSS when using 1000–5000 IU, but this study was not controlled; hence, it has been suggested that a dose of 5000, rather than 10 000 IU be used in the presence of risk factors for OHSS (Navot *et al.*, 1992; Amso, 1995; Whelan and Vlahos, 2000).

Alternatives to hCG: As LH activity is characterized by a shorter duration compared with hCG, LH administration may reduce stimulation of the luteal ovary. Some authors have proposed using the flare-up effect of the GnRH agonists to produce ovulation (Gonen *et al.*, 1990; Emperaire and Ruffie, 1991; Imoedemhe *et al.*, 1991; Itskovitz-Eldor *et al.*, 1993; Balasch *et al.*, 1994; Shalev *et al.*, 1995a; Ben-Arie *et al.*, 1996; Kol *et al.*, 1996; Olivennes *et al.*, 1996; Kol and Itskovitz-Eldor,

2000; Fauser *et al.*, 2002). Indeed, the rise in LH and FSH lasts for only 34 h following a GnRH agonist flare-up (500 µg leuprolide acetate given subcutaneously).

This alternative can be applied when no down-regulation is used for stimulation. The recent development of a GnRH antagonist to avoid a spontaneous LH surge, also permits the use of a GnRH agonist to induce the LH peak (Albano *et al.*, 1997; Wu, 2000). This combination of initial gonadotrophin 'flare-up' followed by pituitary down-regulation offers a unique advantage to minimize the risk of OHSS. Some authors have used this method to treat women with extremely high levels of E₂ (>4000 pg/ml) (Imoedemhe *et al.*, 1991; Itskovitz *et al.*, 1993), though in none of these studies did patients develop any sign or symptoms of OHSS. Using this approach in a large group of 682 high responders (mean E₂ 7817 pg/ml) with PCOS, the former group (Imoedemhe *et al.*, 1999) observed only 0.1% incidence of severe OHSS. Some investigators triggered ovulation with different subcutaneous doses of triptorelin in ovulation induction, and reported similar observations (Shalev *et al.*, 1995a). However, the triptorelin dosage necessary to induce ovulation (0.1 mg) seems to be lower than that used to prevent OHSS (0.5 mg). The nasal dose route also seems to be less efficient in inducing ovulation (van der Meer *et al.*, 1993; Shoham *et al.*, 1995; Kol *et al.*, 1996). Indeed, among eight cases of OHSS that occurred using this method of ovulation induction, none developed ascites (Kol *et al.*, 1996), whereas most of these cycles were at increased risk of OHSS and hCG supplementation was used during the luteal phase (Casper, 1996).

Unfortunately, insufficient controlled studies have been carried out to validate this practice; very few controlled studies have compared the mid-cycle use of hCG with a GnRH agonist (Segal and Casper, 1992; Kulikowski *et al.*, 1995; Shalev *et al.*, 1995b), and none of these small series has permitted any definitive conclusions to be made.

Native GnRH also constitutes alternatives, but their efficiency in reducing OHSS incidence still needs to be assessed. In one controlled study with native GnRH, GnRH agonist and hCG (Gerris *et al.*, 1995), it was observed that cycles with an endogenous LH surge generally resulted in fewer subclinical signs of OHSS (recorded by a subtle luteal score to detect minor OHSS signs). The same authors observed one case of OHSS, after use of native GnRH (500 µg). These results were interpreted by others (Kol *et al.*, 1996) as a consequence of successful ovulation triggering, without critical gonadotrophin suppression which is one of the elements that prevents OHSS by use of a GnRH agonist. In addition, one group substituted purified human pituitary LH for hCG in ovulation induction cycles, without avoiding OHSS (Vande Wiele *et al.*, 1970).

Finally, a recent European prospective randomized double-blind ($n=259$) multicentre study assessed the safety and minimal effective dose of recombinant human LH (rhLH) in patients undergoing IVF in comparison with 5000 IU of urinary hCG. This study concluded that a doses of 5000 and 15 000 IU rhLH induced significantly fewer moderate cases of OHSS and ascites compared with 5000 IU doses of hCG (respectively 18% and 21% versus 45%). The difference was not statistically significant between repeated doses and a single dose of 30 000 IU rhLH, and the presence of ascites correlated with the total rhLH dose

administered (The European Recombinant LH Study Group, 2001).

Response to ovulation stimulation

Many investigators have shown that elevated levels of estrogen constitute a risk factor for OHSS (Crooke, 1970; Haning *et al.*, 1983; Navot *et al.*, 1988). In 1970, a correlation was demonstrated between the pre-ovulatory urinary estrogen and the incidence of severe OHSS (Crooke, 1970), while in a series of 70 ovulation induction cycles with menotrophins (Haning *et al.*, 1983) serum E₂ level was found to be the only predictive factor for OHSS. Others (Asch *et al.*, 1991) attempted to identify a high-risk group among 637 IVF patients, with six (0.94%) suffering from severe OHSS. In this group, none of the patients with E₂ serum levels <3500 pg/ml developed OHSS, while 1.5% of those with E₂ levels of 3500–5999 pg/ml and 38% with E₂ levels >6000 pg/ml developed OHSS. These authors identified a sensitivity of 83% and a specificity of 99%, but the positive predictive value was only 38%.

Another group (Morris *et al.*, 1995) discussed the predictive value of E₂, and found only 8.8% of OHSS cases among patients with E₂ levels >6000 pg/ml ($n=34$). This rather low incidence was probably due to the mixed population studied, which also included oocyte donors, as when a more homogeneous group of IVF cycles with oocyte transfer was considered the incidence was 17% ($n=18$). An additional group, using a cohort of 78 early and late OHSS patients, determined the oocyte number and peak E₂ level that best discriminated cycles with and without OHSS (Marthur *et al.*, 2000). These authors calculated the sensitivity and specificity for different cut-off limits: only a moderately significant positive likelihood ratio (LR) of 6.37 was obtained for an E₂ level >2642 pg/ml, while a moderately significant negative LR (0.13) was obtained for an E₂ level <1847 pg/ml. Although mean E₂ levels are significantly higher in patients who develop OHSS compared with controls, E₂ alone is not a sufficiently predictive factor. Indeed, an extensive overlapping of E₂ values was found between a series of 54 OHSS patients (Navot *et al.*, 1988) and a series of 128 patients (Delvigne *et al.*, 1993).

Severe OHSS has been observed in patients with very low E₂ levels of 475 and 29 pg/ml (Levy *et al.*, 1996; Shimon *et al.*, 2001); likewise, five atypical cases of severe OHSS characterized by a mean E₂ level of only 2138 pg/ml has been reported (Delvigne *et al.*, 1997), thereby underscoring the inadequacy of considering E₂ as the sole predictive factor.

Rate of E₂ increase during stimulation: This is also a risk factor, as has been shown in a multicentre study evaluating 128 OHSS cases. The discriminant analysis selects the increase in E₂ expressed semi-logarithmically for the mathematical model. Some authors also take this parameter into consideration when deciding on preventive measures (Enskog *et al.*, 1999; Fluker *et al.*, 1999).

