

Ovarian hyperstimulation syndrome – A short report for the HFEA.

February 2005.

Professor Adam Balen MB,BS, MD, FRCOG
Department of Reproductive Medicine
Clarendon Wing, The General Infirmary, Leeds, LS2 9NS
Adam.balen@leedsth.nhs.uk

Background

- The Human Fertilisation and Embryology Authority (HFEA) are currently reviewing sperm, egg and embryo donation (*The SEED Review*).
- In response to the public consultation a reply has been received by the HFEA suggesting that :

“With so little known about the causes, course and the cures for ovarian hyperstimulation syndrome (OHSS), we can see no possible justification for the harvesting of eggs from women who are not undergoing fertility treatment for themselves.”
- I have been provided with an anonymised copy of this response to the SEED consultation and at the request of Dr Peter Mills, Policy Development and Co-ordination Manager of the HFEA, I have prepared this short report.
- The scope of the report is to provide a brief overview of OHSS, its incidence and the spectrum of the condition. I have not expanded on its pathophysiology or discussed research into the science and management of OHSS but have described key issues, with particular reference to women donating oocytes.

Personal Statement

I am the Person Responsible for the IVF unit at the General Infirmary, Leeds (Centre 0052), which currently performs approximately 1100-1200 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 (see second part of reference list, which is a selected bibliography and a small part of my personal bibliography).

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 causes salt retention.

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 diameter greater than 5 cms. Grade 2 ovarian hyperstimulation is associated with the development of nausea and vomiting. The ovarian enlargement and abdominal distension are greater 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.

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 LH and/or hCG. 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- 2% of IVF cycles [1].

A distinction has been made between early and late OHSS [2], with those presenting early (that is 3 – 7 days after hCG administration) having significantly higher serum oestradiol concentrations than those presenting late (12 – 17 days after hCG), whilst there is no difference in the number of oocytes collected. 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* [3]. The polycystic appearance occurs in 20%-33% of normal women but approximately 40% of patients undergoing IVF, irrespective of the indication for treatment [4]. 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 gonadotropins 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 [5]. *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 ovum 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” or uncontrollable multiple follicle development when the ovaries eventually do respond [6].

4. Development of multiple follicles during treatment

The development of large numbers (greater than 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 gonadotropin in women with normal ovaries.

5. Exposure to LH/hCG

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 neovascularisation and vascular permeability. Indeed late presentation with

severe OHSS has been suggested as being diagnostic of a clinical IVF pregnancy [7]. Furthermore multiple pregnancy adds an additional risk to the development of OHSS [2].

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 discuss the pathophysiology of OHSS. There has been a lot of research in this subject but it is not pertinent to the questions posed by the HFEA. Should more detail be required then I will be happy to supply it.

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. Indeed there has been an expanding literature on this association in recent years [8]. 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 world 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 [9]. 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 [10-12].

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 [13] or lead to various forms of long term disability [14, 15].

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 [18].

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. 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 [17-22].

It has been suggested that the use of GnRH antagonist cycles might reduce the risk of OHSS [23] combined also with administration of a GnRH agonist to trigger oocyte maturation [24], although there is as yet insufficient data.

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% ($p < 0.023$) (Tang T, Balen AH – unpublished data).

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 usual dose of 10,000

IU) 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.

In patients having IVF if the serum oestradiol concentration becomes greater than 17,000 pmol/L (5500 pg/ml) with more than 40 follicles, hCG should be withheld and treatment abandoned. 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. Treatment with the GnRH analogue is however continued and, when the ovaries regain their normal size, ovarian stimulation is resumed at a lower dose. When serum oestradiol 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.

Management of the ovarian hyperstimulation syndrome

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. 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 so 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, 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 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) 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.

If urine flow 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.

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. Each IVF 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 [25, 26]. The reported incidence of OHSS is 1% of egg donation cycles [26] 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.

There is no justification for giving higher doses of gonadotropins 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 [25, 26].

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 recent policy document of the American Society for Reproductive Medicine [25] 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 [25]*), 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” [25]. 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.

