CHAPTER 14

Management of ovarian hyperstimulation syndrome

Mark Sedler and Adam H Balen

INTRODUCTION

Consequences of stimulation of the ovaries include the serious and potentially life-threatening condition of ovarian hyperstimulation syndrome (OHSS). This can occur with any type of ovulation induction or superovulation therapy for assisted conception procedures. The development of OHSS can be reduced by the cautious use of preparations, careful monitoring of stimulation cycles, and prediction of 'at risk' patients. This overview will describe the syndrome and its pathophysiology in order to understand appropriate preventative strategies and management options.

The pathophysiologic hallmark of OHSS is a sudden increase in vascular permeability which results in the development of a massive extravascular exudate. This exudate accumulates primarily in the peritoneal cavity, causing protein-rich ascites. Loss of fluid into the third space causes a profound fall in intravascular volume, hemoconcentration, and suppression of urine formation. Loss of protein into the third space causes a fall in plasma oncotic pressure, which results in further loss of intravascular fluid. Secondary hyperaldosteronism occurs and causes salt retention. Eventually peripheral edema develops.

OHSS occurs after overstimulated ovaries have been exposed to hCG. The condition therefore results most commonly when sensitive (usually polycystic) ovaries are exposed to excessive quantities of FSH and then to hCG. That severe OHSS is often associated with pregnancy is probably related to the persistence of hCG in this situation. Even when the ovaries have been severely overstimulated, OHSS can be prevented by avoiding exposure of the ovaries to LH and/or hCG.

PREVALENCE

Most methods of ovarian stimulation can cause OHSS and it can even result from the use of oral anti-estrogens. In programs of ovulation induction the risk is related to the dose of gonadotropins and is rarer with low dose protocols. The overall risk is estimated to be about 4% and that of the severe form about 0.25%. In in-vitro fertilization (IVF) the prevalence varies in published series from 1 to 10%, being highest in those combining gonadotropin stimulation with treatment with a GnRH analog. Severe cases occur in 0.25–2% of IVF cycles[1].

There are no good data on the overall incidence of severe OHSS, as the severity of OHSS

is often not standardized, although severe cases are those most likely to be reported. There have been case reports of thromboembolism and other severe sequelae of ovarian hyperstimulation, but good data are not kept centrally. The latest European database of all reported IVF cycles performed in 2000 presents the incidence of OHSS from registers of 17 of the 22 countries that submitted data[2]. There were 1586 cases of OHSS out of 146 342 cycles, equivalent to 1.1% of all stimulated cycles[2]. There were 376 cases reported from the UK to this database out of a total of 28 474 stimulated cycles, equivalent to 1.3%[2]. The North American databases do not report rates of OHSS[3].

A WHO report in 2002 estimated the overall incidence of severe OHSS as 0.2–1% of all assisted reproduction cycles[4] and the mortality has been estimated at 1:450 000–1:500 000 women undergoing superovulation[5]. There were no deaths in the European registry of 146 342 cycles in 2000[2]. A detailed assessment of mortality in a cohort of 29 700 Australian patients who had in the past undergone IVF failed to identify OHSS as a contributing cause to any of the 72 deaths from any cause[2]. Thus the mortality rate from OHSS would appear to be extremely low and difficult to quantify. It goes without saying that there is no acceptable rate of mortality as a result of fertility treatment. Furthermore there is no doubt that OHSS is a condition that should be taken extremely seriously because of the physical and emotional distress that it can cause and the thromboembolic risks.

CLASSIFICATION OF OHSS

Currently there is no unanimity in the classification of OHSS. The syndrome is graded according to its severity, with the 1989 classification by Golan et al.[6] having several clinical and practical advantages. Mild ovarian hyperstimulation is divided into grades 1 and 2, moderate into grade 3, and grades 4 and 5 hyperstimulation equate to severe OHSS. Grade 1 is defined as abdominal distension and discomfort, progressing to grade 2 if additional clinical features of nausea, vomiting, ± diarrhea occur with additional ultrasonographic features of ovarian enlargement at 5–12 cm in diameter. Grade 3 includes the features of mild OHSS with the additional evidence of ascites by ultrasound scan. Grade 4 includes the features of moderate OHSS, with the addition of clinical evidence of ascites and/or hydrothorax and breathing difficulties. Grade 5 includes all the above features and a change in the blood volume with increased blood viscosity, hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function.

The severest form of OHSS is a critical and life-threatening stage of the illness, with clinical evidence of intravascular volume depletion and hemoconcentration (reduced CVP, reduced cardiac output, hematocrit level >55%), severe expansion of the third space (tense ascites, pleural and pericardial effusions), and the development of hepatorenal failure (serum creatinine >1.6 g/dl, creatinine clearance <50 ml/min).

Additional risks include thromboembolic phenomenon, cerebrovascular and subclavian vein thrombosis, renal failure, adult respiratory distress syndrome, and cardiac tamponade secondary to pericardial effusion. Deaths have been recorded in women with the most severe form of OHSS. The advantages of Golan's classification are not needing to include cases of biochemical hyperstimulation (almost always present in assisted conception), abdominal distension/discomfort are the minimal presenting symptoms, and the incorporation of ultrasonographic findings (as OHSS is more frequently diagnosed by USS).