Follicle number and size during stimulation: Most studies have found that a large number of pre-ovulatory follicles is a risk factor for OHSS. Moreover, according to different authors the size of the follicles which should be considered as a threshold value for risk is variable. One group (Blankstein *et al.*, 1987) evaluated a cohort of 65 patients treated with ovulation induction and found that patients with OHSS had significantly more follicles at the time of

hCG than did patients without OHSS. In moderate to severe OHSS, 95% of the pre-ovulatory follicles were <16 mm, and 55% were <9 mm; in contrast, in mild OHSS 69% of the follicles were of intermediate size (9–15 mm). Although this study is often cited for reference purposes, these results should be distinguished from those of other reports, because the stimulation conditions were quite different. For example, hCG was administered to all patients when their 24-h urinary excretion of E₂ was 80–180 µg, independent of any maturation criteria assessed by ultrasound (Blankstein *et al.*, 1987).

A significant correlation was found between the presence of multiple (> 4.2) secondary follicles of size 14–16 mm and severe OHSS (Tal *et al.*, 1985), while others (Navot *et al.*, 1988; MacDougall *et al.*, 1993) found respectively that during ovarian induction and IVF cycles, follicles of 12–14 mm or <18 mm were associated with an increased risk of OHSS. Finally, it was observed that, during IVF, OHSS patients had more follicles >15 mm in size (Enskog *et al.*, 1999).

The discussion regarding follicular size may be obsolete because stimulation criteria are totally different according to whether ovarian induction or IVF is applied. Furthermore, the error in follicle measurement and counting is related to their number (Asch *et al.*, 1991). Hence, the risk of OHSS is often related to the total number of developing follicles and to the number of collected oocytes (90 % of follicles seen) (Asch *et al.*, 1991).

In the latter study (Asch *et al.*, 1991), no patient developed severe OHSS when fewer than 20 oocytes were collected, whereas 1.4% of those patients with 20–29 oocytes and 22.7% with more than 30 oocytes developed this complication. Retrieval of more than 30 oocytes was associated with a sensitivity of 83%, a specificity of 67%, and a positive predictive value of only 23%.

Another group (Morris *et al.*, 1995) evaluated the incidence of OHSS among oocyte donors and classical IVF patients who yielded more than 30 oocytes. Only 6.5% of OHSS cases were in the combined group of oocyte donors and classical IVF, and 14% if only classical IVF was considered.

These two criteria, namely E₂ level and number of follicles and/or oocytes collected, are often used together to predict OHSS occurrence: according to one group (Asch *et al.*, 1991), for patients with an E₂ level >6000 pg/ml and more than 30 oocytes collected, the incidence of severe OHSS was 80%. Others (Morris *et al.*, 1995) reported an incidence of 20% of cases of OHSS when they considered only classical IVF and excluded oocyte donors. Once more, markedly elevated estradiol concentrations and/or numerous oocytes may be favourable, but are not sufficient for the development of OHSS (Morris *et al.*, 1995). Some oocyte donors did not develop OHSS, even in the presence of high E₂ levels (maximum 9590 pg/ml) and increased numbers of collected oocytes (maximum 58).

According to one investigation (Lyons *et al.*, 1994), early OHSS is predicted by E₂ level and the number of oocytes retrieved, while late OHSS is related to the number of gestational sacs seen at ultrasound. These contradictory data may be due to a mixture of early and late OHSS cases in most studies. Although such a distinction is theoretically possible, in clinical practice, many cases evolve from one situation to the other.

The considerable overlap of the distribution of values for different parameters between control and OHSS populations

makes any single variable inefficient for risk prediction. Combinations of variables were studied in a discriminant function in order to increase predictivity and decrease the false-negative rate. Progressive introduction and automated stepwise selection of variables were applied to IVF patients, all OHSS cases (*n* = 128). The best prediction (78.5%) was obtained in OHSS cases under post-oocyte retrieval conditions using log E₂, slope of log E₂ increment, hMG dosage, number of oocytes retrieved and LH:FSH ratio, in the formula with a corresponding false-negative rate of 18.1%. However, effective prevention of OHSS implies the ability to withhold hCG injection. Therefore, a formula for pre-oocyte retrieval conditions was established yielding a prediction rate of 76.1% with a false-negative rate of 18.1%. To be validated, such formulae would have to be applied to another population of IVF cases used as a 'testing-set' (Delvigne *et al.*, 1993b).

Other ovarian products: Several such products have been studied as putative predictors of OHSS, including inhibins A and B (Enskog *et al.*, 2000). These were evaluated in 15 patients with severe OHSS and 15 controls matched for age and number of follicles. Inhibin A and B levels were followed from the start of ovarian stimulation until at least 3 days post-embryo transfer. Inhibin A, in the OHSS group, showed a continuous increase during the stimulation to embryo transfer, but this elevation was significantly higher than in the controls only at the point where OHSS had developed. Inhibin B levels also rose from the start of the stimulation, but the peak value 3 occurred days before oocyte retrieval and then declined. This elevation was significantly higher in OHSS patients as well as on the day of oocyte retrieval. The authors suggested that inhibin levels may serve as indicators of OHSS risk, but threshold levels have still to be defined.

Levels of vascular endothelial growth factor (VEGF) and others interleukins have also been assessed in attempts to predict the presence of OHSS (Abramov *et al.*, 1997).

Follicular aspiration

Follicular aspiration may have a protective effect against OHSS (Rabinovici *et al.*, 1987), the concept being that aspiration of granulosa cells will reduce the ability of the corpora lutea to produce factors that may cause OHSS. Nevertheless, it has been demonstrated (Friedman *et al.*, 1984; Golan *et al.*, 1988; Tan *et al.*, 1992) that follicular puncture did not have this suggested protective effect against OHSS. Indeed, the incidence of OHSS increased when IVF was introduced, even if this technique is associated with systematic follicular emptying. In a retrospective study, stimulation with GnRH agonist and hMG for IVF was compared with intrauterine insemination (Aboulghar *et al.*, 1992). The incidence of OHSS was not decreased after follicular aspiration for IVF; this indicated that, if there were some preventive effect, then emptying most of the large and medium-sized follicles of their content of follicular fluid and granulosa cells would certainly not ensure absolute protection. However, this comparison could be criticised as the risk of OHSS is certainly higher in IVF than in ovarian induction and intrauterine insemination. Nonetheless, some investigators (Vrtovec and Tomazevic, 1995; Egbase *et al.*, 1999) were successful in applying follicular emptying prior to oocyte maturation in a prevention programme (see Prevention strategies).

In conclusion, at the time of oocyte retrieval, meticulous puncture and aspiration of all stimulated follicles has remained common practice.

