

Ovarian hyperstimulation syndrome (OHSS):

A short report for the HFEA, August 2008.

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Background

- The Human Fertilisation and Embryology Authority (HFEA) commissioned this report in 2005 at the time of *The SEED Review* as there was concern expressed about the potential risks to women donating oocytes. An update has been commissioned in 2008 to include additional data and publications over the last 3 years.
- The scope of the report is to provide a brief overview of Ovarian hyperstimulation syndrome (OHSS), its incidence and the spectrum of the condition. I have not expanded in detail on its pathophysiology or discussed research into the science and management of OHSS. I refer the interested reader to *Further Reading* at the end of this paper.

Personal Statement

I am the Person Responsible for the IVF unit at the General Infirmary, Leeds (Centre 0052), which currently performs approximately 1100 stimulated IVF cycles per annum. We perform oocyte donation (approximately 35 cycles per annum) but do not perform “egg sharing”, whereby patients undergoing IVF for themselves donate some of their oocytes to recipients who require donated eggs. I have long had an interest in OHSS and ovarian stimulation regimens. I also have a significant research interest in polycystic ovary syndrome (PCOS) and polycystic ovaries (pco). It is women with polycystic ovaries who are at particular risk of developing OHSS and I have written a number of reviews and papers on the management of patients with PCOS undergoing IVF and also on OHSS and its management.

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a consequence of superovulation therapy for assisted conception procedures. This potentially fatal condition is avoidable by the judicious use of gonadotropins and careful monitoring of stimulation regimens. Women who are at particular risk of developing the syndrome include those who have polycystic ovaries and those who are young (under 30 years).

The pathophysiological hallmark of the ovarian hyperstimulation syndrome is a sudden increase of vascular permeability which results in the development of a massive extravascular exudate. This exudate accumulates primarily in the peritoneal cavity, causing a protein rich ascites. Loss of *fluid* into the "third" space causes a profound fall in intravascular volume, haemoconcentration 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 may cause hyponatraemia.

The syndrome is graded according to severity. Mild ovarian hyperstimulation is characterised by fluid accumulation, as evidenced by weight gain, and abdominal distension and discomfort. Ultrasound examination shows enlarged ovaries with a mean diameter greater than 5 cms but less than 8cm. Grade 2 (moderate) ovarian hyperstimulation is associated with the development of nausea and vomiting. The ovarian enlargement and abdominal distension are greater, with ovarian diameter 8-12cm, and cause more discomfort and dyspnoea. Ascites can be detected by ultrasound.

Grade 3 (severe) ovarian hyperstimulation syndrome is a life threatening condition in which there is clinical evidence of contraction of the intravascular volume (subnormal central venous pressure with reduced cardiac output), severe expansion of the third space (tense ascites, pleural and pericardial effusions, all of which compromise the circulation and breathing), severe haemoconcentration and the development of hepatorenal failure. In addition to the circulatory crisis these patients are at risk from intravascular

thrombosis. Deaths have been recorded in women with Grade 3 ovarian hyperstimulation syndrome, caused usually by cerebrovascular thrombosis, renal failure or cardiac tamponade resulting from pericardial effusion. Some authors have classified the most severe group as “Critical OHSS”, when the haematocrit is $> 55\%$, there is oliguria/anuria, thromboembolism and acute adult respiratory distress syndrome (ARDS) [1].

Risk factors for OHSS

OHSS generally only occurs after overstimulated ovaries have been exposed to human chorionic gonadotropin (hCG). The condition therefore results most commonly when sensitive ovaries are exposed to gonadotropin preparations that contain follicle stimulating hormone (FSH) and then to hCG. The finding that severe ovarian hyperstimulation syndrome is often associated with pregnancy is probably related to the persistence of hCG in this situation. Even when the ovaries have been severely overstimulated, ovarian hyperstimulation syndrome can usually be prevented by avoiding exposure of the ovaries to hCG and/or LH. Thus in the context of a woman undergoing a cycle of ovarian stimulation whilst donating oocytes, hyperstimulation is likely to be a self-limiting situation as a pregnancy, by definition, will not occur.

