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Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS)

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The ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation occurring during the luteal phase or during early pregnancy. This complication is unusual as it is not the consequence of a treatment which is vital or mandatory for the patient's health. Nevertheless, it can be accompanied by severe morbidity and may even be fatal. Data pertaining to the clinical course and consequences of OHSS in women and its treatment were searched using Medline, *Current Contents* and PubMed. To date, only a few studies have collected a large number of cases of OHSS. The clinical course of OHSS may involve, according to its severity and the occurrence of pregnancy, electrolytic imbalance, neurohormonal and haemodynamic changes, pulmonary manifestations, liver dysfunction, hypoglobulinaemia, febrile morbidity, thromboembolic phenomena, neurological manifestations and adnexal torsion. Treatment of the acute phase relies only on an empirical and symptomatic approach. The general approach will be adapted to the levels of severity. Specific approaches such as paracentesis, pleural puncture, surgical approach of OHSS and specific medication during OHSS were evaluated sporadically. More adequate treatment methods would require a better understanding of the underlying pathophysiological mechanisms, to promote an aetiological therapeutic approach. Properly conducted studies, including large numbers of patients are required in order to determine the best method of prevention and management.

Key words: clinical course/coasting/IVF/OHSS/treatment

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation occurring during the luteal phase or during early pregnancy. The syndrome has been known since 1943, when gonadotrophins (gonadotrophic preparations from the serum of pregnant mares or extracts of sheeps' pituitary gland and urine of pregnant women) were first used to induce ovulation (Rydberg *et al*., 1943; Davis *et al*., 1944). At that time, this disease was called (in French) 'syndrome d'hyperlutéinisation massive des ovaires'. The first fatal cases were described in 1951 by Gotzsche (Esteban-Altirriba, 1961) and later also in 1958 (Figueroa-Casas *et al*., 1958). In 1957, Le Dall described this syndrome in his thesis (Le Dall, 1957), and reported acute cases necessitating a laparotomy and unilateral or bilateral ovariectomy or puncture and suture of ruptured cysts. Further subacute situations have also been mentioned, characterized by pain and healing in 58% of the cases after bed rest and antispasmodic treatment. Oliguria and renal failure was the principal complication leading to death at that time.

Later, OHSS appeared to be a possible complication of the induction of ovulation by almost every agent used for this purpose. The presentation and severity of this clinical syndrome has evolved with time in relation to stimulation protocols. For instance, the development of IVF and of other techniques such as cryopreservation has led to increasingly aggressive treatment schemes aimed at obtaining sufficient numbers of oocytes and embryos, but leading consequently to an increased risk of OHSS. Today, it is the loss of control over hyperstimulation which constitutes the 'ovarian hyperstimulation syndrome'.

The most common form occurs a few days after follicular rupture or puncture, when follicular growth has been medically induced by using either clomiphene citrate or gonadotrophins, sometimes in conjunction with GnRH agonists or antagonists and following final follicular maturation and luteinization achieved by administration of hCG.

Some other particular forms of OHSS have also been reported: spontaneous OHSS, sometimes occurring repeatedly in the same patient (Rotmensch *et al*., 1989; Zalel *et al*., 1995; Ayhan *et al*., 1996; Lipitz *et al*., 1996; Olatunbosun *et al*., 1996; Abu-Louz *et al*., 1997; Di Carlo *et al*., 1997; Nappi *et al*., 1998; Todros *et al*.,

1999; Pentz-Vidovic *et al*., 2000; Hee-Dong *et al*., 2001; Jung and Kim, 2001), OHSS consequent to a flare-up effect of a GnRH agonist, whether or not in conjunction with gonadotrophins (Hampton *et al*., 1991; Weissman *et al*., 1998; Campo *et al*., 2000; Khalaf *et al*., 2000; Letterie, 2000; Sommergruber *et al*., 2000). A rare event is the occurrence of OHSS following an ovarian stimulation without hCG induction, due to the endogenous LH surge. OHSS is probably uncommon when human menopausal gonadotrophin (hMG) alone is used due to the blocking of the endogenous LH surge of 80% in these conditions (Lipitz *et al*., 1991). Gonadotrophin surge attenuating factor may also have a possible influence in the rarity of OHSS without hCG administration (Balen and Jacobs, 1991; Pappa *et al*., 1999; Fowler *et al*., 2001).

Apart from these rare events, OHSS generally occurs only after exposure to either the endo- or exogenous LH or to its surrogate hCG (Editorial, 1991). This iatrogenic complication is unusual as it is not the consequence of a treatment which is either vital or mandatory for the patient's health. However, it can be fatal as its mortality rate has been estimated at 1 in 45 000 to 1 in 500 000 (Brinsden *et al*., 1995), and with a morbidity even higher though not accurately quantified.

Clinical description

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 have become cystic and this will often result in abdominal distension and pain, nausea, vomiting and sometimes diarrhoea. These digestive symptoms may be present as soon as 48 h after hCG administration, but they become most severe between days 7 to 10 after hCG.

The subsequent clinical signs are likely to result from a circulatory dysfunction corresponding to an increased vascular permeability and marked arterial dilatation (Fabregues *et al*., 1998). The first sign of OHSS is the formation of a small amount of ascites which is sometimes only visualized through vaginal ultrasound and difficult to distinguish from the frequent bleeding occurring after oocyte retrieval. In more severe forms, ascites is clinically identifiable, but is very uncommon before day 7 after hCG administration. The cystic ovaries are enlarged and may reach a size of >12 cm. Cases of rupture and/or haemorrhage of ovarian cysts have been observed (Rizk and Aboulghar, 1991), sometimes masking an ectopic pregnancy (Paulson and Lobo, 1988; Moosburger and Tews, 1996). Compression by enlarged ovaries can induce hydroureters (Schenker and Weinstein, 1978). A series of other complications may occur, some of them ending in complex end organ failure.

Ascites is characterized by a high concentration in proteins (4.8 g/100 ml), a low leukocyte count, and the presence of relatively high numbers of red blood cells. The extravascular protein-rich exudate accumulated in the peritoneum, in the pleura and even in the pericardiac space is associated with intravascular volume depletion and haemoconcentration, activation of vasoconstrictor and anti-natriuretic factors, severe hypoalbuminaemia and sometimes vulvar, or generalized oedema (anasarca) (Coccia *et al*., 1995; Vavilis *et al*., 2002).

The cardiovascular effects include arterial hypotension, reduced fluid volume, low central venous pressure, tachycardia, increased cardiac output, low peripheral resistance, increased vascular stasis, haemoconcentration and hypercoagulation (Cremisi and Mitch, 1994). The associated hypovolaemia can induce oliguria and electrolyte imbalance. Oliguria exists in about 30% of cases, and renal failure secondary to hypoperfusion or to compressive obstruction occurs in about 1.4% of the severe forms of OHSS (Abramov *et al*., 1999a; Khalaf *et al*., 2000).

Decreased renal perfusion induces a stimulation of renal tubules and resorption of sodium and water that result in clinical manifestations of oliguria and sodium retention. Electrolyte imbalance is then observed, typically hyponatraemia and hyperkalaemia.

Together with ascites, the associated paralytic ileus can impair diaphragmatic movement to such an extent that respiratory problems ensue. If pleural effusion also develops, lung function may be seriously affected and result ultimately in an adult respiratory distress syndrome (ARDS). Pleural effusion can complicate massive ascites or exist as an isolated manifestation of OHSS without peritoneal fluid accumulation. Liver dysfunction can also occur. Thromboembolic phenomena are the ultimate complication of OHSS and capable, despite appropriate treatment, of killing the patient.

So far, a limited number of fatal cases have been reported: one in New Zealand, one in Japan, one in Israel, one in Egypt, and four in the Netherlands (Mozes *et al*., 1965; Cluroe and Synek, 1995; Beerendonk *et al*., 1998; Serour *et al*., 1998; Semba *et al*., 2000).

The aim of this report is to review thoroughly the clinical course, consequences and treatment strategies related to OHSS.

Clinical course

Electrolytic imbalance

Haemoconcentration was found in 95.2% of 209 patients affected by severe OHSS (Abramov *et al*., 1999a) and in 71.1% of 128 patients affected by mild or moderate forms of OHSS (Delvigne *et al*., 1993). Others (Engel *et al*., 1972) were probably the first to consider this massive fluid shift as the 'cardinal event' of OHSS.

The haemoconcentration and severity of OHSS are much more reflected by the increase in haematocrit, rather than by white blood cell or platelet modifications. This has been documented by the important correlation between the haematocrit and the vasoactive substances that are dependent on plasma volume [renin activity, aldosterone, norepinephrine (noradrenaline) and antidiuretic hormone (ADH)] (Fabregues *et al*., 1998).

Some authors consider that leukocytosis and thrombocytosis are also markers of haemoconcentration, but others (Fabregues *et al*., 1998) considered these to be the stress responses similar to the non-infectious systemic inflammatory response. It has also been suggested (Fabregues *et al*., 1998) that gonadotrophins stimulate follicular cells to secrete cytokines, and that cytokines are responsible for the increased numbers of leukocytes and platelets (Hock *et al*., 1997).

Ascites is often accompanied by oliguria and a decrease in urinary sodium excretion, and by hyponatraemia. In cases of severe OHSS associated with clinical ascites, about one-third of the patients suffered from oliguria (urine volume <500 ml/day or <30 ml/h), while two-thirds had a urinary sodium level <30 mEq/

l. A urinary sodium level <10 mEq/l occurs in 24% of these cases (Fabregues *et al*., 1999).

Hyponatraemia (serum Na <130 mEq/l) was observed in 56% of patients (Fabregues *et al*., 1999). This feature may be due to dilution resulting from hypersecretion of ADH with water resorption exceeding the sodium resorption. Hyponatraemia may also be responsible for cerebral oedema, which in turn results in loss of consciousness (Pham *et al*., 1995). The inadequate urinary secretion of sodium induces potassium and hydrogen excretion disorder at the level of distal renal tubules, resulting in hyperkalaemia and acidosis. One group (Delvigne *et al*., 1993) observed electrolyte disorders in 54.6% of 128 cases of OHSS: 24.2% of these were related to potassium and 22.7% to sodium.