A more recent classification[7] subdivides the severe form of OHSS into three grades (Table 14.1). Here, the mild form of the disease is omitted from classification, as this can occur

Table 14.1 Clinical grading of ovarian hyperstimulation syndrome

Mild
Weight gain, thirst, abdominal discomfort
Mild distension
Ovaries >5 cm diameter
Moderate
Nausea and vomiting, distension, and pain
Dyspnea
Abdomen distended but not tense
Ascites detected by ultrasound
Severe
Evidence of intravascular fluid loss
Third space fluid accumulation (tense ascites, hydrothorax)
Hemoconcentration, hypovolemia, oliguria, hepatorenal failure

in most patients with ovarian stimulation and, moreover, the condition has no complications and does not require special treatment. The moderate condition includes symptoms of abdominal pain, distension and discomfort, nausea, and ultrasonic evidence of enlarged ovaries and ascites, but with normal hematologic and biochemical profiles. The severe form is subdivided into A, B, and C. Grade A includes symptoms of nausea, vomiting, diarrhea, oliguria, abdominal pain, and dyspnea, with clinical evidence of marked distension of the abdomen, ascites, and/or hydrothorax. Ultrasound scan shows evidence of large ovaries and marked ascites, but again the biochemical profile is normal. Grade B includes features of grade A with the addition of massive tension ascites, markedly enlarged ovaries, marked oliguria, and severe dyspnea, with the addition of a raised hematocrit, elevated serum creatinine, and abnormal liver function. Grade C includes further complications such as respiratory distress syndrome, renal shutdown, or venous thromboembolism.

CLINICAL PRESENTATION

The mild form includes weight gain, thirst, abdominal discomfort with bloating, and mild nausea. There are no clinical signs of dehydration or significant abdominal findings apart from some distension. Moderate OHSS is associated with more pronounced symptoms of nausea, vomiting, abdominal distension with pain, and dyspnea. The abdomen is distended but not tense and the ovaries may be palpable per abdomen with associated tenderness. Ascites may not be clinically demonstrable. No clinical evidence of fluid or electrolyte depletion is demonstrated.

Severe cases present with pronounced features of the moderate disease with clinical evidence of intravascular fluid loss (tachycardia, hypotension) and third-space fluid accumulation such as ascites and hydrothorax. Hypovolemia, hemoconcentration, oliguria, and electrolyte imbalance occur. The ovaries are usually grossly enlarged and can reach the level of the umbilicus. They are tender to palpation. In extreme cases acute respiratory distress from gross ascites and pleural effusion can occur. Other complications include pericardial effusion, hepato-renal failure, and thromboembolic phenomena[7].

A distinction has been made between early and late OHSS[8], with those presenting early (that is 3–7 days after hCG administration) having significantly higher serum estradiol concentrations than those presenting late (12–17 days after hCG), whilst there is no difference in the number of oocytes collected. Those presenting late are more likely to be pregnant and have a severe form of the syndrome, due to persistent hCG stimulation of the ovaries.

PATHOPHYSIOLOGY OF OHSS

The exact pathogenesis is unknown. The main pathophysiologic features are increased capillary permeability, new capillary formation (angiogenesis), and the existence of a vasoactive ovarian

biochemical factor. All these factors are most prominent in the ovarian vasculature. While it has been known for many years that high circulating concentrations of estradiol are an immediate predictor of the syndrome, estrogen itself is not the cause of the sudden increase in vascular permeability. Such a change is not after all a feature of treatment with estrogen itself, even when the levels rise very abruptly, such as after an implant. While numerous compounds, such as prostaglandins, kallikreins, histamine, serotonin, and prolactin, etc., have been considered to mediate the process, the two prime movers in the development of OHSS are activation of the ovarian prorenin–renin–angiotensin system[9] and release of vascular endothelial growth factor (VEGF) from the ovary.

The follicle contains renin in an inactive form which is activated at mid cycle by LH (and by exposure of the ovary to hCG) and which then causes conversion of angiotensinogen to inactive angiotensin I and subsequent conversion to the active angiotensin II. This ovarian prorenin–renin–angiotensin system is thought to be involved in the neovascularization, which is so central a feature of the conversion of the avascular preovulatory follicle into the richly vascularized corpus luteum. Some years ago we reported excessive levels of renin activity in the plasma of a woman with severe, grade 3 OHSS at a stage of her illness when, as a consequence of treatment, the central venous pressure was several centimeters higher than normal (i.e. when secretion of renal renin would have been suppressed). Subsequent studies have shown that ascitic fluid in this syndrome contains very large amounts of angiotensin II compared with ascitic fluid obtained from women with liver failure. In rabbits angiotensin II increases peritoneal permeability and neovascularization. Moreover, in that species, treatment with an angiotensin-converting enzyme (ACE) inhibitor blocks the increase in peritoneal permeability that occurs in response to superovulation. Parallel studies have not, however, been performed in humans because of concerns over the use of ACE inhibitors in pregnancy. There is no doubt of the involvement of the renin–angiotensin system in the pathogenesis of OHSS, with severity of OHSS and hematocrit being directly related to plasma renin activity (PRA) and also aldosterone concentration (the increased aldosterone production in OHSS is associated with increased PRA)[10].

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor, also known as vascular permeability factor or vasculotropin, is a dimeric glycoprotein, which promotes growth and cell division of vascular endothelial cells. It increases capillary permeability. VEGF is expressed in steroidogenic and steroid-responsive cells, such as those involved in repair of endometrial vessels and in implantation[11]. In primates, production of VEGF increases after the LH surge and is reduced by suppression of LH secretion during the luteal phase. VEGF production by human luteinized granulosa cells is increased by incubation in vitro with hCG, as detected by measuring messenger RNA (indicating synthesis by the luteal cells), and VEGF itself, as detected by an immunofluorescent assay. Using a bioassay, which measured extravasation into the skin of an injected dye, McClure and colleagues[12] found increased amounts of VEGF in ascitic fluid obtained from patients with OHSS but not in ascitic fluid obtained from patients with liver failure. Most of the activity could be neutralized by incubation with an antiserum to recombinant human VEGF, indicating that VEGF is the major capillary permeability agent in OHSS. One might speculate that the activity that was not neutralized by the antiserum to VEGF was attributable to angiotensin II. Further studies have correlated follicular fluid concentrations of VEGF with OHSS and also with ovarian blood flow, as assessed by Doppler ultrasound flow studies[13]. Indeed serum VEGF concentrations have been

proposed as a predictor for the development of the syndrome[14]. In hyperstimulated rats, vascular endothelial growth factor receptor-2 activation induces vascular permeability; this effect can be prevented by receptor blockade. A specific VEGF receptor-2 inhibitor, SU5416, has been shown to reverse increased vascular permeability[15].