In IVF the rate of OHSS varies in published series from 1-10%, being highest in those combining gonadotropin stimulation with treatment with a GnRH analogue. Severe cases occur in 0.25- 8% of IVF cycles [2, 3, 4] with mild cases occurring in up to 33% of cases [4]. The IVF treatment regimen in most cases involves a degree of ovarian stimulation, other than in completely “natural”/unstimulated cycles – although even the latter will usually employ a pre-ovulatory trigger of hCG. The incidence of clinical OHSS is dependent upon how the diagnosis is made and the degree of follow-up provided by the IVF clinic. There is certainly huge variation in follow-up between clinics and no statutory requirement to record all cases of OHSS. In The U.K. the HFEA keeps a record only of “Cycles reporting the risk of OHSS”, in other words cycles which have usually been cancelled, either before or after egg collection, because of a perceived risk as opposed to patients who have

experienced clinically important OHSS. In 2007 this applied to 611 out of a total of 35946 cycles (HFEA, personal communication).

A distinction has been made between early and late OHSS [5,6], with those presenting early (that is 3 – 7 days after hCG administration) having significantly higher serum oestradiol concentrations and more follicles than those presenting late (12 – 17 days after hCG). Those presenting early usually have a self-limiting condition of relatively short duration whilst those presenting late are more likely to be pregnant and have a severe and more prolonged form of the syndrome, due to persistent stimulation of the ovaries by hCG from the placenta.

Two of the important risk factors can be identified before treatment starts, the others as ovarian stimulation proceeds:

1. The presence of polycystic ovaries

Several studies have confirmed that patients most at risk are women with the characteristic appearance on ultrasound of polycystic ovaries, not necessarily the polycystic ovary *syndrome* [7]. The polycystic appearance occurs in 20%-33% of normal women but approximately 40% of patients undergoing IVF, irrespective of the indication for treatment [8]. Women with polycystic ovaries on ultrasound but without the clinical features of the syndrome have a typical polyfollicular response to stimulation with gonadotropins that is indistinguishable from that seen in the patients with the clinical features of the syndrome. These observations indicate the value of identifying polycystic ovaries before treatment starts so that the dose of gonadotropin for stimulation can be adjusted appropriately.

2. The patient's age

Most cases of ovarian hyperstimulation syndrome occur in younger women, consistent with the greater ovarian responsiveness in this group compared with older women [4,8]. *Low body weight* has also been associated with an increased risk for OHSS, presumably because of increased bioavailability of gonadotropins.

3. Use of GnRH agonists.

GnRH agonists protect the ovary from an endogenous LH surge, so facilitating more convenient scheduling of oocyte pick up. The protection so afforded renders the ovary more amenable to stimulation of multifollicular development by high dose gonadotropin treatment. Not surprisingly this very advantage makes ovarian hyperstimulation syndrome more common in treatment programs utilising pituitary desensitisation. In some individuals it is harder to reach the “threshold” for ovarian stimulation and so higher doses of gonadotropins are administered in order to achieve an ovarian response, with an increased likelihood of an “explosion” of uncontrollable multiple follicle development when the ovaries eventually do respond [9].

The introduction of GnRH antagonist protocols involves stimulation first with a gonadotrophin and the addition of GnRH antagonist usually from day 6 of stimulation. Because the pituitary is not desensitized, the pre-ovulatory trigger of oocyte maturation can then be achieved by using a GnRH agonist. It has been suggested that significant luteolysis occurs because of the short half life of the endogenous LH so produced, thereby minimizing or possibly removing any risk of OHSS [10, 11].