Luteal supplementation

hCG is a promoter of OHSS, and luteal supplementation using a single injection or repeated doses of this hormone exacerbates OHSS (Smitz *et al.*, 1990; MacDougall *et al.*, 1992; Navot *et al.*, 1992; Araujo *et al.*, 1994). In one retrospective study (McClure *et al.*, 1992), 12% and 0% ($P < 0.001$) severe OHSS was observed when the luteal phase was supported by hCG or progesterone. Others (Herman *et al.*, 1990), in a randomized prospective study ($n = 36$), observed respectively 28% and 0% ($P < 0.03$) of moderate and severe OHSS in the same conditions. It is also known that patients with severe OHSS who did not become pregnant generally received exogenous hCG for luteal support (Friedman *et al.*, 1984; Forman *et al.*, 1990; McClure *et al.*, 1992).

Finally, a recent review concerning luteal phase support confirmed that, excepting oral progesterone, results are similar in terms of implantation and clinical pregnancy rates, whether hCG, vaginal or intramuscular progesterone is used. However, progesterone was deemed to be the best choice as it is associated with a lower incidence of OHSS (Penzias, 2002).

Pregnancy rate

In all of the studies in which the incidence of OHSS was analysed it was noted that the occurrence of the syndrome was linked to the chance of pregnancy. The risk of developing OHSS is two- to five-fold higher when pregnancy occurs, both in IVF and in ovarian induction cycles (Haning *et al.*, 1983; Tulandi *et al.*, 1984; Golan *et al.*, 1988; Navot *et al.*, 1988; Forman *et al.*, 1990; Herman *et al.*, 1990; Padilla *et al.*, 1990; Asch *et al.*, 1991; McClure *et al.*, 1992; Delvigne *et al.*, 1993a; Enskog *et al.*, 1999).

One group (Morris *et al.*, 1995) assessed the incidence of OHSS among oocyte donors and classical IVF patients who presented risk factors for OHSS (E_2 level >4000 pg/ml and >25 oocytes). These investigators did not observe OHSS among the donor patients, while there were six OHSS cases in the series of classical IVF patients ($P < 0.05$). The calculated relative risk of OHSS with pregnancy was 12-fold (95% CI 2.2–66.1, $P < 0.01$). By contrast, in another analysis of a series of 1000 cycles of oocyte donation, three cases of severe OHSS were recorded (Sauer, 2001), with all three patients having E_2 levels >5000 pg/ml and yielding >25 oocytes.

The incidence of OHSS appears to be directly related to hCG levels: multiple pregnancies develop more often with OHSS (MacDougall *et al.*, 1992). The number of gestational sacs was also shown to be predictive of the incidence of late OHSS (Ferrareti *et al.*, 1992; Lyons *et al.*, 1994; Mathur *et al.*, 2000). Nevertheless, it was also suggested that undiagnosed biochemical pregnancies, occurring during the first 2 weeks after hCG administration, may also play a causative role in those cases of severe OHSS in which clinical pregnancy is not present (Morris *et al.*, 1995). The role of biochemical pregnancy in unpredictable cases of OHSS was also underlined (Delvigne *et al.*, 1997).

Prevention strategies

Prevention and early recognition of OHSS are important in order to ensure the patient's safety. The first step of prevention is the identification of risk factors, in order to individualize the patient's stimulation regimen. The correct adaptation of stimulation schemes for ovulation induction results in a decreased incidence of OHSS (Franks *et al.*, 1991). Then, it is mandatory to strictly monitor the ovarian response to gonadotrophins in order to adapt the stimulation to ovarian response.

Monitoring ovulation, using ultrasound and E_2 assays constitutes the 'gold standard' (Karam *et al.*, 1973; Schenker and Weinstein, 1978; McArdle *et al.*, 1983). Several studies evaluated the impact of follow-up by either technique alone or in combination, and concluded that the combination of both methods provides the best results (Karam *et al.*, 1973; Haning *et al.*, 1983; Check *et al.*, 1985b; Diamond and Wentz, 1986). However, two observations suggested that using ultrasonography alone is as efficient, cheaper and less time-consuming (Murad, 1998; Ben Shlomo *et al.*, 2001).

While it is believed that both E_2 and ultrasound monitoring is necessary, it is insufficient as most IVF centres still report the occurrence of severe forms of OHSS, even though such monitoring is practised (Delvigne *et al.*, 1993a). Strict monitoring does however allow the application of a number of preventive measures when ovarian response is exaggerated.

Cancelling the cycle

Some authors suggest not giving hCG when several risk factors of OHSS are present, but to cancel the cycle because hCG triggers the development of OHSS. As early as 1970, preliminary data (Hancock *et al.*, 1970) indicated that the complications of superovulation could be totally avoided if the ovulatory hCG stimulus were to be withheld. Similarly, in 1978, it was established that, by withholding hCG when estrogen levels were too high, then severe OHSS could be prevented (Schenker and Weinstein, 1978). During the 1990s, others (Balen *et al.*, 1994) were able to avoid OHSS cases in an ovulation induction programme by cancelling cycles at risk.

In ovulation induction cycles, 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. In situations where natural conception is possible, the couple should be advised to avoid intercourse or to use condoms, as spontaneous ovulation may occur up to 11 days after discontinuing gonadotrophin treatment (Lipitz *et al.*, 1991).

This attitude is much more difficult to apply in an IVF programme, since the goal here is—by definition—to increase the number of oocytes. Therefore, it is much more difficult to establish a danger threshold. Furthermore, physicians may also feel more reluctant to propose cancellation to patients as IVF implies a great commitment on the patients' part in terms of procedures, time and money; moreover, the physicians are also under pressure to obtain a 'successful' outcome and to transfer more embryos when there is no insurance cover (Jain *et al.*, 2002). On the other hand, as LH surge inhibitors (GnRH agonists and antagonists) are almost always used, cancelling results is an absolute prevention in these much more dangerous situations. It

has been suggested that, after stopping hMG, the GnRH agonist treatment should be continued until the ovaries recover to a normal size, and then to re-stimulate them using lower doses of gonadotrophins (Forman *et al.*, 1990). Unfortunately, such lower doses may lead to an inadequate ovarian response in these patients (Amso *et al.*, 1991; Wada *et al.*, 1993a).

In the future, in-vitro maturation of human oocytes, with and without stimulation, will be available and will yield several oocytes, thereby avoiding hCG administration (Jaroudi *et al.*, 1997).

Cancelling the cycle and withholding hCG is the only method which totally avoids the risk of OHSS in ovarian induction cycles or in IVF. All other procedures usually succeed in decreasing either the risk or the severity of OHSS rather than totally preventing it.

The coasting approach

This technique was first described in overstimulated cycles during the late 1980s and early 1990s (Rabinovici *et al.*, 1987; Urman *et al.*, 1992), and shortly afterwards applied to IVF cycles (Sher *et al.*, 1993). The method is based on the assumption that E₂ levels reached at the time of hCG administration are predictive of the risk for OHSS. When a patient considered at risk has a high E₂ level, exogenous gonadotrophins are stopped while GnRH agonists are maintained. hCG administration is then postponed until the patient's serum E₂ level decreases to 'a safer zone', attesting to the atresia of granulosa cells. In a recent survey, conducted among gynaecologists specialized in infertility treatment, 'coasting' appeared to be the most popular method used to prevent OHSS (Delvigne *et al.*, 2002a).