When hypovolaemia and haemoconcentration are not corrected quickly, a hypoperfusion of the kidney occurs followed by prerenal insufficiency associated with an increase in serum urea (due to an increase in reabsorption) which is dissociated from almost normal creatinine (creatinine not being reabsorbed). The clinical manifestation of these modifications is oliguria.

The previous observations were reported in women who had already fully developed OHSS or were pregnant. One group (Evbuomwan *et al*., 2000) carried out a longitudinal study of women undergoing superovulation to obtain data about haematocrit and osmolality before the onset of clinical symptoms of OHSS. These authors showed that in OHSS patients a loss of around 20% of blood volume occurred between days 2 and 4 after administration of hCG, followed by a sustained increase of 30% above baseline from day hCG +8 to +12. These alterations in blood volume were not seen in patients with uncomplicated cycles ($P < 0.006$). In OHSS patients, an unexpected significant increase in osmolality was observed, during the later stages of follicular growth, before hCG administration. Thereafter, the osmolality decreased until day 17 after hCG administration. In control patients, osmolality decreased gradually from the start of superovulation until day hCG +2 and began to recover from day hCG +4. These observations suggest that osmoregulation and volume homeostasis are altered in patients with severe OHSS, and that such alterations start much earlier than previously suspected. Some authors consider vascular endothelial growth factor (VEGF) to be the main mediator of fluid shift, haemoconcentration and electrolyte imbalance (Insler and Lunenfeld, 1997).

Neurohormonal and haemodynamic changes and contribution of arteriolar vasodilatation

Systemic, endogenous vasoactive neurohormonal factors as well as renal function was evaluated in 31 patients suffering from severe OHSS (Balash *et al*., 1994). These patients were assessed at the appearance of the syndrome and again at 4–5 weeks later, after their condition had receded. The authors recorded increased haematocrit, decreased mean arterial pressure, increased cardiac output and reduced peripheral vascular resistance. This was accompanied by marked increases in levels of plasma renin, norepinephrine (noradrenaline), ADH and atrial natriuretic peptide. Haemoconcentration was observed in 50% of the patients. The authors compared the previous results in women with and without haemoconcentration: similar values were observed for arterial pressure, cardiac output and peripheral vascular resistance, but patients with haemoconcentration had higher levels of renin, norepinephrine (noradrenaline) and ADH. These observations suggest that, in addition to increased capillary permeability, severe OHSS is associated with arterial vasodilatation. Indeed, if circulatory dysfunction was due solely to an extravascular shift, the contraction of the circulating blood volume should induce a reduction in cardiac output and an increase in peripheral vascular resistance as well as a decrease in atrial natriuretic peptide. In contrast, cardiac output and atrial natriuretic peptide were increased and peripheral vascular resistance was markedly reduced. These findings indicate a marked peripheral arteriolar vasodilatation. The simultaneous occurrence of these disorders leads to hyperdynamic circulatory dysfunction with marked stimulation of the sympathetic nervous system, renin-angiotensin system and ADH. The renal vasoconstrictor effect of these endogenous neurohormonal factors is counteracted by the increased renal production of vasodilator prostaglandins which maintains renal perfusion and glomerular filtration rate in normal limits for the majority of patients. However, the renal system promotes sodium and water retention, which contributes to oedema formation.

One group (Evbuomwan *et al*., 2000) observed an alteration of osmoregulation during OHSS, with an osmotic threshold for arginine vasopressin secretion that is reset to lower plasma osmolality during superovulation, this new lower body tonicity being maintained in OHSS patients until at least day 10 after hCG administration. These authors suggested that a decrease in plasma osmolality and plasma sodium levels was due to altered osmoregulation rather than to electrolyte losses.

Pulmonary manifestations of severe OHSS

Symptoms

Respiratory distress is often due to a restrictive syndrome induced by ascites, increased ovarian size and associated paralytic ileus (which raise the diaphragm), and more rarely by pleural and pericardiac effusions. Similarly, atelectasia of the pulmonary bases is the consequence of compression due to pleural effusion. No radiological signs of interstitial or alveolar oedema of the pulmonary bases are found (Levin *et al*., 1995).

Pulmonary manifestations were reported in 209 patients suffering from severe or critical OHSS among the 2902 registered cases of OHSS between 1987 and 1996 in Israel (78% IVF and 22% ovulation induction) (Abramov *et al*., 1999a). Dyspnoea was the most frequent respiratory symptom (92.3%). The majority of patients (92%) also suffered from tachypnoea and bilateral decrease of respiratory sounds (80%), a minority presenting some severe complications, such as lobar pneumonia (4%), ARDS (2%) or pulmonary embolism (2%).

X-Radiographic findings

Among the non-complicated cases, X-radiography showed a raised diaphragm in 71% and pleural effusion in 29%. These changes were predominantly found on the right side (51% were unilateral on the right, 21% were unilateral on the left, and were 27% bilateral). Atelectasia was found in 20% of the cases in Abramov's series, and in 9% of Levin's series.

The diagnosis of pulmonary embolism should always be considered after stimulation, when a patient develops with

dyspnoea associated with hypoxia in the absence of a hydrothorax, ascites or pulmonary atelectasia.

Blood gas analysis

These data show respiratory alkalosis with hypocarbia and a certain degree of metabolic compensation associated with a decrease in bicarbonates. Hypoxaemia is generally mild or moderate and associated with a decrease in oxygen saturation and in P_{O_2}. The mechanism behind this arterial blood gas profile consists of an extraparenchymal restrictive type of pulmonary dysfunction. Uncoordinated ventilation, leaving substantial hypoventilated areas of the lung, leads to ventilation–perfusion mismatch and hypoxaemia.

Pulmonary infections

These more often affect the inferior left pulmonary lobe. The aetiological agents are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Although the high incidence of pulmonary infections (4 to 30%) is generally attributed to a diminished ventilation and atelectasia, some authors also implicate hypogammaglobulinaemia associated with severe OHSS. The resulting decrease in immune defences may be responsible for these infections (Abramov *et al*., 1998a, 1999a,b).

Pleural effusion

A uni- or bilateral pleural effusion can be found in cases of severe hyperstimulation. Different authors observed pleural effusion varying between 10% and 29% of severe cases of OHSS (Golan *et al*., 1989; Levin *et al*., 1995; Abramov *et al*., 1999a). About 4.5% of severe OHSS cases necessitated thoracentesis. These effusions may appear early (6 days after hCG administration) or late (9–14 days after hCG). The classical manifestations are dyspnoea, dullness at pulmonary percussion and decreased respiratory sounds.

Although pleural effusion is generally thought to be a 'consequence' of pronounced ascites, associated with a shift of liquid from the peritoneal cavity to the pleura (either through a lymphatic route or an anatomic defect in the diaphragm), several observations have been reported of unilateral or bilateral pleural effusions in the absence of ascites. These data are summarized in Table I: it was observed that for 70% of isolated pleural effusion, OHSS was of a late-onset type. Pregnancy occurred in about 92% of the cases (Jewelewicz *et al*., 1975; Kingsland *et al*., 1989; Jiva and Israel, 1993; Daniel *et al*., 1995; Bassil *et al*., 1996; Man *et al*., 1997; Friedler *et al*., 1998; Wood *et al*., 1998; Gregory and Patton, 1999; Rabinerson *et al*., 2000; Roden *et al*., 2000; Tansutthiwong *et al*., 2000).

How can an isolated involvement of the pleura be explained? Although it is tempting to speculate that ovarian factors act electively on pleural tissues, a direct and localized action would appear unlikely. One group (Gregory and Patton, 1999) suggested that isolated hydrothorax may result from the combination of positive intra-abdominal pressure, and diaphragmatic defects that promote the transfer of intra-abdominal fluid into the pleural space, resulting in a hydrothorax and absence of abdominal fluid. The transfer of vasoactive factors from the abdomen to the pleural space could amplify or alter pleural fluid dynamics, promoting the formation of a large hydrothorax. This mechanism could reduce the volume of abdominal fluid necessary for the formation of a hydrothorax.

Several authors investigated these cases and were able to demonstrate small quantities of ascites in some of them, thereby questioning the theory of 'elective pleural action of vasoactive factors' (Hsieh *et al*., 1994; Loret de Mola *et al*., 1999). Unilateral recurrent effusion was observed in one patient during successive cycles of stimulation, suggesting the existence of pleural pathology, or an anatomical defect of the diaphragm (Friedler *et al*., 1998).

Chemical analysis of the fluid obtained from paracentesis revealed both transudate (Daniel *et al*., 1995; Bassil *et al*., 1996; Friedler *et al*., 1998; Wood *et al*., 1998; Rabinerson *et al*., 2000) and exudates (Kingsland *et al*., 1989; Man *et al*., 1997; Gregory and Patton, 1999; Roden *et al*., 2000). This observation remains unexplained, as this may reflect the possibility of multiple mechanisms involved in the pathogenesis of isolated hydrothorax.

Another question is why the frequency is higher on the right pleural side. One group (Man *et al*., 1997) attributed this preferential location of the disease to decreased lymphatic drainage, compared with the drainage of the left side. These isolated cases do not fit into the classical classification of OHSS.

Ultimate complications

ARDS is defined as severe hypoxaemia of acute clinical onset and bilateral scattered pulmonary infiltrates on a frontal chest radiograph (alveolar infiltrate) after exclusion of left atrial or pulmonary capillary hypertension. All cases of ARDS registered in one study (Abramov *et al*., 1999a) appeared after significantly more pronounced hydratation than in the uncomplicated cases. All patients with ARDS had dyspnoea and severe tachypnoea, and 80% had a temperature >38°C and a bilateral decrease of the respiratory sounds. All had bilateral pulmonary rales. Prostaglandins and cytokines may play a role in the pathophysiology of ARDS, as they are also incriminated in the pathophysiology of OHSS (Zosmer *et al*., 1987; Shigematsu *et al*., 2000). The increase in vascular permeability associated with the increased production in prostaglandins may lead to the deterioration of vessels and alveolar endothelium with liberation of blood, plasma and colloids, ultimately resulting in pulmonary oedema and atelectasis. If this complication is not treated urgently, interstitial fibrosis and cardiac arrest will occur in 90% of cases. Using adequate treatment, 50% of the patients will recover without sequelae (Schenker and Ezra, 1994). Corticoids are sometimes necessary to inhibit the immune response common in both OHSS and ARDS (Shigematsu *et al*., 2000).