The angiogenic response to LH or hCG is normally confined to a single dominant follicle. OHSS may be seen as an exaggeration of this response. Because of gonadotropin-stimulated overgrowth of follicles, VEGF, the major angiogenic mediator of vascularization of the corpus luteum, can no longer be confined to the ovary but spills over, first into the peritoneal cavity and then into the general circulation. Interestingly, a case report of OHSS in a spontaneous pregnancy, with fetal and placental triploidy (partial hydatidiform mole), has been reported[16], suggestive of the theory that VEGF is a causative factor of OHSS, but has no impact on the course of the disease.

Two other important factors for the genesis of OHSS are the use of luteal phase hCG support, potentially augmenting the already prevailing condition, and the risk associated with conception cycles. It has been found that OHSS is four times as frequent in conception cycles than in non-pregnant cycles. An increased incidence is also seen in multiple pregnancies, possibly the higher the multiple order, the increased risk and severity of the disease. This is certainly due to the continuing stimulation of the ovaries by the increasing levels of hCG produced by the conception cycle, causing longer duration and a more severe expression of the disease. Simply put, the addition of hCG to the situation is like adding 'fuel to the fire'.

RISK FACTORS FOR THE DEVELOPMENT OF OHSS (TABLE 14.2)

Two important risk factors can be identified before treatment starts, namely the presence of polycystic ovaries and young age.

Table 14.2 Prevention of ovarian hyperstimulation syndrome

- Pretreatment ultrasound assessment of ovaries: PCO?
- Care with gonadotropin administration: use low doses in women with PCO
- Care with GnRH analogs:
  - emphasize use of ultrasound rather than estradiol concentrations
  - note whether an LH-depleted gonadotropin preparation is being used
- Reduce use and dose of hCG:
  - consider withholding ovulatory dose of hCG
  - substitute progesterone for hCG in luteal phase
- Meticulous aspiration of all follicles
- Consider cryopreservation with deferred embryo transfer

Polycystic ovaries

Several studies have confirmed that patients most at risk are women with the characteristic appearance on ultrasound of polycystic ovaries. The essential point is the presence of polycystic ovaries, as detected by ultrasound, not the polycystic ovary syndrome. The polycystic ovary appearance (presence of >12 follicles of <9 mm diameter)[17] occurs in approximately 33% of normal women[18], but in 40% of patients undergoing IVF, irrespective of the indication for treatment[19]. The polycystic ovary is highly sensitive to gonadotropic stimulation.

Young age

Most cases of OHSS occur in younger women, usually less than 30 years, consistent with the greater ovarian responsiveness in this group compared with older women.

Factors as ovarian stimulation proceeds

Use of GnRH agonists

GnRH agonists protect the ovary from an endogenous LH surge, so facilitating more convenient scheduling of ovum pick-up. The protection so afforded renders the ovary more amenable to stimulation of multi-follicular development by high-dose gonadotropin treatment. Not surprisingly, this very advantage makes OHSS more common in treatment programs utilizing pituitary desensitization.

Development of multiple immature and intermediate sized follicles during treatment

The development of large numbers of immature and intermediate follicles during treatment indicates an exuberant response to gonadotropic stimulation, caused either by very sensitive, i.e. polycystic ovaries (the usual situation), or too high a dose of gonadotropin in women with normal ovaries. A large number of medium sized follicles (<14 mm in diameter) is an important risk factor, rather than a large number of mature follicles.

Exposure to LH/hCG and dose involved

The clinical observation that exposure of the ovaries to LH, and usually to hCG, is a sine qua non of its development and that pregnancy is frequently associated with the OHSS is consistent with the role of LH and hCG in stimulating the processes that mediate neovascularization and vascular permeability. An endogenous LH surge rarely provokes the development of OHSS unless pregnancy ensues. This may be due to the fact that the half-life of hCG preparations is longer than of natural hCG and possibly that the large doses of hCG given lead to a greater activity than natural LH produces. It is possible that the higher the doses of exogenous LH/hCG used, the worse the potential for OHSS. These observations add plausibility to the clinical practice of attempting aspiration of all follicles in patients considered at risk because it is luteinized granulosa cells that are the source of the permeability factors.

PREDICTION AND PREVENTION OF OHSS

OHSS is an iatrogenic condition. The most effective management of OHSS is the accurate prediction and prevention of the disease. Ultrasound scanning and endocrine monitoring of follicular development are the main ways of prediction of the development of OHSS during ovarian stimulation. All patients undergoing ovarian stimulation, whether to correct anovulation or for assisted fertility techniques, should have a pretreatment ultrasound scan and if polycystic ovaries are detected, the dose of gonadotropin should be lowered, titrated gradually and slowly, and ultrasonographic follicular assessment and serum estradiol levels measured on day 5 of stimulation of IVF cycles, so that the dose can be adjusted accordingly, if needs be, for prevention of overstimulation. If pituitary desensitization has been used one should be sensitive to the loss of the normal 'protection' of the ovary caused by the block to estrogen-mediated positive feedback of LH release. If a long protocol of GnRH analog treatment is followed by treatment with one of the pure FSH preparations, one must also be aware that the lack of LH changes the usual relationship of follicle maturation and number to circulating estradiol levels. In this situation measurement of serum estradiol concentrations underestimates follicle development. It is therefore essential that endocrine monitoring is supported by high-quality ultrasound, otherwise low circulating estradiol concentrations may encourage further and

inappropriate gonadotropic stimulation despite adequate follicular development. Meta-analyses of the different gonadotropin preparations have indicated no significant difference in risk of developing OHSS[20–24].