A systematic review, aimed at deciding whether there is sufficient evidence to justify the general acceptance of coasting was also prepared (Delvigne and Rozenberg, 2001). This involved 493 patients in 12 studies, and showed the data to be highly heterogeneous in terms of characteristics and numbers of patients, stimulation schemes and coasting procedures. In most studies, either a threshold value of E₂ was used (often a value of 3000 pg/ml), and/or the number of follicles was considered. Fertilization rates (36.7–71%) and pregnancy rates (20–57%) were acceptable in terms of IVF results in comparison to those of large IVF databanks. In 16% of the cycles, ascites was described; in 2.8% haemoconcentration was recorded, and 2.5% of the patients required hospitalization. While coasting does not totally avoid the risk of OHSS, it certainly decreases its incidence in high-risk patients.

There are many advantages to using this technique. First, the cycle is not abandoned. Second, in contrast to cryopreservation (another method used to avoid OHSS), it enables the transfer of fresh embryos. Finally, no supplementary procedure or medical therapy is involved, in contrast to early unilateral follicular aspiration (EUFA) or albumin infusion, for example. It is therefore not surprising that some two-thirds of physicians who chose to apply a preventive method advocated the use of coasting (Delvigne and Rozenberg, 2002).

A relevant problem is to decide how coasting should be managed to obtain the best results in terms of oocyte quality and IVF outcome. Indeed, some investigators suggested that oocyte quality deteriorates when using coasting under certain conditions. In a prospective controlled study in 32 patients (Laufer *et al.*,

1984), it was observed that an interval longer than 24 h between the last hMG injection and hCG administration may result in decreased fertilization rates, probably consecutive to atretic changes in the follicles. Similarly, others (Aboulghar *et al.*, 1997) reported a low number of good quality oocytes in cases of OHSS and recommended using a 'modified form of coasting', by decreasing the doses of hMG before withholding them completely (Aboulghar *et al.*, 2000). In fact, these investigators observed a decrease in oocyte quality, fertilization and pregnancy rates when E₂ levels suddenly fell very low (unpublished data). It was also reported that allowing E₂ levels to decrease ultimately results in poor oocyte quality (Whelan and Vlahos, 2000). These authors proposed that, under risk conditions, all stimulatory medication should be stopped and that follicle size and E₂ levels should be monitored daily once E₂ levels had plateaued for 2–3 days; hCG could then be administered and oocyte retrieval planned.

By contrast, others (Ulug *et al.*, 2002), in a retrospective study of 207 coasted patients (when E₂ levels were >4000 pg/ml and >20 follicles were present), found that coasting for more than 3 days appeared to reduce implantation and pregnancy rates, while oocyte and embryo quality did not appear to be affected. These authors suggested that for patients who require coasting for more than 3 days, cryopreservation of embryos should be considered.

Another large cohort of 157 patients was evaluated retrospectively and compared to a control group of 208 IVF cycles which had reached serum E₂ levels of at least 4000 pg/ml without being coasted (Delvigne *et al.*, 2002b). In the group of coasted cycles, the question of whether indirect parameters related to coasting had an effect on IVF results was also analysed. Coasted patients showed higher maximum E₂ levels and greater numbers of large follicles ($P < 0.001$) and lower oocyte recovery rates ($P < 0.001$) than the control group, whereas IVF outcomes were similar. Within the group of coasted patients, no significant relationship was found between the number of coasting days, the E₂ levels on the day of hCG, or the fall in E₂ level and the outcome, whether measured in terms of oocyte quality, pregnancy rate or OHSS occurrence.

In conclusion, coasting is a popular and effective method to reduce OHSS rates, but it does not totally eliminate the condition. However, this procedure appears to be associated with a reduced oocyte collection rate, and especially so when the coasting period is prolonged. The quality of oocytes after coasting is still the subject of debate, as is endometrial receptivity after E₂ lowering. The collected data are nevertheless reassuring in terms of pregnancy rates.

EUFA

In 1991, it was reported that follicular aspiration induces an intrafollicular haemorrhage which has a negative impact on the corpus luteum function (Gonen *et al.*, 1991). It has therefore been suggested that growing follicles be punctured, with the hope that withdrawal of the follicular contents may significantly interfere with follicular maturation and modify the intra-ovarian mechanisms responsible for OHSS. Contradictory results of follicular aspiration during oocyte retrieval have been reported (Friedman *et al.*, 1984; Hazout *et al.*, 1984; Golan *et al.*, 1988; Laufer *et al.*, 1990; Aboulghar *et al.*, 1992). The timing of the trigger dose of hCG in relation to the expected protective effect of follicular aspiration may be of importance for preventing OHSS.

In 1995, early follicular aspiration was first applied to 17 patients at risk of OHSS (excessive E_2 values, multiple follicles), 12 h after hCG administration, followed by regular oocyte retrieval 36 h later (Vrtovec and Tomazevic, 1995). The method of post-hCG aspiration in one ovary was effective, leading to the withdrawal of all signs of OHSS within 6 days after the second aspiration post-hCG. For these authors, this is a quick, simple and effective method that prevents the development of OHSS and allows pregnancy in the treated cycles.

In 1997, a prospective randomized study was performed to evaluate unilateral ovarian aspiration 6–8 h before hCG administration (Egbase *et al.*, 1998). In an IVF programme, 31 patients at risk (E_2 levels >3269 pg/ml; >12 follicles of 12 mm per ovary) were randomized between EUFA ($n=16$) or no pre-treatment ($n=15$). Fewer oocytes were recovered in the pre-treated group, but fertilization, embryonic cleavage and pregnancy rates were similar. OHSS was recorded in 25% of the EUFA group and in 33.3% of the control group (12.5% and 6.6% of severe forms respectively). The authors concluded that unilateral ovarian aspiration before hCG administration failed to prevent or diminish the occurrence of severe OHSS.

Two years later, the same group performed a prospective randomized study comparing EUFA 10–12 h after hCG administration with the coasting method for high-risk patients (defined as E_2 level >6000 pg/ml and >15 follicles of >18 mm per ovary). Oocyte retrieval was carried out in the contralateral ovary at 35–36 h after hCG administration. Fewer oocytes were recovered in the coasted group, but fertilization, embryonic cleavage and pregnancy rates were similar. Neither method completely prevented the occurrence of severe OHSS as 26.6% in the EUFA group and 20.0% in the coasted group developed the severe condition. This may be explained by the rather loose criteria used to identify high-risk patients (Egbase *et al.*, 1999).

In conclusion, it was expected that intra-ovarian bleeding induced by aspiration of granulosa cells from one ovary would limit the production of ovarian mediators of OHSS and thus reduce the risk of developing severe OHSS. These data are, however, contradictory and the number of cases insufficient to establish the efficacy of the method. The invasive nature of the method, necessitating two oocyte retrievals (sometimes under anaesthesia), is indicative of why it has been attempted less often than coasting.