Liver dysfunction

Incidence

The first description of liver abnormalities in OHSS after IVF was reported during the late 1980s (Younis *et al*., 1988). Two patients with OHSS had increased levels of serum aspartate aminotransferase (GOT) and alanine aminotransferase (GPT), while the levels of gamma-glutamyl transpeptidase (γGT) and bilirubin remained within normal values and alkaline phosphatases were at the superior limit of normality. Several authors found abnormal liver tests in 26–40% (mean 27.5%) of OHSS patients (Forman *et al*., 1990, $n = 8$; Delvigne *et al*., 1993, $n = 128$; Fabregues *et al*.,

Table I. Reported acute isolated cases (without ascites) of pleural effusion in patients affected by ovarian hyperstimulation syndrome (OHSS)

Reference	Treatment	Estradiol (pg/ml)	Oocytes (*n*)	Luteal supplementation	Days after hCG	Side (ml)	Other manifestations	Pregnancy Yes/No (number of fetuses)
Jewelewicz *et al.* (1975)	OI	–	–	NA	10	Bilateral	Haemoconcentration	Yes
Kingsland *et al.* (1989)	IVF	–	7	NA	12	Right (3500)	Haemoconcentration	Yes[a]
Jiva *et al.* (1993)	OI	–	–	–	15	Right	Large ovaries; minimal amount of Douglas fluid	Yes (1)
Daniel *et al.* (1995)	IUI	1900	–	NA	10	Right (2000)	Large ovaries	Yes (1)
Bassil *et al.* (1996)	IVF	2650	11	P	13	Left (2500)	Hypoalbuminaemia	Yes (2)
Man *et al.* (1997)	4 OI	NA	–	NA	7–10	3 right; 1 left (mean: 1675)	Large ovaries; minimal amount of Douglas fluid	NA
Wood *et al.* (1998)	IVF	3479	18	hCG	4	Right (3200)	Haemoconcentration; GPT elevated; Hypoalbuminaemia	NA
Friedler *et al* (1998)	IVF	2536[b]	27	P/hCG	13	Right (1700)	Large ovaries	NA
	IVF	>3000[b]	22	P	6	Right	Large ovaries	Yes (2)
	IVF	>3000	19	P	6	Right (4500)	Large ovaries; haemoconcentration	No
Gregory *et al.* (1999)	IVF	2663	17	NA	NA	Right (1150)	Large ovaries; haemoconcentration	Yes (1)
	OI	1140	–	NA	6	Right (NA)	Large ovaries; haemoconcentration	Yes (NA)
Tansutthiwong *et al.* (2000)	IVF	3322	10	hCG	14	Right (2700)	Haemoconcentration	Yes (2)
Roden *et al.* (2000)	IVF	NA	NA	NA	NA	Right (10 000)	Large ovaries; haemoconcentration	Yes (NA)
	IVF	NA	NA	NA	14	Right (–)	Large ovaries; haemoconcentration	Yes (NA)
	IVF	NA	NA	NA	11	Right (0)	Large ovaries; haemoconcentration	NA
Rabinerson *et al.* (2000)	IVF	7340	13	P	19	Right (6800)	Large ovaries	Yes (1)

[a] This patient had a spontaneous abortion.
[b] Same patient.
IUI = intra-uterine insemination; NA = not available; OI = ovulation induction; P = progesterone.

1999, $n = 50$). All of these abnormalities reverted to normal after resolution of the syndrome.

Origin of hepatic anomalies in OHSS

The origin of hepatic anomalies in OHSS is largely unknown. Among two autopsies obtained in OHSS patients, the first showed a normal lobular pattern by light microscopy (Sueldo, 1988), whilst the other was characterized by macrovesicular steatosis involving the periportal areas and liver parenchyma between the tracts (acinar zone 1), with an inflammatory infiltrate composed mainly of mononuclear cells and marked Kupffer cell hyperplasia (Ryley *et al.*, 1990). In both cases, electron microscopic ultrastructural examination of hepatocytes disclosed the presence of mitochondrial crystalline inclusions and dilatation of the rough endoplasmic reticulum, similar to that observed occasionally in pregnancy or during administration of oral contraceptives or anabolic steroids (Perez *et al.*, 1969; Adlercreutz and Tehunen, 1970). These observations and the supraphysiological level of estradiol seen during ovarian stimulation suggest a role for estrogens as pathogenic factors, with a compensatory structural rearrangement of enzyme protein subunits to enhance the metabolic degradation of these increased estrogens (Sueldo, 1988). Nevertheless, no significant correlations were found between estradiol levels and the appearance or severity of hepatic disorders (Forman *et al.*, 1990). In addition, pregnancy and oral contraceptives are mainly characterized by cholestasis which is rarely seen in OHSS (Shimono *et al.*, 1988). Only two observations of cholestasis were reported during OHSS (Nawroth *et al.*, 1996; Midgley *et al.*, 1999).

Alternatively, the hypothesis of a circulatory dysfunction has also been proposed (Balasch *et al.*, 1990; Shimono *et al.*, 1998). One group (Younis *et al.*, 1988) suggested that the increase of vascular permeability seen in OHSS may be responsible for hepatic oedema and the consecutive elevation of GOT and GPT. The increase of different mediators which has been observed in OHSS [e.g. renin-angiotensin or interleukin (IL)-6], may induce microvascular thromboses and liver tissue ischaemia, resulting in hepatic dysfunction (Shimono *et al.*, 1998; Borgaonkar and Marshall, 1999). This hypothesis was supported by the observations of others (Chen *et al.*, 2000), who found that serum IL-6 levels in the active phase of OHSS were higher when liver tests were also abnormal. Others (Balasch *et al.*, 1990) found that levels of renin, aldosterone and ADH were higher in severe OHSS associated with cholestasis. Nevertheless, one case of hepatic

disorder has been documented in a moderate OHSS case in the absence of any sign of increased vascular permeability (Wakim and Fox, 1996).

In conclusion, hepatic manifestations are present in about one-quarter of OHSS cases, generally in association with severe OHSS, and disappear with the recovery from OHSS.

Hypoglobulinaemia

It has been observed that immunoglobulins of molecular weight <200 0000 Da leave the plasma compartment to fill the third space (Abramov *et al*., 1999b). Indeed, blood levels of gamma-globulins IgA and IgG were significantly lower in severe OHSS cases than in a control group, while high levels were found in the peritoneal and pleural liquids in OHSS cases. However, this finding does not apply to alpha or beta-globulins, or to IgM, because of their higher molecular weights. The same process is thought to be responsible for hypoalbuminaemia. Furthermore, infections encountered in OHSS cases are seldom seen in young and healthy patients, but rather in nosocomial pathologies or in debilitating or immunosuppressed patients, which suggests that hypoglobulinaemia associated with OHSS favours infection by these agents.

Febrile morbidity

One report was made (Abramov *et al*., 1998a) that among a series of 209 severe cases of OHSS, 83.3% had a temperature above 38°C for at least 24 h. In about one-third of these cases, this could be attributed to infection (most frequently urinary), but in about two-thirds of the cases no infectious agent was identified. Fever, occurring in about 50% of OHSS cases, in the absence of any infection, may be considered as a symptom of OHSS. This may result from an endogenous inflammatory process due to the production of cytokines [IL-1, -6, -8 and tumour necrosis factor (TNF)] or of prostaglandins, as these materials have been implicated in the pathophysiological process of OHSS and are known also to cause fever.

Thromboembolic phenomena

Thromboembolic accidents are the ultimate complication that, despite appropriate treatment, can lead to the death of the patient. It is thus the most feared complication of OHSS. Because this complication may be unpredictable, an exhaustive review of this topic is provided herein.

Incidence

The incidence of thromboembolism is difficult to estimate because no systematic registration exists of OHSS cases or of their complications. Three large retrospective series of OHSS cases reported thromboembolic cases. A total of 128 cases of OHSS (86.7% moderate and severe forms) was documented in Belgium during a period of 4 years, and these included one case of cerebral thrombosis. In Israel, over a period of 10 years, among 209 registered cases of the severe form, an incidence of 2.4% was observed (Delvigne *et al*., 1993; Abramov *et al*., 1998a). In a series of 2924 IVF cycles of which 1.7% developed severe OHSS, four deep venous thromboses and two hemiparesis cases were registered (Serour *et al*., 1998); that is, an incidence of 0.2% of thromboembolic phenomena among IVF cycles and an incidence of 10% for severe cases of OHSS. This is the highest rate reported in the literature.

Localization

Initially, the legs were thought to be the privileged site of thrombosis due to a decrease in venous circulation that could be caused by compression associated with ascites and large ovaries, with immobilization, hyperestrogenaemia and smooth muscle relaxation due to luteal supplementation (Kaaja *et al*., 1989). However, the accumulation of observations showed that the factor responsible is rather a state of hypercoagulopathy, which may explain why these thromboses are characterized by a special occurrence in young women and are localized at uncommon sites involving limb, cerebral and cardiac vessels.

According to one group (Stewart *et al*., 1997a), 60% of thromboemboli are localized in the upper part of the body, with venous thrombosis in 75% and arterial in 25% of these cases, while 4–12% are recorded as pulmonary embolisms. A systematic review of the published literature was performed (Table II) which included 68 reported cases of thrombosis: 34.3% in arterial and 65.7% in venous sites. Of these, 83% were localized in the upper part of the body (60% venous, 40% arterial) and 17% in the lower part (81% venous, 18% arterial).

Severe forms

Two fatal cases were the consequence of a cerebral infarction occurring after a thromboembolic stroke (Mozes *et al*., 1965; Cluroe and Synek, 1995). Most of the reported cases of cerebrovascular thrombosis presented as ischaemic infarcts, though one case of haemorrhagic lesion has been reported (Shan Tang *et al*., 2000). Others (Yoshii *et al*., 1999) estimated that the incidence of cerebral thromboembolism associated with OHSS was far more common than what has been previously believed, as it may often be overlooked in patients who are asymptomatic or show only mild neurological signs. One case of myocardial infarction after thrombosis of the coronary arteries has been reported (Ludwig *et al*., 1999). In reviewing the literature, 11.8% of pulmonary embolisms were recorded (summarized in Table II).