4. Development of multiple follicles during treatment

The development of large numbers (greater than 20 - 30) of immature and intermediate follicles during treatment indicates an exuberant response to gonadotrophic stimulation, caused either by very sensitive, ie polycystic, ovaries (the usual situation) or too high a dose of gonadotropins in women with normal ovaries [12].

5. Exposure to LH/hCG

The clinical observation that exposure of the ovaries to LH, usually in the form of 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 neovascularisation and vascular permeability. Indeed late presentation with severe OHSS has been

suggested as being diagnostic of a clinical IVF pregnancy [6]. Furthermore multiple pregnancy adds an additional risk to the development of OHSS [5].

The finding of a significant reduction in OHSS in GnRH antagonist cycles in which a GnRH agonist has been administered instead of hCG indicates that the short half life of endogenous LH cannot sustain ovarian follicular activity. This also suggests that hCG alone is certainly the prime driver for OHSS [10, 11].

6. Previous episodes of ovarian hyperstimulation syndrome

It is self apparent that a woman who has already experienced OHSS is more at risk if she undergoes further ovarian stimulation.

Pathophysiology

It is beyond the scope of this short report to provide a detailed account of the pathophysiology of OHSS. 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. While numerous compounds, such as prostaglandins, kallikreins, and various growth factors have been considered to mediate the process, the two prime movers in the development of OHSS appear to be activation of the ovarian renin–angiotensin system and release of vascular endothelial growth factor (VEGF) from the ovary [13].

The follicle contains renin in an inactive form which is activated at mid-cycle (and by exposure of the ovary to hCG) and which then causes conversion of angiotensinogen to angiotensin I. This ovarian 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. Excessive levels of renin activity have been reported 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 hemotocrit concentrations being directly related to plasma renin activity and aldosterone concentrations [14].

Vascular Endothelial Growth Factor (VEGF) increases capillary permeability and is expressed in steroidogenic and steroid-responsive cells, such as those involved in repair of endometrial vessels and in implantation. Follicular fluid concentrations of VEGF have been correlated with OHSS and also with ovarian blood flow, as assessed by Doppler ultrasound flow studies [15]. Indeed serum VEGF concentrations have been proposed as a predictor for the development of the syndrome [14].

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.

The ovarian hyperstimulation syndrome and thromboembolism

The greatest cause of morbidity and potential mortality in OHSS is from thromboembolism. When considering the pathophysiology of the OHSS it is easy to appreciate the potential risk of deep venous thrombosis (DVT) and thromboembolic events [16]. Not only is there a hypercoagulable state but also the combination of enlarged ovaries and ascites leads to reduced venous return 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 literature found that 75% of cases reported were in venous sites, with 60% in the upper limb, head and neck veins, with an associated risk of pulmonary embolism of 4 –12%, whilst the remaining 25% were arterial thromboses and were mostly intracerebral [17]. It is difficult to give an explanation for these more unusual sites of thrombosis in young women, unless there is relative over-reporting because of their rarity [18-21].

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 [22] or lead to various forms of long term disability [23, 24].

The prevalence of thrombophilia may be increased in women with severe OHSS and prophylactic screening for thrombophilia has been advocated in those who have experienced severe OHSS [25].

Prevention of ovarian hyperstimulation syndrome.

All patients undergoing ovarian stimulation, whether to correct anovulation or for assisted fertility techniques, should have a pre-treatment ultrasound scan and if polycystic ovaries are detected the dose of gonadotropin lowered (to a starting dose of no more than 50 – 150 IU depending upon age and other factors). If pituitary desensitisation has been used one should be sensitive to the loss of the normal "protection" of the ovary caused by the block to oestrogen mediated positive feedback of LH release. If a long protocol of GnRH analogue 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 number to circulating oestradiol levels. In this situation measurement of serum oestradiol concentrations underestimates follicle development. It is therefore essential that endocrine monitoring is supported by high quality ultrasound, otherwise low circulating oestradiol concentrations may encourage further and inappropriate gonadotrophic stimulation despite adequate follicular development. Meta-analyses of the different gonadotropin

preparations have indicated no significant difference in risk of developing OHSS [27-28].