STRATEGIES FOR PREVENTING/ REDUCING OHSS RISK

For the patient with overstimulated ovaries who is approaching the time of hCG administration, several strategies to make treatment safer may be considered. The first is to administer a low dose of hCG to initiate oocyte maturation and/or ovulation (i.e. not more than a single injection of 5000 IU) and, in patients receiving GnRH analog treatment and who therefore require luteal support, to give progesterone (400 mg per vaginum for 14 days or gestone injections im) rather than hCG. It is current practice now to use progesterone routinely for luteal support. Recombinant LH has a shorter half-life than hCG and so may reduce the risk of short-term OHSS, although it will not influence OHSS resulting from hCG produced from the trophoblast of a developing pregnancy. In protocols where GnRH antagonists are used, the preovulatory trigger can be with a single dose of a GnRH agonist, instead of hCG – again a shorter-acting preparation, which should reduce the short-term risk of OHSS.

Consider the treatment of anovulatory infertility and the prevention of OHSS. Here the issue is the development of multiple *small* follicles. Thus, if there are more than six follicles with a diameter of 12 mm or more we advise discontinuing treatment or converting it to IVF. In the latter situation, having meticulously aspirated as many follicles as possible, one may cryopreserve the embryos and defer their transfer to another cycle. Alternatively, one may withhold hCG, continue treatment with the GnRH analog, and restart gonadotropin stimulation at a lower dose.

Follicular aspiration

Multiple follicular aspiration in IVF cycles (emptying most of the follicles of their follicular fluid and granulosa cells) has been suggested as a way of protecting against the development of OHSS[25]. Some studies show a confirmed benefit of using this technique, and others have shown no protective effect against OHSS development. However, a 20% incidence of severe OHSS occurred with repeated aspirations, against 70% in matched historic trials. It is also possible to aspirate most of the ovarian follicles 35 hours after the administration of hCG. The remaining intact follicles can still result in a singleton or twin pregnancy, whilst minimizing the risk of OHSS developing. Follicular aspiration induces intrafollicular hemorrhage, which has a negative impact on corpus luteum function[26]. Withdrawal of the follicular contents may significantly interfere with follicular maturation, potentially modifying the intraovarian mechanism responsible for the development of OHSS.

Early unilateral ovarian follicular aspiration (EUFA) has been performed in a prospective randomized study, versus no intervention[27]. Here, unilateral ovarian aspiration occurred 6–8 h prior to hCG administration. Fewer oocytes were recovered in the EUFA group, as expected, however fertilization, embryonic cleavage, and pregnancy rates were similar between the two groups. Although the development of OHSS was recorded in 25% of the EUFA group and 33.3% of the control group, severe OHSS developed in 12.5% and 6.6% of patients, respectively. The authors of this study concluded that early unilateral follicular aspiration, prior to 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 versus coasting, for high-risk patients. Oocyte retrieval was then carried out in the contralateral ovary, 35–36 h after hCG administration. Interestingly,

fewer oocytes were retrieved in the coasted group, but fertilization, embryonic cleavage, and pregnancy rates were similar in both groups. Severe OHSS occurred in 26.6% of the EUFA group, against 20% in the 'coasted' group. In conclusion, it was suspected that intraovarian bleeding induced by the aspiration of granulosa cells from one ovary may limit the production of ovarian mediators implicated in the pathogenesis of OHSS, thus reducing the risk of developing the severe condition. However the data on this are somewhat contradictory, and the number of cases insufficient to establish the efficacy of this method[28].

The coasting approach

Coasting, or delaying hCG, uses a controlled 'drift' period as an alternative to cancellation of the cycle, yielding favorable pregnancy rates (25% per cycle) with low severe OHSS complications (2.5%). In one study by Sher et al.[29], gonadotropins were withheld in 17 patients whose serum estradiol levels were >6000 pg/ml and daily administration of the GnRH analog was continued until estradiol levels had fallen to <3000 pg/ml. At this point, 10 000 IU hCG were administered to trigger ovulation. During the first 48 h of initial coasting, the estradiol levels continued to rise, but the follicular diameter reduced by approximately 2.3 mm/day. The estradiol levels plateaued and fell after 96 h. No follicular increase in diameter was seen after 72 h of coasting. The coasting period lasted 4–9 days; hCG administration was reduced on days 12–16. Interestingly, 35% of the cycles led to viable pregnancies and all 17 patients developed signs of grade 2–3 OHSS, however none led to severe OHSS. An update review abstract from the Cochrane Library[30], however, identified 13 studies (of which only one met the strict inclusion criteria), showing no difference in the incidence of moderate or severe OHSS, or pregnancy rates, between the groups.

Abandoning the treatment cycle

In patients having IVF and using gonadotropin containing LH activity (i.e. HMG preparations), the following are conservative criteria for ovarian responses, above which there is a significant risk of OHSS: a serum estradiol of greater than 10 000 pmol/l (3000 pg/ml) together with 20 or more follicles of 12 mm diameter or more. In the interpretation of estradiol concentrations one needs to recognize the aforementioned effects of using LH-depleted gonadotropin preparations in women receiving GnRH analogs in a 'long' protocol (less estrogen than usual is made so estradiol concentrations underestimate the intensity of the ovarian response). For patients with a serum estradiol greater than 17 000 pmol/l (5500 pg/ml) with more than 40 follicles, hCG should be withheld and treatment abandoned. Treatment with the GnRH analog is, however, continued and when the ovaries regain their normal size, ovarian stimulation is resumed at a lower dose.