Various authors described thromboembolic phenomena during ovulation induction or IVF, without any other signs of OHSS (Crooke *et al*., 1964; Dalrymple *et al*., 1983; Boulieu *et al*., 1989; Inbar *et al*., 1994; Thill *et al*., 1994; Aurousseau *et al*., 1995; Benshushan *et al*., 1995; Kligman *et al*., 1995; Huong *et al*., 1996; Stewart *et al*., 1997b; Ludwig *et al*,. 2000; Akdemir *et al*., 2002). According to this review, when thrombosis occurred, severe OHSS was present in 76.3% of cases and pregnancy in 85%. There were as many early and late OHSS complicated by thrombosis and also as many singleton or multiple pregnancies complicated by thrombosis. One should always be careful after ovulation induction however, as about 12% of thromboses complicated moderate as well as 12% mild OHSS.

Timing of thrombosis

Various thromboses appeared quite late after the embryo transfer, rendering the diagnosis difficult. Therefore, physicians should be alerted, when neurological symptoms occur after ovarian induction until 20 weeks of pregnancy, even in the absence of haemoconcentration (Belaen *et al*., 2001). Furthermore, in various

case reports, thrombosis appeared several weeks after total resolution of OHSS (Mills *et al*., 1992).

Risk factors

Some authors reported a number of risk factors in relation to thromboembolic phenomena, including: low antithrombin III (AT III) (Kaaja *et al*., 1989), decreased protein S activity (Benifla *et al*., 1994) and Leiden factor V mutation (Hollemaert *et al*., 1996; Horstkamp *et al*., 1996). Others described thrombotic accidents during uncomplicated IVF or during ovulation induction without any signs of OHSS, associated with hereditary AT III deficiency (Kligman *et al*., 1995), systemic lupus erythematosus (Huong *et al*., 1996) or cardiovascular risk factors (Aurousseau *et al*., 1995).

In one prospective study (Dulitzky *et al*., 2002), the prevalence of markers of thrombophilia was evaluated in 20 women who were hospitalized for severe OHSS. The following markers were assessed: plasma levels of AT III, protein C and protein S, antiphospholipid antibodies, the Leiden factor V mutation and mutation of the methyltetrahydrofolate reductase (MTHFR) gene. Some 85% of patients with OHSS were carriers of one or more positive markers of thrombophilia, and all the thrombotic events occurred in women who had more than one marker for thrombophilia (40%). In addition, 27% of controls were carriers of one marker of thrombophilia, and none carried more than one marker.

Using a matched control study of 25 patients with OHSS, no increase in the prevalence of markers of thrombophilia was observed for several months after the OHSS episode (Delvigne *et al*., 2002). These discordant results may be due, at least partially, to the different timing of screening for thrombophilia markers. Indeed, one group (Dulitzky *et al*., 2002) evaluated their patients during the acute phase of OHSS, and therefore the coexisting hyperestrogenaemia may contribute to a decrease in AT III or protein S levels.

In conclusion, it is suggested that it might be worthwhile screening women with a family or personal history of thrombosis or of OHSS for thrombophilia, before they undergo ovulation induction.

Migraine has also been suggested as yet another sign of risk (Cluroe and Synek, 1995). In these conditions arterial spasms may trigger thrombosis under the influence of very high estradiol and progesterone levels. These authors reported one fatal case of cerebral infarction and attributed it to arterial spasm.

Aetiopathogeny of thrombosis

In view of the localizations and timing of thromboses, it is likely that the initial process is not a simple venous stasis but rather a systemic coagulation disturbance. Several investigators assessed coagulation markers in severe OHSS, and one group (Phillips *et al*., 1975) reported increased levels of factor V, platelets, fibrinogen, profibrinolysin, fibrinolytic inhibitors and increased thromboplastin generation in two patients with severe OHSS. During the same period, in a review of 25 hospitalized patients (Schenker and Weinstein, 1978), it was found that blood coagulation parameters including clotting time, bleeding time, platelet count, prothrombin time and fibrinogen were within normal limits.

Additional studies (Kim *et al*., 1981) showed that the increase in fibrinogen levels and decrease in AT III were correlated with increased estradiol levels induced by hMG administration, and suggested that this correlation is a potential explanation for the thromboembolism phenomenon observed in cases of OHSS. Others (Manaka *et al*., 1991) reported that levels of fibrinopeptide A and B, D-dimers and thrombin–AT III complexes were increased in 11 OHSS patients. This report suggested that activation of the blood haemostasis occurred at subclinical levels in the majority of severe OHSS cases. Therefore, careful monitoring of these molecular markers may be useful in evaluating blood haemostasis in OHSS patients. Along the same lines, another group (Aune *et al*., 1991) assessed blood coagulation and fibrinolytic activity, after stimulation in 12 IVF patients. These authors observed a significant rise in plasma fibrinogen and a reduction in AT III. The blood fibrinolytic activity was significantly reduced, as evaluated by an increase in the clot-lysis time, and the authors concluded that there is a state of hypercoagulability during ovarian stimulation.

A decrease in serum AT III levels in patients with severe OHSS has also been described (Ryo *et al*., 1999), and this occurred without the existence of thrombotic complications. These authors showed that a shift of AT III towards the ascites was at the origin of this decrease in serum AT III, and they hypothesized that AT III synthesis was insufficient to compensate this loss.

In an original investigation (Kodama *et al*., 1995), the blood haemostatic markers of 22 severe OHSS patients without thromboembolic complications were compared with one case of severe OHSS complicated by a cerebral thromboembolism. This led to the observation that approximately 14 h before the onset of the thrombotic event, an increased concentration of white blood cells and activation of the markers related to the fibrinolytic system take place. The involved fibrinolytic markers were a decreased level of alpha2 plasmin inhibitor, an increased level of plasmin-alpha2 antiplasmin complexes, and increased D-dimers.

Later, the same group (Kodama *et al*., 1996) measured serum concentrations of plasma thrombin–AT III and plasmin–alpha2 antiplasmin complexes from the day of hCG administration to the mid-luteal phase in OHSS cases ($n = 13$) and in two control groups ($n = 27$), characterized by two different levels of estradiol. These authors studied the evolution of coagulation factors during OHSS associated with or without pregnancy: in simple OHSS cycles, the levels of the two complexes began to rise within a few days after hCG administration and were significantly higher during the mid-luteal phase. In OHSS associated with pregnancy, these elevations persisted for three or more weeks after the onset of disease. Without pregnancy, however, concentrations of both complexes decreased markedly one week after the onset of OHSS.

A decrease in AT III was also observed in this study. The higher levels of activation in fibrinolytic markers are thought to be indicative of the formation of considerable amounts of subclinical thrombi in the bloodstream. These markers appear, therefore, to be useful for predicting the risk of thromboembolism in OHSS patients and detecting subclinical thrombosis.

Another study suggested that the protease released by activated neutrophils, cathepsin G, may play a role in thrombus formation in OHSS. Cathepsin G destroys endothelial cells and exposes subendothelial collagen. Therefore, it also promotes platelet

Table II. Reported cases of thrombosis in patients affected by ovarian hyperstimulation syndrome (OHSS)