Furthermore with respect to ultrasound monitoring, a recent systematic review found that there is no evidence from randomised trials to support cycle monitoring by ultrasound plus serum estradiol as more efficacious than cycle monitoring by ultrasound only for the detection of ovarian hyperstimulation (RR 0.73, 95% CI 0.30 to 1.78) [29]. The authors concluded that a randomised trial with sufficiently large sample size to test the effects of different monitoring protocols on OHSS would “pose a great challenge”. They suggest that “until such a trial is considered feasible, cycle monitoring by transvaginal ultrasound plus serum estradiol may need to be retained as a precautionary good practice point” [29].

OHSS is usually associated with the presence of a large number of small to moderate sized follicles (< 14 mm diameter) rather than larger, more mature follicles. When serum oestradiol concentrations are 10,000-15,000 pmol/L with 20-30 follicles, the patient is at risk of OHSS. In some cases a low dose of hCG (5,000 units) may be given but the embryos should be cryopreserved and transferred at a later date, in order to avoid the chance of pregnancy, which would then increase the risk for late-onset and prolonged OHSS. In patients having IVF if the serum oestradiol concentration becomes greater than 15,000 pmol/L (5000 pg/ml) with more than 30-40 follicles, hCG should be withheld and the treatment cycle cancelled. Treatment with the GnRH analogue is however continued and, when the ovaries regain their normal size, ovarian stimulation is resumed at a lower dose.

For the patient with overstimulated ovaries who is approaching the time of hCG administration several strategies to make treatment more safe may be considered. The first is to administer a low dose of hCG to initiate oocyte maturation and /or ovulation (ie not more than a single injection of 5000 IU, rather than the dose of 10,000 IU which many clinics use in routine practise) and, in patients receiving GnRH agonist treatment and who therefore require luteal support, to give progesterone rather than hCG. The use of recombinant

LH, which has a shorter half life than hCG may also be of benefit, although there is limited data [30]. As mentioned already, it has been suggested that the use of GnRH antagonist cycles might reduce the risk of OHSS combined also with administration of a GnRH agonist to trigger oocyte maturation, although there is as yet insufficient data [10,11, 30, 31].

A recent prospective trial randomized 66 patients under 40 years of age undergoing IVF with polycystic ovary syndrome, polycystic ovarian morphology, or previous high response to an ovarian stimulation protocol consisting of either GnRH agonist trigger after cotreatment with GnRH antagonist or hCG trigger after pituitary suppression with a GnRH agonist [32]. Both groups received luteal phase and early pregnancy supplementation with IM progesterone, and patients in the study group also received oestradiol patches. None of the patients in the study group developed any form of OHSS compared with 31% (10/32) of the patients in the control group. There were no significant differences in the implantation (22/61 [36.0%] vs. 20/64 [31.0%]), clinical pregnancy (17/30 [56.7%] vs. 15/29 [51.7%]), and ongoing pregnancy rates (16/30 [53.3%] vs. 14/29 [48.3%]) between the study and control groups, respectively. Suggesting that the use of a protocol consisting of GnRH agonist trigger after GnRH antagonist cotreatment combined with adequate luteal phase and early pregnancy oestradiol and progesterone supplementation reduces the risk of OHSS in high-risk patients undergoing IVF without affecting implantation rate [32].

New concepts in ovarian stimulation involve the use of “mild strategies”, which in the context of GnRH antagonist cycles are becoming more popular than the more traditional long GnRH agonist cycles [33]. Long acting preparations of FSH are attractive as they provide a single injection that lasts seven days [34], yet recent data if anything suggests an association with a slightly greater degree of ovarian hyperstimulation [35]. There is also the possibility to consider the in vitro maturation of oocytes collected from unstimulated or minimally stimulated ovaries, although this requires particular expertise in the clinic and laboratory [36].