Modification of methods to trigger ovulation

Reduction of the hCG dose or triggering ovulation with rhLH or endogenously induced LH surge are different approaches to reduce the incidence of OHSS, and this is discussed in more detail in the section relating to risk factors.

Administration of glucocorticoids

The use of steroids in patients at high risk for OHSS has been evaluated in a randomized study in which a group of 17 patients received corticoids. Treatment was as follows: 100 mg intravenous hydrocortisone immediately after oocyte recovery, followed by 10 mg, three times daily for 5 days, starting on the day of oocyte recovery; followed by 10 mg twice daily for 3 days and then 10 mg per day for 2 days. The control group comprised 14 patients who did not receive any glucocorticoid treatment. Ovarian response was similar in both groups, while 41.2% of

treated patients developed OHSS compared with 42.9% in the control group. Even when considering only the moderate or severe forms, the incidence of OHSS remained high in all groups (respectively 11% and 6% in the corticoid-treated group, and 7% and 7% for the control group). The authors concluded that glucocorticoids did not reduce the OHSS rate (Tan *et al.*, 1992). This study is generally considered as sufficient proof that glucocorticoids should no longer be used to reduce OHSS risk. It is believed, however, that clear conclusions cannot be drawn from these data in view of the small number of cases that were randomized. It is possible that recent theories suggesting an inflammatory aetiopathology of OHSS will bring about reconsideration of the use of corticosteroids and other anti-inflammatory drugs in this context.

Macromolecules and progesterone

Albumin

Albumin is thought to prevent the development of OHSS by increasing plasma oncotic pressure and binding of the OHSS mediators of ovarian origin. However, because capillary permeability is compromised, the duration of the oncotic effect would be insufficient to prevent OHSS.

A pilot study was performed in rabbits, with or without bovine serum albumin (BSA) pre-treatment. Despite an increase in serum protein levels, the BSA-treated group showed a comparable increase in body weight and degree of ascites formation. The authors concluded that albumin did not prevent severe OHSS despite its oncotic or carrier protein properties in this model (Orvieto *et al.*, 1999).

Others (Doldi *et al.*, 1999) evaluated the possible effect of albumin on VEGF, one of the aetiological factors of OHSS (Elchalal and Schenker, 1997). These authors reported that in cultured human luteinizing granulosa cells, VEGF mRNA expression was increased after human albumin administration, with maximal expression being observed in cultured cells from patients with high E_2 levels ($P<0.05$).

A series of clinical studies have evaluated the efficacy of albumin in preventing OHSS. The dose varied from 10 to 125 g in one or five administrations, also with a variable duration from 1 day before until 5 days after oocyte retrieval. For these reasons, it is impossible to pool all results, though the principal observations of these studies are summarized in Table I. It is possible that some authors used doses too small to obtain a result, as a 15–50 g albumin dose is usually retained for only a short time in the bloodstream. It has been suggested (Orvieto and Ben-Rafael, 1996) that albumin dosing be repeated every 1–2 days in order to achieve a continued effect.

Studies have also been limited by the low sensitivity and predictive values of the criteria used to define high-risk patients. Because most cases of severe OHSS, after albumin treatment, seem to be associated with pregnancy, it is possible that intravenous albumin might be more effective in preventing the occurrence of early OHSS than late OHSS. In two studies, the pregnancy rate was significantly lower after albumin i.v. infusions, though this may be the consequence of prolonged infusion (Shaker *et al.*, 1996; Costabile *et al.*, 2000). Indeed, albumin administration close

Table 1. Design of study, population characteristics, selection criteria, and IVF data for cycles treated with albumin

Reference	Study design (n)	Control group	Risk patients	OHSS incidence with albumin use	OHSS incidence in controls	Comment
Asch <i>et al.</i> (1993)	Not controlled (36)	Historical high-risk patients	E ₂ >6000 pg/ml and >30 oocytes	0% OHSS	80 % OHSS	In 21 patients no transfer occurred
Shoham <i>et al.</i> (1994)	Prospective Randomized Controlled (31)	Placebo of NaCl	E ₂ >1906 pg/ml and multiple follicular development	0/16 OHSS	4/15 severe OHSS (P < 0.05)	No information about moderate forms
Shahata <i>et al.</i> (1994)	Retrospective (200)	Historical whole IVF population	E ₂ >2997 pg/ml and >20 oocytes or >30 follicles	0/104	8/96	Only 18% of controls had E ₂ >2997 pg/ml
Ng <i>et al.</i> (1995)	Prospective controlled (207)	Placebo of Ringer's solution	E ₂ >2724 pg/ml and >15 follicles	2/49	10/158	Albumin blunted the severity of OHSS
Mukherjee <i>et al.</i> (1995)	Case report (2)	-	E ₂ >4500 pg/ml and >20 oocytes	2 severe OHSS (1 early, 1 late)	-	-
Orvieto <i>et al.</i> (1995)	Case report (1)	-	E ₂ 2293 pg/ml and 46 oocytes	Early severe OHSS	-	-
Ben-Rafael <i>et al.</i> (1995b)	Case report (1)	-	E ₂ >2293 pg/ml, >35 oocytes	Early severe OHSS	-	-
Halme <i>et al.</i> (1995)	Case report (1)	-	1 oocyte donor, E ₂ 2400 pg/ml, 15 oocytes	Early severe OHSS	-	-
Shalev <i>et al.</i> (1995b)	Prospective Randomized (40)	No treatment	E ₂ >2500 pg/ml and >20 follicles	0/22	4/18	No transfer in 5.5% of controls and 13.6% of study group
Shaker <i>et al.</i> (1996)	Prospective Randomized Controlled (26)	Cryopreservation	E ₂ >3540 pg/ml or >2745 pg/ml and >15 oocytes	4/13 moderate OHSS (no severe)	3/13 moderate OHSS (not severe)	Pregnancy significantly higher in controls
Isik <i>et al.</i> (1996)	Prospective Randomized Controlled (55)	No treatment	E ₂ >3000 pg/ml	0/27	NS	-
Lewit <i>et al.</i> (1996)	Retrospective cases review (5)	-	Previous OHSS, E ₂ >3600 pg/ml and large number of follicles	2/5 early severe, 2/5 moderate	1 severe and 4 moderate/28	The most severe received 75 g, and had no transfer
Orvieto and Ben-Rafael (1996)	Retrospective review (30)	-	-	2/30 early severe OHSS	-	-
Chen <i>et al.</i> (1997)	Prospective (72)	Historical controls	E ₂ >3600 pg/ml and >20 oocytes	4/30	14/42; P = 0.047	Prevention is effective in non-pregnant and singleton pregnancies
Egbase <i>et al.</i> (1997)	Uncontrolled (31)	-	E ₂ >3269 pg/ml and >12 follicles >12 mm per ovary	0/16 non-pregnant 4/14 pregnant 9.7% severe	5/23 non-pregnant 9/19 pregnant	Early follicular aspiration before hCG was also performed (n = 16)
Ndukwe <i>et al.</i> (1997)	Retrospective (60)	-	E ₂ >4086 pg/ml and >20 follicles	5/60 severe (1 early, 4 late); 8/60 moderate	-	No preventive effect, especially in pregnant patients
Koike <i>et al.</i> (1999)	Prospective Randomized	No treatment	>20 oocytes	11 early, 2 late severe OHSS /43	15 early, 6 late severe OHSS/55	-
Controlled (98)					NS	
Panay <i>et al.</i> (1999)	Prospective Randomized (86)	No treatment	E ₂ >3541 pg/ml or >20 follicles	2 mild, 2 moderate/37	4 mild/49	PR per cycle significantly higher in controls