Reference	Type of thrombosis	OHSS	Pregnant	Timing (day after hCG)[a]
Mozes *et al.* (1965)[b]	1) Right femoral, left popliteal arteries and left femoral vein with pulmonary embolism	Moderate	NA	15 > hCG (E)
	2) Left internal carotid artery	Severe	NA	5 > hCG (E)
Humbert *et al.* (1973)[b]	Left vertebral artery and basilar artery	Severe	NA	1 > hCG (E)
Nwosu *et al.* (1974)[b]	Left superficial thrombophlebitis of the leg with massive pulmonary embolism	Severe	Twin	18 and 46 > hCG (L)
Schenker *et al.* (1978)[b]	Thrombophlebitis, leg deep vein thombosis (2 cases)	Yes	No	NA
Dumont *et al.*** 1980	Cerebral anterior and middle left artery	Severe	Quintuplet	9 > hCG (E)
Salat-Baroux *et al.* (1987)	Probably small right pulmonary embolism	Yes	Yes	NA
Boulieu *et al.* (1989)	Right venous innominate trunk	Severe	Twins	30 > hCG (L)
Neau *et al.* (1989)[b]	Right middle cerebral artery	Severe	Septuplet	14 > hCG (NA)
Kaaja *et al.* (1989)	Left fibular vein	Severe	Singleton	24 > hCG (L)
Makhmakhi (1989)	5 cases:	Mod	Singleton	60 > hCG (NA)
	1) Right internal jugular vein and superior vena cava	Severe	Singleton	40 > hCG (NA)
	2) Left internal jugular and subclavian vein with pulmonary embolism	NA	NA	NA
		NA	NA	NA
	3) Humeral artery	NA	Sextuplet	40 > hCG (NA)
	4) Massive pulmonary embolism (?)			
	5) Right axillary, subclavian veins and Right venous innominate trunk **			
Rizk and Aboulghar (1990)	Right middle cerebral artery	Severe	Singleton	13 > h CG (L)
Rajah *et al.* (1991)[b]	Left internal jugular vein	Severe	Yes	42 > hCG (L)
Ong *et al.* (1991)[b]	Pulmonary emboli associated with left internal jugular vein	Severe	Singleton	27 and 50 > hCG (L)
Fournet *et al.* (1991)	Right internal jugular, subclavian veins and superior vena cava and right atrium	Severe	Twin	32 > hCG (L)
Mills *et al.* (1992)	Right subclavian vein	Severe	Blighted ovum	50 > hCG (L)
	Left subclavian vein	Severe	Twin	50 > hCG (L)
Kermode *et al.* (1992)	Left internal carotid artery and right internal iliac vein	Severe	No	10 > hCG (NA)
Waterstone *et al.* (1992)[b]	Internal cerebral vein and Galen's vein	Severe	Biochemical	12 > hCG (E)
Delvigne *et al.* (1993a)	Cerebral thrombosis	Severe	NA	NA
Ayhan *et al.* (1993)[b]	Left internal jugular vein	Severe	No	13 > hCG (E)
Vauthier-Brouzes *et al.* (1993)	Left internal jugular, subclavian and axillary vein	Mild	Singleton	140 > hCG (NA)
Bachmeyer *et al.* (1994)	Internal jugular vein	Severe	Singleton	35 > hCG (L)
Benifla *et al.* (1994)	Left internal jugular and subclavian veins	Severe	Twin	49 > ET (L)
El Kouri *et al.* (1995)	Left internal jugular vein	Severe	Yes	42 > hCG (L)
	Right internal jugular and subclavicular veins	Severe	Yes	49 > hCG (E)
Cluroe and Synek (1995)	Right middle cerebral artery	Severe	NA	6 > ET (E)
Choktanasiri *et al.* (1995)	Bilateral external iliac and femoropopliteal arteries	Severe	Singleton	16 > hCG (L)
Hignett *et al.* (1995)	Right internal jugular vein	Severe	Twin	43 > hCG (E)
Kodama *et al.* (1995)	Right middle cerebral artery	Yes	Yes	14 > hCG (NA)
Hocke *et al.* (1995)	Right humeral and internal jugular veins	Severe	Triplet	49 > hCG (NA)
	Right subclavian and internal jugular veins[b]	Mild	Sextuplet	40 > hCG (NA)
	Superior sagittal sinus	Severe	Twins	17 > hCG (NA)
Hulinsky and Smith (1995)	Right external jugular vein	Severe	Yes	38 > hCG (L)
Horstkamp *et al.* (1996)	Right internal jugular vein	Yes	Yes	30 >hCG (NA)
Hollemaert *et al.* (1996)	Right humeral, axillary, subclavian and internal jugular veins	Severe	Twin	19 > hCG (E)
Germond *et al.* (1996)	Left aortosubclavian and axillary artery	Moderate	No	7 > hCG (E)
Moutos *et al.* (1997)	Bilateral internal jugular veins	Severe	Singleton	31 > hCG (E)
Stewart *et al.* (1997a)	Left axillary vein	Severe	Singleton	37 > hCG (E)
	1 case of pulmonary embolism (limb origin?)	Yes	Yes	NA
Hwang *et al.* (1998)	Right middle cerebral artery	Severe	Yes	15 > hCG (L)
Ellis *et al.* (1998)	Bilateral jugular veins	Severe	Twin	28 > hCG (L)
Aboulghar *et al.* (1998)[b]	Cerebrovascular (2 cases)	Moderate	No	12 > hCG (L)
		Mod	NA	10 > hCG (E)
El Sadek *et al.* (1998)	Left choroidal cerebral artery	Severe	Biochemical	8 > hCG (E)
Davies and Patel (1999)	Right middle cerebral artery	Severe	NA	NA
Morris and Paulson (1999)[b]	Brainstem infarction	Mild	NA	4 > hCG (E)
Ludwig *et al.* (1999)	Coronary artery and myocardial infarction	Mild.	No	5 > hCG (E)
Yoshii *et al.* (1999)	Right internal carotid artery	Severe	Yes	6 > start treatment(E)
Jacob *et al.* (1999)	Left internal jugular and subclavian veins	Severe	Singleton	29 > hCG (L)
Todros *et al.* (1999)[b]	Left internal jugular vein (spontaneous OHSS)	Severe	Singleton	119 gestation (L)
Lamon *et al.* (2000)	Right jugular and subclavian veins and superior vena cava	Severe	Yes	49 > hCG (E)

Reference	Type of thrombosis	OHSS	Pregnant	Timing (day after hCG)[a]
Shan Tang *et al*. (2000)	Cortical vein thrombosis and left common femoral, left external iliac, right common iliac veins and inferior vena cava	Severe	Singleton	14 > ET (L)
Loret de Mola *et al*. (2000)	1) Left subclavian deep vein extending to internal jugular vein	Mild	Singleton	21 > hCG (L)
	2) Left subclavian deep vein	Moderate	Singleton	25 > hCG (L)
Cil *et al*. (2000)	Left ileofemoral vein	Severe	–	5 > hCG (E)
Schanzer *et al*. (2000)	Left internal jugular vein	Mild	Twin	28 > hCG (NA)
Belaen *et al*. (2001)	Left internal jugular vein	Moderate	Twin	34 > hCG (L)
Mancini *et al*. (2001)	Subclavian artery	Mild	NA	NA (E)
Heinig *et al*. (2001)	Left ulnar artery	Severe	No	NA (E)
Dulitzky *et al*. (2002)	Pulmonary embolism (2)	Severe	NA	NA
	Cerebral ischaemic attack	Severe	Yes	

[a]Timing means number of days after embryo transfer (ET) or hCG for sign of thrombosis (L/E for late or early onset of OHSS).
[b]With ovulation induction but no IVF.
NA = information not available or not found.

adhesion and aggregation, resulting in thrombus formation (Hwang *et al*., 1998).

Numbers of white blood cells and, more particularly, the monocyte expression of tissue factor, were evaluated in nine severe OHSS patients (Balasch *et al*., 1996). These authors found that procoagulant activity of blood monocytes, which is principally mediated by tissue factor expression, was increased as compared with controls. Monocytic expression of the tissue factor decreased to normal values after recovery from OHSS. Moreover, this study confirmed the prothrombotic state characterized by increased levels of markers of thrombin (thrombin–AT III complexes and prothrombin fragment) and fibrin (D-dimers).

In summary, haemoconcentration resulting from the extravasation of fluids towards the third space is considered as the main cause of activation of the coagulation cascade. Haemoconcentration induces increased blood viscosity and a slower blood flow. Platelets and neutrophils may easily adhere to the vascular wall and activate the coagulation cascade. Nevertheless, the increase in complexes of thrombin–AT III and plasmin–alpha2 antiplasmin appear respectively 2 and 4 days after hCG administration, well before haemoconcentration is observed. Early peripheral arterial vasodilatation has also been observed in OHSS before the onset of haemoconcentration and the appearance of OHSS symptoms (Balasch *et al*., 1994). This vasodilatation may result in vascular stasis and trigger the coagulation cascade. Thereafter, the balance between coagulation and thrombolysis is modified and the coagulation process becomes enhanced (Loret de Mola *et al*., 2000).

Neurological manifestations

Some rare neurological manifestations have been attributed to OHSS, such as benign intracranial hypertension, which is otherwise an idiopathic pathology, with an incidence of about 0.7 to 1.7 per 100 000 in the general population. One case was reported in 1999 (Lesny *et al*., 1999) following the development of severe OHSS after IVF in a patient who became pregnant and developed persistent headaches, diplopia and transitory confusion. She received a treatment consisting of 10 consecutive lumbar punctures and administration of oral diuretics. The different mediators implicated in the OHSS process (renin system, prostaglandin, interleukin, VEGF) may have affected the balance between the production and resorption of cerebrospinal fluid.

Most patients recover from thrombosis linked to OHSS, though in some cases neurological sequelae have been described such as hemiparesis, dysphasia, fine movement disturbances and persistent electroencephalogram (EEG) disorders (Humbert *et al*., 1973; Neau *et al*., 1989; Kermode *et al*., 1992; Waterstone *et al*., 1992; Hwang *et al*., 1998).

Adnexal torsion

During the early stages of OHSS, abdominal pain is due to the increase in ovarian size and the presence of numerous luteal cysts. This may favour adnexal torsion particularly in the case of pregnancy; indeed, this complication was observed in 16% of pregnant patients and 2.3% of non-pregnant patients among a series of 201 OHSS cases over a 10-year period (Mashiach *et al*., 1990). The diagnosis is difficult during OHSS because the symptoms are not specific for torsion; this may lead to delayed diagnosis and intervention, and to definite damage with loss of ovarian function in these patients.

The presence of large ovaries, nausea, abdominal pain and progressive leukocytosis and anaemia are suggestive of a torsion. Generally, symptoms appear between the 6th and 13th weeks of pregnancy, except in one case where they started during the 20th week (Mashiach *et al*., 1990). In the series reported by these authors, both ovaries were similarly affected and the mean interval between admission of the patient and surgery was 15.5 h; however, the delay between the onset of symptoms and admission was up to 43 h. A simple de-torsion should first be attempted, even when the ovaries have an ischaemic aspect, because in about 73% of cases this procedure is sufficient to maintain ovarian function. Among 12 cases of torsion, 42% also had ruptured cysts and 50% had ovarian bleeding. The evolution of pregnancy after this type of surgery seems mostly favourable, the rate of miscarriage being 16.6% (Mashiah *et al*., 1990).

Only one group (Jahier *et al*., 1985) suggested proceeding to laparoscopic punction of cysts of size >4 cm in order to avoid

torsion. This procedure may reduce the incidence of torsions and have an analgesic effect, though this report was limited to only four cases. This approach was not advocated by others in order to avoid manipulating these frail and hypervascularized ovaries.

Pregnancy after OHSS

Different authors have reported generally compromised obstetric outcome after OHSS. Several hypotheses have been suggested to explain these observations:

- It is generally accepted that ovarian hyperstimulation entails very high serum estradiol levels and altered progesterone/estradiol ratios; the latter situation has also been reported to be associated with impaired endometrial receptivity (Gidley-Baird *et al*., 1986).
- Abnormal cytokine levels in patients with severe OHSS may *per se* affect early pregnancy (Raghupathy, 1997). Cytokine levels in serum and ascitic fluid are elevated in OHSS patients. Furthermore, some gene polymorphism for cytokines (TNFα), has been associated with a higher incidence of pre-eclampsia (Chen *et al*., 1996b). However, the prevalence of this gene polymorphism has not been studied in OHSS patients. A lower pregnancy rate was also found in a group of patients with abnormal liver tests and high IL-6 serum concentration (Chen *et al*., 2000).
- A higher incidence of positive markers of thrombophilia were reported (86.6%) among women hospitalized for severe OHSS (Dulitzky *et al*., 2002), and this may be a common risk factor for poor obstetric outcome (miscarriages, pre-eclampsia and placental insufficiency).
- Polycystic ovary syndrome (PCOS) is associated with OHSS, but a higher incidence of miscarriages and pre-eclampsia have been reported in women affected by PCOS. This has been attributed to hypersecretion of LH, which may be corrected by the use of a GnRH-agonist. Nevertheless, not all the data concur, as in a recent study of IVF patients with a PCOS ovarian morphology under GnRH-agonist, no difference in the risk of miscarriage was observed for women suffering from OHSS and those who did not (11.1 versus 6.9%) (Engmann *et al*., 1999).
- A higher incidence of miscarriage may also result from hypoxia, which is present in severe OHSS, or from dysfunction of key organs such as the liver and the kidney.
- The incidence of late OHSS is correlated to the number of gestational sacs, and thus the higher incidence of multiple pregnancies is yet another reason for an increase in poor outcome of pregnancies complicated by OHSS.