In patients with polycystic ovaries we have found in a prospective randomised 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% ($p < 0.023$) [37].

An interesting new strategy is the use of dopamine agonists, such as cabergoline, which inhibit phosphorylation of the receptor for VEGF and have been shown in preliminary studies to significantly reduce the incidence of OHSS [38].

Management of the ovarian hyperstimulation syndrome [1]

Mild ovarian hyperstimulation is 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, particularly if a pregnancy occurs. The patient should be encouraged to weigh herself daily and take plenty of oral fluids. A marked increase in weight (more than 5 kgs) with the development of abdominal distension, nausea and vomiting indicate the onset of Grade 2 hyperstimulation and the need for hospitalisation. 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 Grade 2 hyperstimulation need reassurance and explanation, together with bed rest in hospital. Oral fluids are encouraged although vomiting may make an intravenous infusion necessary. Full length TED stockings are advised to reduce the risk of deep vein thrombosis. Adequate analgesia is required. Preferred drugs are paracetamol, with or without codeine and pethidine for very severe pain.

The development of clinically detectable and usually painful ascites, together with a deterioration in respiration, circulation and renal function indicates the development of severe Grade 3 hyperstimulation and may require admission to an intensive care unit [1]. The intravascular volume should be monitored by measurements of central venous pressure, renal function by meticulous

attention to input and urine output and haemoconcentration by measurement of haematocrit, whose level reflects intravascular volume depletion and blood viscosity. A haematocrit of over 45% is a serious warning sign and a measurement greater than 55% signals a life threatening situation. There may be a striking leucocytosis, the WBC count rising up to 40,000/ml. Measurement of body weight, serum urea, creatinine and electrolytes, together with serum albumen and liver function tests and periodic assessments of the coagulation profile are mandatory.

Infusion of colloid (e.g. human albumen or 6% hydroxyethyl starch (HES)) is required to maintain intravascular volume, as indicated by restoration of normal central venous pressure. Crystalloid (normal saline usually) is administered for rehydration, although with careful monitoring of fluid balance. Prophylactic heparin should be given to prevent thromboembolism and as the risk continues up to the end of the first trimester of pregnancy there is an argument to continue heparin until that time [1].

A further concern is the development of hyponatraemia, secondary to antidiuretic hormone hypersecretion. If urine output remains suppressed despite restoration of central venous pressure and rehydration, abdominal paracentesis, under ultrasound guidance, should be undertaken. The indications for this procedure are therefore the need for symptomatic relief of a tense ascites, oliguria, rising serum creatinine, falling creatinine clearance and haemoconcentration unresponsive to medical therapy. Severe oliguria or renal failure persisting despite these measures usually necessitate dialysis [1].

Paracentesis of hydrothorax should be considered for relief of dyspnoea. Cardiac tamponade from pericardial effusion may prove fatal if not rapidly relieved. Careful cardiological assessment together with cardiac ultrasound should therefore feature in the management of these patients. One must be aware of the possibility of re-accumulation of fluid in any of these cavities.

A more detailed description of management is beyond the scope of this paper. The RCOG Guideline is an important reference [1] and more detailed advice is found in [39]. Each IVF clinic should have clearly written protocols both for use by their clinic staff and also available for each gynaecological ward into which patients might be admitted – which might include distant district general hospitals that may be closer geographically to the home of patients who in some parts of the U.K. travel long distances for IVF treatment.

OHSS in the context of oocyte donation

Women undergoing ovarian stimulation in order to donate oocytes should be at no greater risk than those who undergo ovarian stimulation as part of their own treatment for IVF, apart from the likelihood that they are from a younger age group [40,41]. As there is no risk of pregnancy, if OHSS occurs it should be early and self-limiting. The reported incidence of OHSS is 1% of egg donation cycles [41] and this was from a series from North America, which is a country prone to higher rates of OHSS because of a tendency to use high doses of gonadotropins during stimulation.