Cryopreservation of all developed embryos

When serum estradiol concentrations are 10 000–17 000 pmol/l with 20–40 follicles hCG may be given, but the embryos are cryopreserved and transferred at a later date. The obvious advantages of this strategy are reduction in the incidence and severity of OHSS, in addition to preserving the potential benefits of the original cycle. Continuing a GnRH analog during the luteal phase can help to keep the ovaries quiescent. However, this may not eliminate the risk completely.

Prevention of OHSS using intravenous albumin

It has been suggested that administration of intravenous albumin to patients at high risk of developing OHSS may prevent the onset of the condition[31]. Albumin potentially increases serum oncotic pressure, reverses leakage of

fluids from the intravascular spaces, and prevents to some degree the shift of fluid into the third space. However, the role of albumin in OHSS prevention is multi-factorial. First, it sequesters the vasoactive substance released from the corpora lutea. Interestingly, OHSS symptoms usually develop 3–10 days after hCG administration, regardless of embryo transfer. As albumin has a half-life of 10–15 days, its timely infusion during oocyte retrieval and immediately afterwards may serve to bind and inactivate this factor. Second, it sequesters any additional substance, which may have been synthesized as a result of OHSS. Third, its oncotic properties serve to maintain the intravascular volume and prevent the ensuing effects of hypovolemia, ascites, and hemoconcentration.

A prospective, randomized, placebo-controlled trial of albumin versus normal saline administration, in patients at high risk of developing OHSS, has been described. Four out of 15 cases in the control group developed OHSS, whereas there were no cases in the 16 patients treated with albumin ($p < 0.05$)[32]. In contrast, however, Ng et al. reported that 2 cases out of 49, treated with albumin, developed severe OHSS. This was similar to a prior incidence of a 6% OHSS rate in 158 historic, matched controls, who received an equal volume of lactated ringers solution[33].

Despite the literature, the efficacy of albumin in preventing OHSS still requires further validation. It is unclear whether albumin administration, at the time of oocyte retrieval, would be effective in preventing the manifestations of late OHSS, which tend to be more severe than the early form of the disease, and also more likely to be associated with pregnancy. Also the dosage and optimal timing of administration of the albumin need to be established.

The use of gonadotropin releasing hormone antagonists

It has been suggested that the use of GnRH antagonist cycles might reduce the risk of OHSS[34] combined also with administration of a GnRH agonist to trigger oocyte maturation[35], although there are as yet insufficient data. In one trial involving 701 patients, the use of the GnRH antagonist Ganirelix versus GnRH agonists (e.g. Buserelin) resulted in fewer cases of OHSS (3.5% vs. 5.9%), however the ongoing pregnancy rate was 20.3%, compared to 25.7% in the GnRH agonist group[36].

Glucocorticoids

Studies comparing the effectiveness of glucocorticoid administration versus no steroid administration in preventing OHSS concluded that there was a similar incidence of the disease in both groups, irrespective of whether all degrees or only moderate and severe OHSS were considered[37].

In-vitro maturation

In-vitro maturation (IVM) of human oocytes is a scientific and clinical challenge, which has potential benefits for certain patient groups undergoing assisted reproductive treatments. These include patients who have a tendency to undergo a vigorous ovarian response to ovarian stimulation and are at risk of OHSS. Patients who have polycystic ovaries with a previous history of excessive ovarian stimulatory response, or who developed severe OHSS, or needed cycles canceling due to the risk of continuing the stimulatory regimen, could benefit from IVM technology in the future. IVM technology could well reduce the risk of OHSS.

Metformin

The association between insulin resistance and PCOS has resulted in the use of metformin to enhance insulin sensitivity and improve ovarian function. Furthermore, metformin has been shown to improve the response of polycystic ovaries to stimulation, with the suggestion of a more co-ordinated follicular response together

with a reduced likelihood of hyperstimulation[38]. Indeed in patients with polycystic ovaries we have found in a prospective randomized trial, in which all patients were given a low dose of stimulation (100 IU FSH) that the use of metformin reduced the incidence of severe OHSS from 20.4% to 3.8% ($p < 0.023$)[39].

COMPLICATIONS OF OHSS

Thromboembolism

The most serious complication of OHSS is cerebrovascular accident. Hemoconcentration, high levels of factor V, platelets, fibrinogen, profibrinogen, fibrinolytic inhibitors, and thromboplastins are all found in patients with OHSS. The cytokine interleukin-6 was also found to be elevated in patients with OHSS[40], as compared to controls. Whether this is directly responsible for or contributes to the clinical manifestations of OHSS is unclear. However, unquestionably, all the above factors will contribute to the vascular complications described.

When considering the pathophysiology of the OHSS it is easy to appreciate the potential risk of deep venous thrombosis (DVT) and thromboembolic events. Indeed there has been an expanding literature on this association in recent years. Not only is there a hypercoagulable state but also the combination of enlarged ovaries and ascites leads to reduced venous return (increased venous pressure) from the lower limbs, which, combined with immobility, places the patient at risk of DVT. Furthermore, the thrombotic event need not only be in the lower limbs. A review of the world literature found that 75% of cases reported were in venous sites, with 60% in the upper limb, head, and neck veins (including internal jugular and subclavian veins), with an associated risk of pulmonary embolism of 4–12%, whilst the remaining 25% were arterial thromboses and were mostly intracerebral[41]. It is difficult to give an explanation for these more unusual sites of thrombosis in young women, unless there is relative overreporting because of their rarity. The hypercoagulable state of OHSS may, in addition to the general vascular changes described in the previous section, relate to a change in clotting factors, which may be due to the recognized hematologic changes of pregnancy:

- Increased concentrations of factors VII, VIII, IX, X, XII, and fibrinogen;
- Reduced concentrations of protein S, antithrombin III, and fibrinolysis.