Table 1. Continued

Reference	Study design (n)	Control group	Risk patients	OHSS incidence with albumin use	OHSS incidence in controls	Comment
Costabile <i>et al.</i> (2000)	Prospective Randomized Controlled (96)	200mg/day progesterone from 1 day post-retrieval Placebo	E ₂ >2452 pg/ml and >20 follicles	4/42 moderate (no severe)	0/54 moderate (no severe)	High progesterone dose is effective in preventing OHSS and better for pregnancy rate
Gokmen <i>et al.</i> (2001)	Prospective Randomized Placebo (168)		E ₂ >3000 pg/ml or >20 follicles	0 severe and 4 moderate/85	4 severe and 12 moderate/83 P < 0.05	

PR = pregnancy rate.

to the implantation period may have bound some factors necessary for this implantation.

The possible adverse effects of albumin should not be underestimated. Albumin may leave the blood vessels and enter the interstitium, whereby it may draw fluid from the intravascular space. Moreover, albumin is a human product, and transmission of infections by blood-borne viruses can never be entirely excluded. Other side effects include nausea, vomiting, febrile reactions and allergic reactions.

In conclusion, when considering data from prospective randomized studies and a single retrospective study which includes a control group, a total of 39 OHSS cases have been recorded among 468 high-risk treated patients (8.3%) and 89 OHSS cases in a control group comprising a total of 611 high-risk patients (14.6%). No more extensive statistical analysis can be achieved because of the disparity of protocols mentioned earlier. When considering further fundamental and animal studies, no additional arguments emerge in favour of using albumin.

To summarize, current published studies do not support a role for albumin in preventing late, severe OHSS. At most, albumin may improve but not eliminate early, severe OHSS, but the results of studies are inconclusive. Only a multicentre, randomized prospective study would provide a definitive answer to this question.

Prophylactic infusion of hydroxyethyl starch solution (HAES)

In view of the potential transmission of infective viruses when administering human albumin, some groups have tested a safe non-biological substitute with comparable physical properties, namely hydroxyethyl starch solution (HAES). HAES has a molecular weight of 200 to 1000 kDa, and significantly increases intravascular volume, therefore raising osmotic pressure. HAES has a serum half-life of 10 h, and also inhibits platelet aggregation.

One prospective study (Graf *et al.*, 1997) investigated the effect of HAES, involving 100 high-risk patients (E₂ levels >3000 pg/ml or >20 oocytes). These patients received 1000 ml 6% HAES at the time of oocyte retrieval, and 500 ml 48 h later. A historical control group of 82 high-risk patients who had not been treated with HAES was included. A significantly lower rate of moderate OHSS using HAES was seen, but there was no reduction in severe OHSS.

Another group (König *et al.*, 1998) evaluated a regimen of 1000 ml 6% HAES given shortly after embryo transfer, in a prospective, randomized, placebo-controlled study, involving a total of 101 high-risk patients (E₂ >1500 pg/ml or >10 follicles). One case of moderate OHSS developed in the HAES group, whereas one severe and six moderate cases occurred in the placebo group (P = 0.031).

Subsequently, others (Gokmen *et al.*, 2001) performed a prospective randomized study to compare the efficacy of 500 ml 6% HAES (n = 85) and of 50 ml 20% human albumin (n = 85) or placebo (n = 83) in high-risk patients (E₂ >3000 pg/ml or >20 follicles). All treatments were administered during oocyte retrieval. No severe OHSS case was observed in the albumin and HAES groups, while four were seen in the placebo group. Moderate OHSS was encountered in four and five patients in the albumin and HAES groups respectively, and in 12 patients

Table II. Summary of the main results concerning cryopreservation as a prevention method of OHSS

Reference	Design	Control group (n)	Risk factors (n)	Pregnancy with thawed embryos	OHSS with cryo-preservation (versus control)	Comments
Amso <i>et al.</i> (1990)	Observational	-	25 to 45 follicles, abdominal pain (4)	100 %/trsf	10% moderate	-
Salat-Baroux <i>et al.</i> (1990)	Observational	-	E ₂ 4722 ± 1190 pg/ml the day after hCG (33)	27 %/trsf	3% severe	-
Wada <i>et al.</i> (1991)	Retrospective observational	Pregnant (49) and non-pregnant (154)	NA (38)	-	18% all grades only if E ₂ >3500 pg/ml (18 and 4%)	0% if E ₂ <3500 pg/ml; 1 with cryopreservation
Wada <i>et al.</i> (1992b)	Retrospective observational	-	E ₂ >3500 pg/ml (78)	26%/trsf	27% all grades (8% severe)	-
Wada <i>et al.</i> (1993c)	Retrospective observational	Historical group without prevention (105)	E ₂ >3500 pg/ml (136)	21%/trsf	8.8%, only 6% severe (9.5%, 60% severe)	71.8% survival embryos
Pattinson <i>et al.</i> (1994)	Retrospective	General IVF without risk factors (564)	E ₂ ≥4086 pg/ml and >50 follicles (69)	25.2%/trsf 40%/patient	1.4% (1.8% severe)	84% survival embryos; 14% cancelling
Tiitinen <i>et al.</i> (1995)	Prospective	General IVF without risk factors (367)	E ₂ >2724 pg/ml and/or >20 oocytes (33)	32.6 %/trsf 65.2%/patient	4.3% moderate (versus 0.5%)	22.7% implantation rate
Awonuga <i>et al.</i> (1996)	Retrospective controlled	E ₂ >2724 pg/ml and/or >15 oocytes (52)	E ₂ >2724 pg/ml and/or >15 oocytes (65)	17%/trsf	3% severe; 3% moderate; (3.8% severe and moderate) NS	Significantly higher PR in controls (35%; P<0.05)
Queenan <i>et al.</i> (1997)	Prospective, non-controlled	-	E ₂ >4500 pg/ml and >15 oocytes (15)	58%/trsf 67%/delivery/patient	13% severe 13% moderate	-
Benavida <i>et al.</i> (1997)	Retrospective controlled	Coasting group (22)	E ₂ >3000 pg/ml (26)	25.6 %/trsf	7.6% (4.5%)	-
Ferraretti <i>et al.</i> (1999)	Prospective randomized	E ₂ >1500 pg/ml and >15 oocytes (67)	E ₂ >1500 pg/ml and >15 oocytes (58)	35.4 %/trsf 48.3% per patient	NS 0% (versus 6%)	-

NS = not significant; PR = pregnancy rate; Trsf = embryo transfer; NA = not available.

receiving placebo ($P < 0.05$). The authors recommended preventing OHSS by using HAES, since it is as efficient but safer and cheaper than human albumin.