Women undergoing oocyte donation should be less than 35 years of age and may be even younger. They are likely to be of proven fertility and have to be screened to ensure that they are of good health. Strict criteria should be employed when screening women who wish to become oocyte donors and those with overt PCOS are likely to be excluded – although not necessarily so. As with all women undergoing an IVF cycle the baseline ultrasound scan should detect the presence of polycystic ovaries, even if the patient does not have PCOS, and the dose of gonadotropin reduced appropriately. Furthermore patients with polycystic ovaries should be monitored carefully during ovarian stimulation – with the potential for reducing dose of stimulation if there are early signs of over-recruitment.

There is no justification for giving higher doses of gonadotropins to egg donors than would usually be given to patients undergoing standard IVF. I am aware of anecdotal reports that some centres “push women hard” with high doses of stimulation if they are either donating oocytes or sharing oocytes.

Although there is no hard evidence of this, such practice would be inappropriate.

By definition women donating oocytes – but not those sharing – will not have an embryo transfer themselves and so will not get pregnant. They therefore are not at risk of the more severe form of late onset OHSS.

There is insufficient evidence to suggest that OHSS is so prevalent that women should not undergo ovarian stimulation for altruistic oocyte donation. All women receiving ovarian stimulation should be given detailed information about the potential risks of OHSS. And if a woman donating oocytes is found to be at risk of developing OHSS then hCG should not be administered and the treatment cycle should be discontinued.

A policy document of the American Society for Reproductive Medicine [39] states that “Currently, there are no clearly documented long-term risks associated with oocyte donation, and as such, no definitive data upon which to base absolute recommendations. However, because of the possible health risks outlined in the preceding discussion (*viz, essentially those associated with all IVF cycles namely OHSS, infection, haemorrhage, anaesthetic complications*), it would seem prudent to consider limiting the number of stimulated cycles for a given oocyte donor to approximately six, and to further strive to limit successful donations from a single donor to no more than 25 families per population of 800,000, given concerns regarding inadvertent consanguinity of offspring. Clearly, restrictions on the number of stimulated cycles that a given donor should undergo will in most instances be the limiting factor” [41]. Similar guidelines are not available for the U.K. but I believe it extremely unlikely that a woman would undergo that many cycles of oocyte donation. Indeed in the U.K. most donors will undergo a single cycle and a few two or maybe three cycles.

Oocyte donation for research purposes

Clinics that perform research on surplus oocytes (or embryos) are bound by extremely tight regulations. Approximately 20-30% of all oocytes collected

during IVF stimulation cycles fail to fertilise and so there is a plentiful supply of oocytes for research purposes. Some clinics have research licenses issued by the HFEA which now allow ovarian stimulation and collection of oocytes solely for research purposes [42]. Information provided to patients and any “counselling strategies which promote the donation of eggs to research” must allow patients sufficient time to consider their options and must not place the patient under any pressure. Ethics committees are very strict in ensuring the rights of the patient to decide whether or not they wish to participate in research. All information provided has to be non-judgemental and make clear that the individual’s treatment will not be affected by their decision.

Women undergoing ovarian stimulation for IVF or oocyte donation should not be put under any pressure to donate oocytes for research and stimulation strategies should not be modified in order to encourage the production of excess oocytes for research processes.

Overall Incidence of OHSS in the U.K.

There are no good data on the overall incidence of severe OHSS, as the severity of OHSS is often not standardised, although it is likely that severe cases will be those most likely to be reported. There have been case reports of thromboembolism and severe sequelae of ovarian hyperstimulation but data is not kept centrally. The latest European database of all reported IVF cycles in 2004 presents the incidence of OHSS from registers of 25 of the 29 countries that submitted data [43]. There were 2,858 cases of OHSS out of 295,069 cycles, equivalent to 0.97% of all stimulated cycles [43]. There were 631 cases reported from the U.K. to this database out of a total of 39,981 stimulated cycles, equivalent to 1.6% [43]. This figure is at variance with number recorded on the HFEA database, which is 609 for 2004 (HFEA personal communication). The large range of reported cases in the European database gives little clue to the severity of OHSS and whether these were cases of ovarian stimulation cancelled because of a risk of OHSS, as is the case for the HFEA figure, or actual admissions to hospital with OHSS of

whatever grade, which again is not stated. The American database does not report rates of OHSS [44].