Even if there are theoretical grounds for expecting an association between OHSS and adverse pregnancy outcome, the literature does not enable us to draw definitive conclusions. Three studies described miscarriage rates in ovulation induction (non-IVF cycles): two of these (Rabau *et al*., 1967; Schenker and Polishuk, 1976) were among the first to report rather high rates of miscarriage of (respectively) 25% ($n = 4$) and 40% ($n = 10$), in a rather small series of patients and in studies without control groups. Others (Caspi *et al*., 1976), in a controlled study, also found a higher incidence of miscarriage in OHSS complicated cycles (10/29, 34.5%) compared with non-complicated cycles (20/114; 17.5%).

In contrast, in an IVF programme, no difference was found in pregnancy rates between classical IVF cycles as compared with donor cycles, despite the fact that a significantly higher incidence of OHSS was observed in the classical IVF cohort (Meldrum, 1990). Others (MacDougall *et al*., 1992) reported a miscarriage rate of 28.6% in IVF cases complicated by OHSS, though without comparison to a control group. A 26.6% miscarriage rate was found in 15 OHSS patients as opposed to 17% in a group of 110 contemporaneous controls (Chen *et al*., 1997). In a study of the largest cohort of severe OHSS pregnant patients during a 10-year period ($n = 163$) (Abramov *et al*., 1998b), it was possible to demonstrate a poorer obstetric outcome after OHSS. Indeed, among a clinical pregnancy rate of 73%, 29.8% of miscarriage, 57.6% of multiple pregnancy and 44% of premature delivery, 44% of Caesarean section (24.1% in singleton), 62.1% of low birth weight (34.5% in singleton) were observed. Frequent antenatal obstetrical complications were hypertension (13.2%), diabetes (5.9%) and abruptio placenta (40.4%). All of these values were much higher than were reported by other groups in IVF patients who did not develop OHSS. However, the incidence of fetal malformations was found not to be elevated (1.9%) (Abramov *et al*., 1998b).

Criticism of the study by Abramov *et al*. has been forthcoming (Mathur *et al*., 2000a), mainly because of the absence of an adequate contemporaneous control group and because the high rate of many complications can be attributed to the high rate of multiple pregnancies. The authors (Mathur *et al*., 2000a,b) evaluated a smaller cohort of moderate and severe OHSS patients ($n = 41$), but using a contemporaneous control group of 501 IVF pregnancies without observing significant differences in miscarriage rates (12.1 and 16.8% respectively). However, the OHSS group was more likely to have multiple pregnancies (41.4 versus 32.9%) and preterm deliveries (21.9 versus 16.1%). Also, the difference in birth weight was not significant when singletons alone were considered. It should be noted that the discordance between both studies might also be due to the higher incidence of severe OHSS in Abramov's cohort.

Another group (Raziel *et al*., 2002) studied pregnancy in 104 severe or critical OHSS cases after IVF and observed higher abortion rates in OHSS patients as compared with IVF patients without OHSS during the same 6-year period (23 versus 15%). However, the pregnancy rate in the OHSS patients was also higher. The ongoing pregnancy rate per cycle in OHSS patients was significantly higher than that of patients without OHSS (30.6 versus 20%). Nonetheless, more severe forms of OHSS (attested by a longer stay in hospital) were correlated with a higher frequency of abortion. It should be noted however that estradiol levels on the hCG day were similar in those who delivered and those who aborted, and that this study did not involve PCOS patients.

Only one prospective study was performed and reported a significantly improved pregnancy outcome after severe OHSS ($n = 18$) (66.7% of live birth rate versus 25% in the control group) (Enskog *et al*., 1999).

In conclusion, the question of whether OHSS itself causes or contributes to any adverse effects on a coexisting pregnancy remains unanswered, since the problem of multiple pregnancy remains one of the key issues of IVF and is often an important confounding factor. Nevertheless, particular attention should be

given to the management of severe OHSS in view of maintaining optimal vital conditions and avoiding hypoxia. Large prospective studies assessing pregnancy outcome must be performed in order to draw definitive conclusions.

Treatment

Prevention and early recognition of OHSS are the most important tools for the patient's safety. The following particular preventative strategies have been assessed: cancelling the cycle; alternatives to hCG administration; 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. These are discussed in a separate review article (Delvigne and Rozenberg, 2002).

Conservative management is often sufficient because the syndrome is self-limiting. Indeed, the functional life-span of luteinized follicles is limited and at a certain moment they cease to produce substances (VEGF, cytokines, renin, etc.) which mediate the pathological process. Resolution occurs within about 2 weeks in the absence of pregnancy in most cases. Clinical resolution seems to parallel the decrease of residual hCG after giving the oocyte maturation dose, but an implanting pregnancy with a subsequent increase in endogenous hCG may prolong or worsen OHSS. Therefore, care should be taken until the diagnosis of pregnancy has been either confirmed or ruled out.

Patients receiving gonadotrophins should be warned about the risk of OHSS and its symptoms. After oocyte retrieval, patients considered at high risk should be given additional information and advised to consult if any relevant symptoms of OHSS appear.

When OHSS is suspected, a full clinical examination should be performed, including weighing the patient. Her general health should be assessed, the degree of hypovolaemia estimated, and the presence of any secondary complications determined.

The first-line investigation should include measurements of full blood count, urea, creatinine and electrolyte concentrations and a pelvic ultrasonography to assess the extent of ovarian enlargement, the size and number of luteal cysts and the degree of pelvic and/or abdominal fluid accumulation.

In the absence of any true understanding of the aetiopathological mechanisms underlying OHSS, no direct aetiological treatment is applicable. Conservative management is the treatment of choice. However, treatment modalities of individual patients with OHSS generally vary according to severity of the disease. It is aimed at controlling plasma volume and renal perfusion until spontaneous recovery. Secondary complications are treated according to their nature.

Mild to moderate cases do not usually entail clinical consequences, but identifying them is essential to prevent the rare, severe complications. Indeed, in some patients the natural course will be the development of severe OHSS while an early diagnosis may be able to prevent it. Abdominal pain a few days after hCG administration should alert clinicians to the development of OHSS, and the following signs should be checked: weight gain, increase of abdominal circumference and, particularly, the size and appearance of ovaries on sonography.

General approach for different levels of severity

Mild OHSS

Mild OHSS does not require any specific treatment. Patients should be reassured, and most of them will fully recover within 1 week. Outpatient surveillance is nevertheless mandatory to detect cases that may progress to moderate or severe OHSS. The patient should be advised to consult if symptoms worsen, i.e. if there is a loss of appetite, weight increase or bloating. In all risk situations, patients are seen after 4–6 days following the appearance of the first symptoms. If at this stage the hyperstimulated ovaries are enlarged, patients should avoid strenuous activity, since they may be at risk for ovarian torsion. The degree of abdominal discomfort may require the use of analgesics.

Moderate OHSS

Rest and adequate fluid intake (quantity defined by in/out fluid balance) is the mainstay of treatment for patients with moderate OHSS. Strenuous physical activity and sport should be avoided. Biological surveillance can be performed every 2–3 days on an outpatient basis, keeping in mind that when embryos are transferred, the occurrence of pregnancy may suddenly aggravate the situation and necessitate hospitalization because of severe OHSS. Ideally, each patient should record her 24-h intake fluid volume and urine output, and these parameters be reviewed daily with the patient over the telephone (Whelan and Vlahos, 2000).

Severe OHSS

Severe OHSS must be regarded as a potentially fatal complication requiring immediate therapy as well as close monitoring. Careful clinical examination should be performed to detect the presence of secondary complications. The haematocrit is a valuable parameter to evaluate the severity of OHSS, hospitalization being required when a value of 45% is reached. Other investigations are recommended at this stage:

- Daily:
  - Input-output chart and abdominal girth and body weight.
  - Leukocyte count (its elevation is an ominous sign of thromboembolism), haemoglobin concentration, full electrolytes panel.
  - Creatinine clearance, urea, creatinine
  - C-reactive protein (to exclude concomitant infection)
  - Coagulation screening (to rely on baseline values in case of further therapeutic anticoagulation), D-dimers (early diagnostics of thrombosis)
- Weekly (according to the clinical evolution):
  - Liver and renal function tests
  - Chest X-radiography (for pleural effusion)
  - Electrocardiogram and eventually cardiac ultrasonography (for pericardiac effusion).

Therapy should remain supportive and conservative, aiming at refilling the arteriolar bed, mobilizing fluid from the third space back to the vessels, maintaining circulatory haemodynamics and preventing haemoconcentration.

Volume replacement may begin with intravenous crystalloid fluids (normal saline solution) at 125–150 ml/h. Plasma expanders (colloids) can be used if necessary,. However, if plasma expanders themselves are transported to the peritoneal cavity,

their use may be counterproductive (Kissler *et al*., 2001). Albumin has often been used (at 200 ml of 25% albumin solution over 4 h), as have dextran, mannitol and fresh-frozen plasma. Recently, the effect of 6% hydroxyaethyl starch (HAES) was compared with that of albumin in a small series of patients suffering from severe OHSS. Results appeared in favour of HAES in terms of higher urine output, fewer paracentesis procedures and shorter hospital stays (Abramov *et al*., 2001). In another comparative study between HAES 10% and Haemaccel, no clinical advantage was found for the HAES (Gamzu *et al*., 2002). However, larger prospective randomized and controlled studies are needed before definite conclusions can be drawn. HAES has the advantage of a non-biological origin and of a higher molecular weight (200–1000 kDa versus 69 kDa for albumin). A recent case report in which a patient was given 10% HAES led to a rapid recovery (Rabinerson *et al*., 2001).