These three studies provide concordant results, thereby suggesting a beneficial effect of HAES in decreasing OHSS incidence. Although the patient cohort was too small to draw definitive conclusions, these preliminary results suggested that HAES rather than albumin should be further evaluated.

High doses of intramuscular progesterone

Three different mechanisms of action of the prophylactic use of progesterone to prevent OHSS have been hypothesized: (i) a general anti-estrogenic effect of progesterone mediated by the down-regulation of estrogen receptors, for example on the vascular endothelium; (ii) a direct inhibition of ovarian hormone secretion, such as prorenin; and (iii) an antagonistic effect against aldosterone. In a prospective randomized controlled study (Costabile *et al.*, 2000), the effectiveness of intramuscular progesterone was compared with i.v. albumin in preventing OHSS. High-risk patients ($E_2 > 2452$ pg/ml and > 20 follicles) received either 200 mg progesterone per day (i.m.) for 14 days starting immediately after oocyte retrieval, or 100 ml 20% albumin intravenously.

Progesterone prevention was significantly more efficient, with fewer moderate OHSS cases (0 versus 5%). No severe forms were observed in these two groups, but a higher pregnancy rate was observed in the progesterone group (68 versus 52.3%).

Cryopreservation of all embryos

Instead of cancelling the cycle, it is possible to administer hCG, retrieve the oocytes, and then cryopreserve all embryos. Using this prevention strategy, the patients are still exposed to exogenous hCG, and early OHSS is not totally avoided. Nevertheless, the risk of a secondary exacerbation of early OHSS is avoided as well as late OHSS, since this is induced by endogenous hCG (Amso *et al.*, 1990; Salat-Baroux *et al.*, 1990; Wada *et al.*, 1992a). This treatment has the advantage of maintaining many of the benefits of the IVF cycle since it is hoped that in a later cycle, thawed embryos may be successfully replaced (Wada *et al.*, 1992b).

Several authors have reported their successful experience in this field (Table II). One group (Amso *et al.*, 1990) reported this practice in four patients at risk of developing OHSS. In one patient, a moderate OHSS occurred and resolved within 8 days, while three patients became pregnant after replacement of the thawed embryos during the two following cycles. A similar experience was reported by others (Salat-Baroux *et al.*, 1990) in 33 patients who presented biological risk signs of OHSS ($E_2 4722 \pm 1190$ pg/ml the day after hCG). These authors observed a rate of pregnancy of 27% using frozen-thawed embryos. Endometrial biopsies were performed during the luteal phase of the cancelled cycle. Half of these biopsies showed glandular stromal asynchrony, suggesting that patients who have very high E_2 levels may have a reduced chance of conception, thereby reinforcing the idea that cryopreservation constitutes a valid alternative. Nonetheless, one severe case of OHSS was observed in this series, emphasizing that caution must be maintained.

A further three studies were reported by the same group (Wada *et al.*, 1991, 1992b, 1993b). The first study collected all IVF

cycles, with ($n = 203$) and without ($n = 38$) embryo transfer. The groups were studied according to the E_2 level and pregnancy. No cases of OHSS were observed in the non-embryo transfer group when E_2 levels were < 3500 pg/ml. However, in the cycles with embryo transfer OHSS was observed in 2.3% and 12% of non-pregnant and pregnant women with E_2 level < 3500 pg/ml respectively. When E_2 levels were > 3500 pg/ml, the OHSS rate was 60% (8% severe) in the non-transfer group, but was respectively 11% and 57% (28% severe) in non-pregnant and pregnant women with embryo transfer. This study underlines the fact that withholding transfer does not reduce the incidence of OHSS in women with E_2 levels > 3500 pg/ml. However, the weakness of the study is that it was retrospective, and that the conditions of cryopreservation were not reported.

A year later, the same authors reported a series of 78 cases of elective cryopreservation for E_2 levels > 3500 pg/ml at the day of hCG administration. Some 27% of OHSS was observed (8% severe forms). Subsequently, frozen-thawed embryo replacement was performed, with 71.8% of surviving embryos entailing an 11.7% implantation rate and producing a pregnancy rate of 26% per cycle. This pregnancy rate was comparable with that obtained by the same group in their general IVF population. Finally, the same authors compared two periods: during the first period, no preventive approach had been used and the patients had been supplemented with hCG during the luteal phase. During the second period, they used cryopreservation as discussed earlier. OHSS occurred in 9.5% and 8.8% of patients during the two periods respectively. However, within the OHSS group, fewer (6%) severe forms were observed when cryopreservation was performed, compared with 60% in women with E_2 levels > 3500 pg/ml who became pregnant. The authors concluded that cryopreservation of all embryos from women with high E_2 levels reduced the severity and the duration of OHSS, but not its incidence.

By contrast, another group (Pattinson *et al.*, 1994) recorded a very low rate of OHSS of 1.4% when cryopreservation was performed in a high-risk group ($E_2 > 4086$ pg/ml and > 50 follicles). This pregnancy rate was significantly higher than that obtained with 'normal' frozen embryo transfer and was equivalent to that following fresh transfer in the same centre. The incidence of OHSS in the remaining IVF patients was 1.8%.

A similar study design was used in a population with a lower degree of risk (Tiitinen *et al.*, 1995). These patients were selected when E_2 levels were > 2724 pg/ml and/or when > 20 oocytes were retrieved. An incidence of 4.3% of moderate forms of OHSS was observed versus a 0.5% rate in the general IVF population without risk factors. The pregnancy rate after frozen-thawed embryo replacement was 32.6 % per transfer, with a cumulative rate of 65% per patient and an implantation rate of 22.7%.

In another study (Queenan *et al.*, 1997) all the embryos of 15 patients with E_2 levels > 4500 pg/ml and ≥ 25 follicles were cryopreserved. Some 13% severe OHSS forms and 13% moderate OHSS forms occurred among these patients. The pregnancy rate per transfer was 58%, with a delivery rate of 67% per patient. Only one other group (Ferraretti *et al.*, 1999) conducted a prospective randomized study, though the selection criteria in this group of 58 patients in whom cryopreservation was undertaken were much more loose than those generally applied. Women with E_2 levels > 1500 pg/ml and > 15 oocytes were selected. The control

group comprised 67 patients who presented the same criteria and in whom fresh embryo were transferred. The pregnancy rates were comparable (46.3 versus 48.3%), and no cases of OHSS occurred in the 58 cycles with cryopreservation, but four cycles were complicated by OHSS in the control group (0 versus 6%).