Deaths from OHSS

It is very difficult to get a reliable figure for the number of deaths that occur as a result of OHSS. Most national databases relate to assisted conception cycles (that is IVF/ICSI and sometimes intrauterine insemination (IUI)) but not ovarian stimulation for ovulation induction in anovulatory infertility. Data on the overall number of gonadotropin stimulated cycles for ovulation induction, intrauterine insemination (IUI) and gamete intrafallopian transfer (GIFT) are generally not available and so it is not possible to give an accurate incidence of mortality from ovarian stimulation other than that for IVF.

When I initially wrote this report in 2005 I was made aware of two deaths in the U.K. following OHSS. At that time there had been in excess of 425,000 cycles of stimulated IVF that had been undertaken in the U.K.. Apparently there had been a death in 2004 reported to the HFEA, due to cerebral oedema and ischaemia, pulmonary embolus and pelvic vein thrombosis, which were secondary to OHSS. The other death was in about 1991, I believe the patient was undergoing drainage of a pericardial effusion and suffered complications and subsequently died. I also believe that the treatment received was ovarian stimulation alone and not IVF. Thus the mortality from OHSS in the U.K. in 2005 appeared to be 1:425,000 IVF cycles. I now believe this to be an underestimate.

A World Health Organisation report in 2002 estimated the overall incidence of severe OHSS as 0.2 – 1% of all assisted reproduction cycles with an estimated 1:45,000 – 1:50,000 mortality in women receiving gonadotropins [45]. The WHO report derived this figure from an estimate presented in an earlier publication [2], which stated 1:450,000 – 1:500,000 and so misquoted this estimate by a factor of ten! The authors have since acknowledged this typographical error. The European registry of 295,069 cycles in 2004 reported 4 deaths, although the cause was not described, a rate of approximately 0.001% or 1:74,000; whereas in the cohort presented in 2000

that I referred to in the last paper, there were no reported deaths out of 146,342 cycles in Europe [46]. A lack of reported deaths of course does not mean that none occurred. 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 [47]. In this study the age-standardised mortality ratio in IVF patients was actually lower than expected for the general population at 0.58 (95% CI 0.48-0.69) [47].

The triennial *Confidential Enquiry into Maternal and Child Health (CEMACH)* in the UK reports on the numbers and causes of maternal mortality. This latest report, entitled *Saving Mothers's Lives*, has for the first time recorded deaths related to OHSS [48]. In the triennium 2003-2005 there were 4 deaths out of approximately 119,641 IVF stimulation cycles, a mortality rate of 1:30,000. Furthermore CEMACH has now made it mandatory to report all deaths from OHSS and others associated with IVF and other Assisted Reproduction Technology procedures, because these deaths have occurred as a direct result of interventions to aid conception and pregnancy.

To quote directly from the report: "Of the four known deaths from OHSS assessed in this triennium, three women were pregnant and the fourth had undergone ovarian hyperstimulation and intrauterine insemination although there are conflicting reports about whether or not her pregnancy test was positive at the time of her death. The four women died from different sequelae of OHSS and their deaths are counted in the Chapters relating to the eventual cause of death. The general lessons are briefly discussed here. Two of these women were known to have had OHSS in the past but had subsequent repeated IVF cycles with many eggs being retrieved in the final cycle, indicating a risk of OHSS. Despite this, embryo transfer was carried out. One of these women was found unconscious a few weeks later and her brain scan showed a large cerebral infarct. There was delay in recognising her OHSS and in getting the brain scan. Earlier recognition of OHSS might have allowed effective treatment with fluids and thromboprophylaxis. The other woman with