Whether this thrombophilic state is secondary to high circulating estrogen concentrations is less clear, as the thrombophilic state of pregnancy tends to occur closer to term and postpartum. It is possible that women who develop OHSS have a tendency to thrombophilias (e.g. deficiency of protein C, S, or antithrombin III or factor V Leiden expression), although the majority of women appear to screen negative after the event. An alternative theory is a leakage of factors such as antithrombin III into the ascitic fluid, thus resulting in a relative plasma deficiency[42]. Venous thrombosis in the lower limb most often resolves without long-term sequelae, unless pulmonary embolism occurs, which may be fatal. Upper limb venous thrombosis may lead to disabling long-term disability, with persistent discomfort, cramp, weakness, and cold hands. Cerebral thrombosis may resolve completely but it can also lead to various forms of long-term disability.

Liver dysfunction

Markedly abnormal liver function tests and significant morphologic abnormality at the ultrastructural level can occur. These changes may be due to the increased estrogen levels (also seen after combined oral contraceptive and anabolic steroid use) and may be compensatory in response to increased demand on the liver enzymes, rather than a true pathologic alteration.

Respiratory complications

Respiratory distress, including adult respiratory distress syndrome, secondary to ascitic fluid accumulation and pleural effusion, has been described. Aspiration of ascitic and pleural fluid usually relieves symptoms – as well as the other management strategies for treating OHSS (see later). An actual case of acute hydrothorax, presenting as the only manifestation of the OHSS, after IVF treatment, has been reported[43].

Renal complications

Prerenal failure (a complication of the hypovolemia secondary to fluid transudation into the third space compartments) and hydro-ureter are associated with OHSS. Pressure on the kidneys by tense ascites may also impair renal output, which can then improve dramatically after paracentesis.

Adnexal torsion

Torsion occurs, mainly due to enlargement with multiple follicular or luteal cysts, which can worsen in pregnancy due to increasing ovarian size. Cohen et al.[44], in one study, reported a 16% torsion rate in pregnant patients, compared with 2.3% in non-pregnant women. Patients with severe OHSS complicated by adnexal torsion have successfully undergone laparoscopic untwisting of ischemic and hemorrhagic adnexum.

MANAGEMENT OF OHSS

In general, all patients receiving gonadotropin therapy should be warned about the risks of OHSS and its symptoms. Information booklets and advice sheets with details about OHSS should be given to these patients. This should include the telephone number and contact name of the liaison person in the treating clinic. If OHSS is suspected, a full clinical examination and assessment of the patient is required. An assessment of the general condition, including vital signs, daily abdominal girth and weight, strict fluid balance, especially urinary output, is undertaken. The degree of hypovolemia and any secondary complications are determined.

Investigations include full blood count, serum urea and electrolytes, liver function, serum proteins, renal function tests, full coagulation profile, weight of the patient, and ultrasonography (transabdominally will give more accurate dimensions of the ovarian enlargement, but estimation of pelvic/pouch of Douglas fluid accumulation will be difficult) of the pelvis and abdomen/liver. If respiratory and/or renal compromise is suspected, then regular blood gases and acid–base balance are also needed. The frequency of these investigations depends on the patient's clinical condition. In patients with OHSS, a raised white cell count, hemoconcentration, hyponatremia, and hypoalbuminemia can occur.

As mentioned above, ultrasonography can visualize the extent of ovarian enlargement, the size and number of corpora lutea cysts, and the degree of pelvic (transvaginal scanning) and/or abdominal fluid accumulation (transabdominal scan). Pleural and pericardial effusions can be visualized by chest X-ray assessment. Invasive hemodynamic monitoring, for example CVP and PAP lines, may be needed under certain circumstances, in which volume expanders are employed in the management of the condition.

Mild OHSS

Mild ovarian hyperstimulation is very common and is managed expectantly, its importance being that it should alert both patient and doctor to the risk of a more severe condition developing. As mentioned above, the patient should be encouraged to weigh herself daily and have a high fluid and protein intake. Full observations with outpatient follow-up and reassurance

are all that is needed. Most cases of the mild condition resolve within 1 to 3 weeks. Women suspected to be at risk of developing moderate/severe OHSS need an appointment for review prior to potential embryo transfer (to decide if clinically well enough for transfer of embryos and potential conception) and/or 4–6 days after oocyte retrieval.

Moderate OHSS

A marked increase in weight (more than 5 kg) with the development of abdominal distension, nausea, and vomiting indicates the onset of moderate hyperstimulation and the need for hospitalization. Patients are often admitted to their nearest hospital and not the specialist unit providing ovarian stimulation, so good liaison is essential. We recommend patients be issued with an advice sheet concerning the symptoms of OHSS and what to do if they suspect it may be happening to them. In non-conception cycles, moderate ovarian hyperstimulation can be expected to resolve with the development of menstruation, although the ovarian cysts may persist for a month or more.

Patients with moderate hyperstimulation need reassurance and explanation, together with hospitalization. Oral fluids are encouraged, although vomiting may make an intravenous infusion necessary. Analgesics may be required for abdominal pain/discomfort. Preferred drugs are paracetamol, with or without codeine and pethidine for very severe pain. Non-steroidal anti-inflammatory drugs such as diclofenac should be avoided, although indometacin has been used experimentally with good results. Anti-emetics such as metoclopramide or stemetil are given as needed. Table 14.3 indicates the surveillance that should be undertaken.