Finally, 26 patients treated by cryopreservation were compared with 22 coasted patients (Benadiva *et al.*, 1997). These authors did not observe any difference in OHSS incidence between the two groups, but fewer cycles had to be cancelled when using cryopreservation. Only one investigation reported a decrease in pregnancy rate after cryopreservation as compared with controls, while OHSS incidence was similar in both patient groups (Awonuga *et al.*, 1996).

One question that remains to be solved is whether GnRH agonist should be continued when embryos are cryopreserved, in order to reduce the risk of OHSS. One group (Norman *et al.*, 1991) showed that LH levels remained low for at least 14 days during the luteal phase after pituitary suppression with GnRH agonist administration and ovarian stimulation with hMG, even though GnRH agonist was discontinued on the day of hCG administration. Others (Wada *et al.*, 1992a) confirmed this observation by comparing the rate of ovarian quiescence, by the weekly fall in serum E₂ concentration, following the stimulation with or without continuing GnRH agonist. There was no difference between the two groups in terms of ovarian quiescence, and serum LH concentration remained low in all women, irrespective of the group.

In conclusion, these controversies may be explained by the different criteria used to define patients at risk, the different freezing procedures adopted, and the lack—for ethical reasons—of a prospective randomized study in two very high-risk groups.

It has not been established whether the elective freezing of all embryos completely eliminates the risk of OHSS, but it does reduce the expected incidence of OHSS in high-risk groups and reduces the duration and severity of OHSS. Indeed, it is not expected that elective cryopreservation would have any influence on early OHSS, which is an acute effect of exogenous hCG administered to trigger ovulation. Therefore, while early OHSS is not avoided, late OHSS—which is induced by endogenous hCG from the trophoblast—is avoided by elective cryopreservation. In all but one report the rate of pregnancy after frozen–thawed embryo replacement was as high as when using fresh embryos.

Electrocautery or laser vaporization of one or both ovaries

PCOS is the major risk for OHSS. The results of preventive methods for OHSS in these patients are unpredictable in terms of ovarian response and OHSS prevention. Several authors observed OHSS despite using a low step-up regimen with gradual increase of the doses of gonadotrophins (Buvat *et al.*, 1989; Rizk and Smitz, 1992). Others noticed that the ovarian response may be unsatisfactory when decreased doses of gonadotrophins were given after a previous experience of OHSS (Amso *et al.*, 1991; Wada *et al.*, 1993a).

One possible treatment of PCOS is destruction of follicles at the surface of the ovary, by wedge resection, or as described more recently by multiple puncture using laparoscopic ovarian electrocauterization (Gjönnaess, 1984). The endocrine effects associated with this treatment include a reduction in serum LH and serum androgens (Donesky and Adashi, 1995), with corresponding

ovulation improvement (in 60% of treated cases) and conception (Armar *et al.*, 1990) and also a reduction of multiple pregnancy, OHSS and probably miscarriage rates (Abdel Gadir *et al.*, 1990). A number of authors have suggested treating patients suffering from PCOS by using these destructive techniques before starting to stimulate them for IVF (Fukaya *et al.*, 1995; Rimington *et al.*, 1997; Egbase *et al.*, 1998; Tozer *et al.*, 2001). This treatment can be performed on one or two ovaries with electrocautery or laser vaporization. The main undesirable side effect of these methods is the development of postoperative adhesions (Greenblatt and Casper, 1993).

Only one prospective randomized study, involving 50 patients, affected by PCOS has been carried out (Rimington *et al.*, 1997). Patients who failed to become pregnant during a previous trial, or whose cycle had been cancelled for high OHSS risk, were randomized between classic IVF treatment and electrocautery of one ovary 1 week before ovarian stimulation. The pregnancy and miscarriage rates were identical, but the rate of cancelling for risk of OHSS was significantly lower in the cauterized group. There was no advantage in terms of miscarriage rate, which remained high in both groups.

Others (Fukaya *et al.*, 1995) reported that they were able to reduce the risk of OHSS after ovarian laser therapy in patients who suffered from PCOS and had developed OHSS in the past, and obtained a pregnancy rate of 73% with COS. However, no control group was included in this study.

Finally, a retrospectively comparison was made of 15 women with clomiphene-resistant PCOS, treated by laparoscopic ovarian diathermy before IVF, and 16 PCOS patients who did not receive surgical pre-treatment (Tozer *et al.*, 2001). In this study there was only a trend towards a lower risk of miscarriage (28.6 versus 66.7%) and of OHSS (0 versus 4.2%), and higher chances of pregnancy (29.4 versus 10.5%) in the group which had been surgically pre-treated, but these differences were not statistically significant.

Others (Balen, 1999) underlined that minimal destruction is necessary to sensitize the PCOS to exogenous gonadotrophins. However, in order to avoid OHSS, a considerable amount of healthy ovarian destruction is required (Rimington *et al.*, 1997; M.R.Rimington, personal communication), with the drawback that under these conditions the ovarian reserve may be hampered.

In conclusion, since only preliminary data are available, and in view of the possible side effects (adhesions and loss of ovarian tissue) and its invasive character, this approach should be restricted to rebel cases of OHSS in patients suffering from PCOS, and applied only as a last resort.

Conclusion

In the prevention of any disease, it should be emphasized that the possibility of primary prevention depends on two main requirements: first, the aetiology of the disease must be known while causal and predisposing factors should be identified; and second, it must be feasible to avoid or manipulate such factors as part of a preventive strategy.

Secondary prevention requires knowledge of the pathophysiological mechanisms of the disease (Elchalal and Schenker, 1997), availability of early detection methods, and means to intervene

and correct the pathophysiological changes (Orvieto and Ben-Rafael, 1996).

There is disagreement regarding the sensitivity and predictive values of the various patient characteristics which may be used to predict OHSS. The greater severity of late OHSS and its poor correlation with conventional ovarian response parameters is a major problem in clinical practice. None of the predictive data for late OHSS is ever available before oocyte retrieval.

Late OHSS is related to hCG levels and probably to the number of ovarian cells capable of producing the causal 'unidentified-ovarian mediator' under the influence of hCG. It may be useful, therefore, to act at two levels: (i) to attempt to limit the dose or concentration of hCG (level 1); and (ii) to find a way to induce luteolysis (level 2) without inducing a detrimental effect on endometrial and oocyte quality.

Intervening at level 1 can in theory be achieved by decreasing hCG doses for ovulation induction, by cryopreservation, and by using progesterone instead of hCG supplementation in the luteal phase. The transfer of a single embryo reduces the number of multiple pregnancies, and probably also the OHSS incidence (Gerris and Van Royen, 2000).

Intervening at level 2 may consist of enhancing luteolysis, as in EUFA, coasting, and electrocautery of one or both ovaries. Albumin is a secondary prevention method.

Finally, apart from cancelling, none of these approaches was totally efficient, although most of the above-mentioned methods decrease the incidence in patients at high risk of OHSS. The effect of combined methods which act at two different levels (1 and 2) should be assessed (Isik *et al.*, 2001).

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