a known past history of OHSS also had a large number of eggs collected and embryo transfer performed. She subsequently developed abdominal pain, collapsed within a few weeks of the procedure and died of thromboembolism. In both cases embryo transfer should not have been performed because of the high risk of OHSS. Neither of these women received thromboprophylaxis, nor did a woman who died of pulmonary embolism associated with OHSS or a woman who was admitted with OHSS and deteriorated before being transferred to Critical Care. The last woman's autopsy showed patchy infarction throughout the body [48]."

Thus the mortality rate from OHSS would appear to be approximately 1:30,000 cycles of IVF in the UK, although still difficult to quantify with complete accuracy. Whilst still relatively low, the rate appears higher than we estimated back in 2005. 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.

Summary and recommendations

1. The ovarian hyperstimulation syndrome is a recognised severe and potentially fatal complication of ovarian stimulation for assisted conception and may also occur after ovulation induction for anovulatory infertility. The development of OHSS may be unpredictable but those at greatest risk are young women with sensitive, usually polycystic ovaries (without necessarily having the polycystic ovary syndrome). Symptoms can be very distressing and are of variable duration, from a few days in most cases to a few weeks, particularly if a pregnancy has resulted from the treatment. Severe OHSS occurs in approximately 1% of ovarian stimulation cycles for assisted reproduction treatments. Mortality from OHSS in the U.K. is approximately 1:30,000 IVF cycles.

2. The risk of OHSS may be minimised by using low doses of gonadotropins and reducing doses in women with polycystic ovaries. If an exuberant ovarian

response is observed then the dose of gonadotropin should be reduced further and the dose of hCG also reduced or hCG not administered, thus cancelling the cycle. If greater than 30 oocytes are collected any embryos generated should be cryopreserved as if a pregnancy were to develop, placental hCG is likely to worsen the development of the syndrome.

3. Treatment requires meticulous attention to fluid homeostasis and prophylaxis against thromboembolism, as the latter may result in long term morbidity. Furthermore thromboprophylaxis should be continued in pregnant women who have experienced OHSS up to 12 weeks gestation. Health professionals practising fertility medicine in the U.K. should follow the RCOG Guideline on The management of ovarian hyperstimulation syndrome [1].

4. All IVF units in the U.K. are well aware of the risks of OHSS and should take a responsible approach to minimising risk.

5. All units should have clear protocols for identifying patients at risk both before and during ovarian stimulation. Furthermore protocols should be in place for the management of patients who develop symptoms.

6. Information should be provided to patients within the general pre-treatment information leaflets and also after the egg collection, so that they are aware of the risk and the symptoms to be aware of.

7. Clinics should keep a record of cases of OHSS, with particular note of patients who require hospitalisation. This should be incorporated in standard risk management protocols.

8. Clinics should ensure appropriate follow up of patients after embryo transfer and be cogniscent of the possibility of admission to a local hospital if the IVF unit is either in a large centre geographically distant from the patient's home or is a private unit without inpatient facilities. Protocols should be in place for communication between the IVF unit and local hospital with clear guidance provided to local gynaecologists who may not be used to dealing with OHSS.

9. There is insufficient evidence to suggest that women should not undergo altruistic oocyte donation because of the risk of OHSS. Indeed because of the self-limiting nature of the condition in women who do not conceive, those undergoing oocyte donation appear to be at lower risk than women receiving IVF treatment for themselves.

10. Women undergoing both altruistic oocyte donation and “egg sharing” should receive low dose stimulation regimens and should not be stimulated with higher doses in order to obtain more eggs than would be expected during a standard IVF cycle. There is no evidence that obtaining large numbers of oocytes is beneficial and all women receiving ovarian stimulation, whether for their own IVF treatment or as an oocyte donor, should receive the lowest effective dose of gonadotropins.

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