If luteal support is required progesterone should be used. Full-length thromboembolic prevention stockings and heparin 5000 IU twice daily are advised to reduce the risk of DVT. The possibility of pregnancy must always be thought of, unless gametes/embryos have not been transferred. Most patients have relief of symptoms by the end of the first week after oocyte retrieval/artificial insemination. The presence of symptoms beyond this period may well reflect the increased corpora lutea activity, secondary to their stimulation by trophoblastic derived hCG, if pregnancy ensues.

Table 14.3 Surveillance of moderate and severe ovarian hyperstimulation

Circulation
• Intravascular contraction: monitor CVP (consider administration of colloids) look for pleural and pericardial effusion
• Hemoconcentration: measure hematocrit, white blood cell count, coagulation profile
Hepatic function
Measure ascites (girth, ultrasound) and consider paracentesis
Monitor liver function tests, in particular serum albumin
Renal function
Monitor urine output (consider administration of crystalloids)
Paracentesis, dialysis

Severe OHSS

The development of clinically detectable and usually painful ascites together with a deterioration in respiratory, circulatory, and renal function indicates the development of severe hyperstimulation and, in most cases, the need for admission to an intensive care unit. The intravascular volume should be monitored by measurements of central venous pressure, renal function by meticulous attention to input and urine output, and hemoconcentration by measurement of hematocrit (or packed cell volume – PCV), whose

level reflects intravascular volume depletion and blood viscosity. A hematocrit of over 45% is a serious warning sign and a measurement greater than 55% signals a life-threatening situation. There may be a striking leukocytosis, the white cell count rising up to 40 000/ml. Measurement of body weight, serum urea, creatinine, and electrolytes, together with serum albumin and liver function tests and periodic assessments of the coagulation profile, are mandatory. A chest X-ray is needed if pleural or pericardial effusions are suspected.

The main treatment policy is the correction of circulating volume and electrolyte imbalance. Infusion of colloid is required to maintain intravascular volume, correct hypovolemia, as indicated by restoration of normal central venous pressure, and to obtain adequate renal function. The choice lies between human albumin (50–100 ml of 20% solution, repeated as required) or intravenous dextran or hydroxyethyl starch, although the latter compounds carry the risk of anaphylactic reaction and dextran has been implicated in severe adult respiratory distress syndrome (ARDS). Crystalloid (usually normal saline) is administered for rehydration.

A CVP line is recommended for gauging fluid balance and IV requirements and daily measurements of abdominal girth and body weight are needed. If urine flow remains suppressed despite restoration of central venous pressure and rehydration, abdominal paracentesis, under direct vision, using ultrasound guidance, should be undertaken. Other indications for this procedure are the need for symptomatic relief from abdominal distension and discomfort, breathing difficulties from a tense ascites, oliguria, rising serum creatinine, falling creatinine clearance, and hemoconcentration unresponsive to medical therapy. Drainage of ascitic fluid can be performed transabdominally or, better still, transvaginally. This must always be performed under direct vision using ultrasound scanning to avoid damage to the enlarged ovaries and bowel[45]. Severe oliguria or renal failure persisting despite these measures usually necessitates dialysis.

A pleural tap of a hydrothorax should be considered for relief of dyspnea or acute respiratory distress[46]. Cardiac tamponade from pericardial effusion is rare but may prove fatal if not rapidly relieved. Careful cardiologic assessment together with cardiac ultrasound should therefore feature in the management of these patients. Urgent drainage of the pericardial fluid by suitable specialists is needed in this situation. One must be aware of the possibility of re-accumulation of fluid in any of these cavities. Anticoagulation is used prophylactically (heparin 5000 IU, twice daily) against the coagulopathy/thromboembolic phenomenon, due to hemoconcentration, and is also indicated for treatment if there is clinical evidence of thromboembolism or a deteriorating coagulation profile (increasing hypercoagulability).

OTHER MEDICAL TREATMENTS FOR OHSS

Prostaglandin synthetase inhibitors

There is no evidence that drugs such as indometacin are protective against OHSS. In fact, they may reduce the renal prostaglandin that maintains renal function, thus reducing the renal perfusion, in an already compromised patient.

Danazol

Rabbit studies have shown no protective effect for this drug against OHSS development.

Antihistamines

These may stabilize membrane permeability, thus reducing the ascites/pleural effusions caused by OHSS. However, the course of the OHSS is not appreciably altered.

Diuretics

The only place for the use of diuretics is where pulmonary congestion or edema is present. Prior volume expansion must be used as, if it is not, further reduction of the intravascular space may occur, worsening the already existing hypovolemia. Otherwise diuretics are contraindicated in these patients.

Dopamine

This is used in oliguric patients with severe OHSS to improve renal function[47]. Dopamine increases renal blood flow and glomerular filtration via stimulation of the dopaminergic receptors present in the kidney vasculature. This will avoid fluid and salt restriction, and prevent acute renal failure.

THE SURGICAL TREATMENT OF OHSS

Surgery should generally be avoided in patients with the OHSS. However, indications for surgical intervention include evidence of ovarian torsion, rupture or marked hemorrhage of the ovarian cysts, intraperitoneal bleeding, and the presence of an ectopic pregnancy associated with OHSS. A laparotomy should be avoided if at all possible and, if necessary, should only be performed by experienced gynecologists. The ovarian tissue is very friable in this situation and so a great deal of care is needed at surgery.

It has been suggested that torsion of ovaries in patients who conceive after gonadotropin therapy represents a special entity, requiring special attention and early diagnosis. The first case of unwinding of a cystic ovary via the laparoscope, in which torsion had occurred in a patient with OHSS, has been reported[48]. Even a dark, hemorrhagic and ischemic looking adnexum, on visualization via laparoscopy, may be saved by simply unwinding it through the laparoscope.