Protein-rich diets were also administered for the same purpose (Scheele *et al*., 1992). Sodium and fluid restriction without the use of volume expanders has been advocated to control rapid fluid accumulation in the third space (Haning *et al*., 1985; Balasch *et al*., 1991), though no randomized trial has been performed to truly evaluate this therapy. On the other hand, it may prove detrimental to fluid and electrolyte balance.

Bed rest and careful monitoring of urinary output will be prescribed, especially when oliguria occurs. Dopamine may be helpful in restoring renal perfusion (Navot *et al*., 1992). An intravenous dopamine regimen of 0.18 mg/kg per hour has been shown to dilate renal vessels and increase renal blood flow without affecting blood pressure and heart rate (Ferraretti *et al*., 1992; Morris *et al*., 1995a). Diuretics are contraindicated when patients display haemoconcentration, hypotension or hyponatraemia. Their use should be restricted to cases in which haemodilution is achieved while oliguria persists (Bar-Hava and Homburg, 1993). Nevertheless, intravenous 20% albumin associated with frusemide at 20 mg every 6 h under careful monitoring, were successfully used in three patients with prerenal azotaemia resistant to other therapeutic measures (Peces *et al*., 1994). The insertion of a central venous pressure line is recommended if fluid balance is difficult to maintain and in case of the use of dopamine.

The patient may leave the hospital when the haemoconcentration decreases and the diuresis increases and no further complications persist. The mean hospitalization stay is about 8 days, but this may be shortened when no pregnancy is involved and when resumption occurs together with menstruation (5 days). However, it may be much longer in severe forms, requiring 2–4 weeks when aggravated by pregnancy (Padilla *et al*., 1990; Delvigne *et al*., 1993; Wada *et al*., 1993).

Some authors evaluated a more economic approach based on outpatient clinic surveillance and treatment. One group (Shrivastav *et al*., 1994) followed 10 severe OHSS patients using daily monitoring and management to avoid prolonged hospitalization. Early abdominal paracentesis, as well as intravenous hydratation, were repeated. Similarly, others (Fluker *et al*., 2000) have organized outpatient management in early stages of OHSS, including paracentesis and albumin administration. Traditional measures involved bed rest and observation until the clinical picture deteriorated sufficiently to require hospitalization. The same group (Fluker *et al*., 2000) also derived an autosurveillance method for patients at high risk (increased weight, abdominal girth, fluid intake and decreased urine output), a consultation being planned if these parameters were suddenly modified. If ultrasonography demonstrated pockets of ascitic fluid of more than 5 cm depth, transvaginal paracentesis was performed. These authors proceeded in the same manner at oocyte collection, but for a longer time (20–30 min), retrieving up to 2 l of peritoneal fluid. In the presence of marked hypoalbuminaemia, 250 ml of 25% albumin was injected in 3–4 h after paracentesis.

Daily monitoring continued at home and follow-up blood analyses were repeated at 2- to 4-day intervals. Out of 13 women who had moderate OHSS, none saw her situation worsen, although they all became pregnant. Recovery and return to work occurred 7.4 days after the first paracentesis. This approach requires motivated, educated and compliant patients who are able to return rapidly to the clinic for reassessment if required. The lack of a control group limits comparisons and conclusions. However, early intervention to avoid progression, rather than waiting passively, remains an attractive approach that deserves prospective evaluation. An additional group of 48 patients undergoing outpatient treatment, which consisted of culdocenthesis, i.v. rehydratation and albumin infusion, was assessed every 1–3 days until resolution of symptoms or hospitalization (Lincoln *et al*., 2002). These authors observed remission of the disease in 91.6% of patients and showed that hospitalization could be avoided altogether.

Specific approach for particular symptoms of OHSS

Paracentesis

Abdominal paracentesis is the most frequent intervention in severe cases of OHSS. This therapeutic approach, which has been exemplified in case reports (Rabau *et al*., 1967; Thaler *et al*., 1981), induces a dramatic improvement of creatinine clearance, and of urine volume as well as weight loss. Others (Borenstein *et al*., 1989) confirmed a significant decrease in haematocrit and blood osmolality in a series of seven cases, which were treated by ascites drainage.

In the large cohort that was studied in Israel (Abramov *et al*., 1999a), abdominal paracentesis was performed abdominally or vaginally in 82% and 4% of the cases respectively. Indication was either deterioration of respiratory function (74%) or oliguria (11%) or haemodynamic instability (2%) or a combination of these different factors (13%). Drainage was associated with dyspnoea improvement in 95%, and increase of diuresis in 73% of patients.

The abdominal approach is favoured of because better accessibility and optimal comfort for the patient. Nevertheless, cutaneous oedema may sometimes render this approach impossible because of the thickening of the abdominal wall and loss of visibility at ultrasound. For this reason, vaginal catheters were developed that can be left in place to drain the peritoneal fluid in a progressive and slow manner (Raziel *et al*., 1998).

Several other groups (Schenker and Weinstein, 1978; Morris *et al*., 1995a; Whelan and Vlahos, 2000) consider that paracentesis should be reserved for patients resistant to conservative management (dextran, mannitol, dopamine, albumin) because of the risk of lesions to hypervascularized and enlarged ovarian cysts or to the bowels and other rare complications such as a post-

paracentesis bilateral massive vulvar oedema (Luxman *et al*., 1996; Vavilis *et al*., 2002). Whichever approach is used however, the procedure should be carried out under ultrasonographic guidance.

Other investigators apply ascites puncture quite liberally because they obtain rapid improvement of the symptoms. One group (Aboulghar *et al*., 1990) compared two approaches: a conservative versus systematic transvaginal puncture of ascites in a randomized trial involving 21 cases of severe OHSS and confirmed their earlier results in a larger series of 42 patients (Aboulghar *et al*., 1993). Conservative management was associated with a significantly longer hospitalization (mean of 11 versus 4 days). Furthermore, electrolyte disturbances disappeared within 24 h in the paracentesis group, but lasted for a mean 9 days in the group with conservative management.

In a larger retrospective series ($n = 30$), it was confirmed that paracentesis performed either for tense ascites or for difficult breathing, improved urinary output the day after the procedure and decreased blood urea nitrogen, blood cell count and haematocrit during the same period in a significant proportion (Levin *et al*., 2002). However, no correlation was found between aspirated volume and change in urine production or blood indices. These authors confirmed that clinical improvement is related to paracentesis rather than to i.v. fluid perfusion, and advocated paracentesis as early as possible.

There are various possible mechanisms by which ascites removal increases urine production and decreases haemoconcentration: (i) a reduction of intra-abdominal pressure may alleviate compression of the vena cava, thereby increasing venous return and cardiac output as well as improving urinary perfusion; (ii) decompression of the ureters may also increase diuresis; or (iii) removal of part of the 'mediator responsible for the OHSS process' present in peritoneal fluid, may occur through paracentesis. In one study (Chen *et al*., 1998), an improved urine production was documented in seven women after ascitic drainage, but not in three others after thoracocentesis; the authors speculated that ascitic puncture has a direct effect on urine production. However, an abrupt decrease in intra-abdominal pressure caused by rapid and total paracentesis facilitates the shifting of fluid from the intravascular compartment to the peritoneal cavity, with rapid reaccumulation of ascites and decrease of effective intravascular volume. The removal of large volumes of ascitic fluid further depletes proteins lost from the intravascular compartment. This often leads to low intravascular protein concentration and electrolyte imbalance, especially when paracentesis is repeated. In turn, low intravascular protein concentration causes further accumulation of fluid in the abdominal or even in the pleural cavity. Therefore, it is suggested that intravenous macromolecules (albumin, HAES) be given, and that the haemodynamic parameters be monitored (Padilla *et al*., 1990).

For such reasons, some authors have suggested the use of autoreinfusion of aspirated ascitic fluid (Aboulghar *et al*., 1992; Fukaya *et al*., 1994; Splendiani *et al*., 1994; Beck *et al*., 1995). Auto-transfusion of the ascitic fluid has been carried out using whole ascitic fluid (Aboulghar *et al*., 1992). Paracentesis is achieved vaginally under strict sterile approach; the removed ascitic fluid is kept in a bag at 4°C to allow bacteriological culture of a sample and reinfused 48 h later. To avoid transfusion of unconcentrated large volumes and contamination by bacteria and cells, another group (Fukaya *et al*., 1994) used ultrafiltration with two filters: a cellulose acetate hollow-fibre filter that removes cells and bacteria, and a polyacrylonitrile hollow-fibre ultrafilter that concentrates the protein before reinfusion. The protein concentration obtained, after filtration, is increased 2-fold and albumin 2- to 5-fold. Fluid is reinfused intravenously at a rate of 300–500 ml every 6 h. In one study (Splendani *et al*., 1994), only one common high-flow dialyser was used for three patients.

Peritoneovenous shunting, as used in cirrhosis (Gines *et al*., 1991), has been carried out in isolated cases of severe OHSS by some authors (Splendiani *et al*., 1994; Beck *et al*., 1995). Another group (Koike *et al*., 2000) have undertaken a prospective randomized and controlled study to evaluate this method. To achieve peritoneovenous shunting ($n = 18$), an abdominal catheter was connected via a peristaltic pump acting through a microfilter (pore diameter 10 µm) to an antecubital venous catheter at a rate of 100–200 ml/h. A control group ($n = 36$) was treated with an i.v. albumin supplement (37.5 g per day). In the peritoneovenous shunting group, clinical discomfort, hospital stay, haematocrit, urinary output, blood pressure and serum concentrations of proteins were significantly improved as compared with the albumin group. The authors hypothesized that recirculation of ascite containing potential OHSS mediators may facilitate degradation of these mediators by the liver, lungs or kidneys while they were previously sequestered in the peritoneal cavity. Indeed, after peritoneovenous shunting, concentrations of mediators such as renin, angiotensin I and II and VEGF were decreased in serum and ascites in patients with severe OHSS (Ito *et al*., 2000). Unfortunately, as no control group assessing the effect of paracentesis and albumin infusion was included, aetiological factors could not be identified. It should be emphasized that peritoneovenous shunting avoids the abrupt decrease in abdominal pressure caused by paracentesis.