ASPIRATION OF ASCITIC FLUID AND PLEURAL EFFUSION IN SEVERE OHSS

Abdominal paracentesis was first proposed for the treatment of OHSS in patients with respiratory distress secondary to massive ascites accumulation[49]. The increased intra-abdominal hydrostatic pressure in patients with tense ascites acts via the diaphragm to increase the intrathoracic pressure and hence decrease the transmural filling of the heart. As the mean right atrial pressure increases, the venous return is thus impeded. Abdominal paracentesis relieves intra-abdominal pressure, which reduces IVC and hepatic wedge pressure, thus increasing venous return and the filling of the heart. This in turn increases cardiac output and stroke volume.

Paracentesis has been shown to be followed by an increase in urinary output and improvement in renal function (increased creatinine clearance of 50%), and a decrease in the patient's weight, leg edema, and abdominal circumference[50]. The use of an ultrasound scan guided procedure reduces the risk of puncturing or damaging the enlarged cystic ovaries and, in general, the risks of paracentesis seem negligible. Repeated procedures may be needed as the fluid recurs in the third spaces, and as the fluid is rich in protein, removal of this fluid in an already hypoproteinemic patient can be disadvantageous.

Nonetheless, early paracentesis may result in a swift resolution of symptoms. Aspiration of ascitic fluid is important in relieving symptoms and improving the general condition of patients, as well as improving urinary output. The average hospital stay, duration of severe symptoms, and disturbed electrolyte balance were found to be much shorter in patients who underwent aspiration of ascitic fluid than in patients who were managed conservatively. No adverse hemodynamic effects were seen as a result of aspiration of a large amount of ascitic fluid, however replacement of plasma proteins is needed due to the high protein content of the aspirated fluid. Repeated aspirations are required in

approximately 30% of patients. It takes on average 3–5 days for a large amount of ascitic fluid to re-accumulate. Transvaginal ultrasound scan guided aspiration of the ascitic fluid is an effective and safe procedure, giving easy access to the most dependent fluid in the pouch of Douglas. As mentioned previously, suitable specialists can perform drainage of pleural and pericardial fluid, if clinically indicated.

SUMMARY

The OHSS is a severe and potentially fatal complication of ovarian hyperstimulation for assisted conception, and may also occur after ovulation induction for anovulatory infertility. The overall incidence of moderate/severe OHSS ranges from 1 to 10% of IVF cycles, however only 0.5–2% of cases will be severe in nature. Those at greatest risk are young women with sensitive, usually polycystic ovaries on ultrasound scan, with at least 50% of PCOS patients developing some degree of OHSS with ovarian gonadotropin stimulation. Patients with anovulatory infertility with menstrual disorders are more likely to develop OHSS than amenhorreic patients. Other risk factors for developing OHSS include a greater ovarian reserve to superovulation therapy, the use of hCG to trigger ovarian response or for luteal phase support and endogenous hCG by early pregnancy in conception cycles. The use of gonadotropin releasing hormone agonist (GnRH-a) and HMG cycles also increases the risk.

OHSS is four times more frequent in pregnant than in non-conception cycles and the pregnancy rate in hyperstimulated cycles is three times that of non-hyperstimulated cycles. The pathogenesis is unknown, but a predominant chemical mediator, possibly a prorenin–renin–angiotensin system, has been implicated.

The most effective management is the accurate prediction of the patients most at risk and prevention. This can be achieved by using cautious, slow, and gradual low doses of gonadotropins and reducing regimens in women with polycystic ovaries. Combined sonography and endocrine monitoring should improve prediction rates. The presence of 20 or more small and intermediate sized follicles and/or a serum estradiol level of >3000 pg/ml should alert the clinician. If an exuberant ovarian response is observed and the patient has clinical symptoms of overstimulation, then the dose of hCG can be reduced, delayed (coasting), or omitted (thus canceling the cycle). Another alternative, if the patient is clinically well, and more than 30 oocytes are collected, is to perform the oocyte retrieval and to cryopreserve all the generated embryos. Although this will avoid a pregnancy in this cycle, preventing any trophoblastic hCG worsening the condition, at least the cycle is not 'wasted'. The embryos can be replaced in subsequent HRT cycles, however this regimen does not eliminate totally the possibility of OHSS developing in the fresh cycle.

In patients deemed at risk, a lower dosage of exogenous hCG, e.g. 5000 IU (instead of 10 000 IU), should be used to trigger ovulation, and progesterone, not hCG, used for luteal phase support. Administration of albumin at the time of oocyte retrieval may reduce the risk of developing severe OHSS.

Mild OHSS is treated conservatively, with outpatient surveillance to detect the minority of patients who will go on to develop the more severe condition. All patients should be advised as regards adequate fluid and protein intake. Patients with moderate or severe OHSS should be hospitalized. Strict fluid balance, regular serum biochemistry, and prophylaxis against thromboembolism are needed in these patients. Fluid and electrolyte imbalance, as well as hypovolemia, should always be corrected. Adequate analgesia is needed for abdominal pain and discomfort. Both transvaginal aspiration and abdominal paracentesis of ascitic fluid, under ultrasonographic guidance (avoiding damage to enlarged ovaries), are used to relieve symptoms of abdominal distension and respiratory

distress, caused by massive ascites accumulation. This improves venous return, cardiac output, renal function, and urinary output. In cases of pleural effusion, a pleural tap can help relieve symptoms.

Such an approach demands close contact with the patient and good liaison with colleagues in other centers who may be providing emergency care. Early referral to an intensive care unit will help to correct hemodynamic disturbances but the reproductive specialist must continue to play an active role in management. Secondary complications of OHSS include venous thromboembolism, respiratory distress, and hepato-renal failure. Although isolated reports of death due to complications of OHSS have been reported[51], death is very rare following ovarian stimulation, occurring in approximately 1 in 400–500 000 stimulation cycles.

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