Finally, it should also be mentioned that blood products, such as commercially available proteins, may for example contain transmissible agents such as parvovirus B19 (Santagostino *et al*., 1994) that are capable of causing hydrops fetalis (Brown *et al*., 1984). The use of peritoneovenous shunting prevents such contamination from occurring. However, peritoneovenous shunting and autoinfusion have not become classical approaches to OHSS treatment, probably because of practical reasons and fear of sepsis.

Pleural puncture and treatment of pulmonary complication

Evaluation of dyspnoeic patients with severe OHSS includes physical examination, chest radiography and arterial blood gas analysis. It is essential to evaluate accurately any pulmonary and ventilation disturbances and resulting hypoxia and to apply appropriate treatment. Maternal hypoxia in the early stages of pregnancy has been associated with an increased risk of miscarriage (Abramov *et al*., 1998b). Oxygen supplementation and early removal of fluid from the third space reduces the risk of hypoxia. Thoracocentesis is not necessary in all cases, but a dramatic improvement in clinical status was noted after paracentesis. The need for repeat thoracocentesis is rare, even in cases of reaccumulated effusion.

The installation of a chest drainage tube for bilateral effusion has been suggested (Rinaldi and Spirtos, 1995). A definite

improvement of the clinical picture was observed after using this procedure; likewise, a concomitant drainage of ascites was also observed without the need of an ascites puncture.

ARDS is encountered after an overload of fluid (>5000 ml/24 h), underlining the need for a strict fluid (in/out) balance in patients and requiring their hospitalization in an intensive care unit. ARDS generally subsides after 3–6 days with fluid restriction, forced diuresis and use of dopamine.

In case of pericardial effusion, drainage of liquid by an experienced specialist becomes necessary (Brinsden *et al*., 1995).

Surgical approach of OHSS

The surgical approach that was advocated during the 1950s should be avoided, unless a haemorrhage due to follicular rupture or torsion of the ovary is suspected. In all cases this surgery should be conservative, with a minimum of invasive manipulations and careful haemostasis in order to preserve ovarian integrity as much as possible. One group (Fakih and Bello, 1992) recommended aspiration of the cysts, believing that elimination of their contents may reduce the ovarian production of OHSS mediators, though this should be balanced against the risk of causing bleeding of the frail ovaries, which may lead to ovariectomy and infertility (Waterstone *et al*., 1992).

Sporadically, vascular surgical procedures are required to treat thromboses that are resistant to medical therapy or are associated with a high embolic risk. Posterolateral thoracotomy and subclavian arteriotomy and thromboarterectomy according to the Fogarthy technique have been reported (Aurousseau *et al*., 1995; Choktanasiri and Rojanasakul, 1995; Germond *et al*., 1996). Inferior vena cava clipping to prevent massive pulmonary embolism has also been applied (Mozes *et al*., 1965).

Amputation due to gangrene despite arterial embolectomy has also been reported (Mozes *et al*., 1965; Mancini *et al*., 2001).

Mesenteric resection after massive mesenteric arterial infarction has also sometimes been necessary (Aurousseau *et al*., 1995).

A case of perforation of a duodenal ulcer attributed to *Helicobacter pylori* in connection with the intense stress linked to critical OHSS has been reported (Uhler *et al*., 2001).

Interruption of pregnancy has been paradoxically carried out in some extreme cases with arterial obstructions, and has improved the clinical picture of neurological, haematological and vascular disturbances (Dumont *et al*., 1980; Neau *et al*., 1989; Aurousseau *et al*., 1995; Choktanasiri and Rojanasakul, 1995; Ryo *et al*., 1999; Southgate *et al*., 1999; Yoshii *et al*., 1999; Shan Tang *et al*., 2000).

Strict preoperative evaluation should be obtained before a surgical procedure is planned in these patients, who may suffer from severe multiple organ dysfunctions. For instance, cholinesterase levels may be temporarily reduced while usually, they are normal in such patients, suggesting temporary disturbance in the expression of the gene regulating this enzyme (Southgate *et al*., 1999).

Particular medication during OHSS

Potassium exchange resin: Administration of this may be needed to correct hyperkalaemia.

Antibiotics: Hypoglobulinaemia is observed in cases of severe OHSS, and this may induce a relative immunodepression. Infections are quite often the consequence of iatrogenic acts, such as urinary catheterization (reported in 81% of cases of urinary infections) (Abramov *et al*., 1998a). Venous catheterization, pleural puncture, paracentesis and surgical procedures may all favour infection. Peroperative antibiotic prophylaxis is therefore advocated. The bacteria involved are most often *Pseudomonas*, *Proteus*, *Klebsiella* and *Enterobacter*, and these are responsible for nosocomial infections. For this reason, hospitalization should be limited to a strict minimum, while ambulatory management is to be favoured. Others (Abramov *et al*., 1998a) also suggest the administration of immunoglobulins, as used in other pathologies associated with hypoglobulinaemia, such as the nephrotic syndrome, or certain enteropathies. This measure still needs to be evaluated.

Indomethacin: It has been suggested that indomethacin could be used as an inhibitor of the prostaglandin synthesis which might play a role in the aetiology of the syndrome. One group (Schenker and Polishuk, 1976) showed that indomethacin can prevent both the shift of fluid associated with ascites and pleural effusion. However, others have demonstrated, using experimental animal studies, that ascites formation is not effectively suppressed by indomethacin (Haning *et al*., 1985). In clinical practice, some authors found no clinical improvement or inhibition of ascites formation in severe OHSS patients by using indomethacin (Borenstein *et al*., 1989; Splendani *et al*., 1994). Furthermore, there is a theoretical risk of teratogenicity when administering indomethacin in significant amounts over several weeks in early gestation (Swedish National Board of health and Welfare, 1983; Katz *et al*., 1984). Finally, oliguria and renal failure have been attributed to the use of indomethacin in cases of OHSS even in the absence of hypovolaemia. Indeed, renal perfusion can be maintained on the basis of a prostaglandin-mediated compensatory vasodilatation, when renin activity is increased and indomethacin may inhibit this mechanism (Balasch *et al*., 1990).

The use of some other drugs such as histamine blockers, antiserotonin drugs and angiotensin-converting enzyme inhibitors remains at the experimental stage (Knox, 1974; Gergely *et al*., 1976; Zaidise *et al*., 1983; Pride *et al*., 1984; Kirshon *et al*., 1988; Morris *et al*., 1995b; Teruel *et al*., 2001).

Preventative treatment: Preventative treatment with heparin should be used whenever the thromboembolic risk is markedly increased. This preventative strategy should be applied just as in other increased risk situations such as pelvic or orthopaedic surgery. In cases of severe OHSS, the following situations are recognized as representing an increased risk for thomboembolism: hyperestrogenaemia, immobilization, compression of pelvic vessels by enlarged ovaries or ascites and pregnancy coagulation anomalies. Some investigators would administer heparin to all patients who are hospitalized for OHSS, while others restrict its use to patients with haemoconcentration (Whelan and Vlahos, 2000). Prevention using mobilization and anti-thrombosis stockings has been shown to be insufficient as thrombosis may occur at all localizations, the aetiology seeming to be of systemic nature.

Prophylaxis with heparin remains debatable for two reasons. First, there are no randomized studies proving its efficacy in preventing thromboembolic complications during severe OHSS. Furthermore, in some cases thromboembolism has been reported in cases where heparin treatment had been given (Horstkamp *et al*., 1996; Todros *et al*., 1999; Cil *et al*., 2000). It should also be noted that in these particular situations associated risk factors

such as resistance to active protein C, mutation for Leiden factor V, or Crohn's disease are always found.

The timing for administration of preventative measures is also a much-debated subject. Some reported late thrombosis up to 20 weeks after embryo transfer, but in such cases the patients had always become pregnant. These observations are in favour of maintaining heparin therapy for at least 4 weeks and even during the whole first trimester of pregnancy (El Kouri *et al*., 1995; Hignett *et al*., 1995; Kodama *et al*., 1996). Others demonstrated that the coagulation cascade is already modified 2 days after hCG administration, and that these changes are maximal 8 days later, suggesting a need for prophylaxis even before the appearance of OHSS symptoms (Kodama *et al*., 1996). This should be applied to patients with known pre-existing thrombophilic factors. It is important, therefore, to obtain a thorough personal and family history before beginning IVF. AT III activity, protein C and S evaluation and a search for mutation of Factor V, II and MTHFR genes in patients with a personal and family history of thromboembolic episodes or previous OHSS should be carried out.

This type of follow-up necessitates precise investigations: indeed, in these patients it is not sufficient to monitor prothrombin time (PT) and activated partial thromboplastin time (APTT) to detect hypercoagulability. Therefore, some authors have suggested following D-dimers, AT III, thrombin–AT III complexes, fibrinopeptide A and B, alpha2 plasmin inhibitor and plasmin–alpha2 antiplasmin complexes (Kodama *et al*., 1996; Yoshii *et al*., 1999).

Conclusion

A major obstacle to studying this life-threatening complication of ovulation is its low incidence (between 0.1 and 0.5%). Today, only two studies collected a large number of cases, namely that by Abramov *et al*. (1998) studying pulmonary complications on 209 severe OHSS cases, and that by Delvigne *et al*. (1993) studying clinical features and predictive factors in 128 cases.

The pathophysiology and management of OHSS remain uncertain. Treatment of the acute phase merely relies on an empirical and symptomatic approach. More adequate methods would require better understanding of the underlying pathophysiological mechanisms, to promote an aetiological therapeutic approach.

Properly conducted studies including large numbers of patients are required in order to determine the best method of prevention and management.

Some authors have suggested that OHSS should be anticipated and studied as soon as hCG is administered, that is, before the appearance of symptoms, to allow aetiological management. This may lead to the development of prevention strategies before the onset of signs of severe OHSS, similar to the prevention of eclampsia in risk patients during pregnancy (Murdoch and Evbuomvan, 1999). Fulfilling this objective requires multicentric cooperative studies (Rimington *et al*., 1999).

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