In the U.K. at the last assessment the number of oocyte donation cycles was 1,783 out of a total of 27,056 stimulation cycles, equivalent to 6.5% [27]. The latest ESHRE database included 6,530 oocyte donation cycles out of a total of 233,467 stimulated cycles in 2000, equivalent to 2.7 % of stimulated cycles [28]. In this survey there were 2,135 oocyte donation cycles reported from the U.K. out of a total of 28,474 stimulated cycles (7.4%) [28]. The U.S. registry reported 6,684 cycles of oocyte donation in 2000, equivalent to 9% of all ART cycles [29].

Oocyte donation for research purposes

The response to the SEED consultation received by the HFEA highlights the possibility that “women will now be offered free IVF in exchange for ‘spare’ eggs, given the demands of research scientists”. I do not believe that any clinical ethics committee would allow such a practice in the U.K.. Research on oocytes is only allowed with the express consent of the patient and then only on oocytes that have

failed to fertilise and therefore cannot be used in the patient's own treatment. 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.

Clinics that perform research on surplus oocytes (or embryos) are bound by extremely tight regulations. 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.

I do not believe that women undergoing ovarian stimulation for IVF or oocyte donation are put under any pressure to donate oocytes for research and I do not believe that there is any risk that this situation will change in the U.K..

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 good data is not kept centrally. The latest European database of all reported IVF cycles in 2000 presents the incidence of OHSS from registers of 17 of the 22 countries that submitted data [28]. There were 1,586 cases of OHSS out of 146,342 cycles, equivalent to 1.1% of all stimulated cycles [28]. There were 376 cases reported from the U.K. to this database out of a total of 28,474 stimulated cycles, equivalent to 1.3% [28]. The American database does not report rates of OHSS [29].

Deaths in the U.K.

I have made general enquiries and to my knowledge there have been two deaths in the U.K. following OHSS. So far there have been in excess of 425,000 cycles of stimulated IVF that have been undertaken in the U.K. (HFEA, Dr Peter Mills, personal communication). Apparently there was 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 (HFEA, Dr Peter Mills, personal communication). 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. Data on the overall number of gonadotropin stimulated cycles for ovulation induction, intrauterine insemination (IUI) and gamete intrafallopian transfer (GIFT) are not available and so it is not possible to give an accurate incidence of mortality from ovarian stimulation other than that for IVF. Thus the mortality from OHSS in the U.K. currently appears to be 1:425,000 IVF cycles.

The paper submitted to the HFEA in response to the SEED consultation quotes a mortality rate of 1:50,000 IVF cycles, as suggested by a WHO report in 2002 [30]. This report actually estimates 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 [30]. I have been able to obtain a full copy of this report and have communicated with the first author, Jean-Noel Hugues. Professor Hugues has informed me that he got the figure from a review article by Brinsden et al [1] (of which I am actually a co-author!!). In that article we “estimate” a mortality of 1:400,000 – 1:500,000 stimulated cycles – thus there has been a transcription error in Hugues’ WHO report, which has been repeated in the letter received by the HFEA.

As mentioned in the previous section the most recent databases record what are probably reasonably accurate rates of OHSS and there were no deaths in the European registry of 146,342 cycles in 2000 [28]. 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 [31]. (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) [31]).

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.

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 1:425,000 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.

4. All IVF units in the U.K. are well aware of the risks of OHSS and I believe that most, if not all, 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 cognisant 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.

11. Health professionals practising fertility medicine in the U.K. could usefully follow the lead of The American Society for Reproductive Medicine and produce a policy and practice document on OHSS [32] (and for that matter on other clinical and ethical issues [33]). I suggest that this is would be better co-ordinated by the British Fertility Society and associated professional bodies rather than the HFEA.

Adam Balen, 10th February 2005.

References

1. Brinsden PR, Wada I, Tan SL, Balen A, Jacobs HS. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. *British Journal of Obstetrics and Gynaecology* 1995, 102: 767-772
2. Mathur R, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. *Fertil Steril* 2000; **73**: 901-7.
3. Balen AH. The pathogenesis of polycystic ovary syndrome: the enigma unravels. *Lancet* 1999; **354**: 966-7.
4. Balen AH, Tan SL, MacDougall J, Jacobs HS: Miscarriage rates following in vitro fertilisation are increased in women with polycystic ovaries and reduced by pituitary desensitisation with buserelin, *Human Reproduction*, 1993; **8**: 959-964.
5. MacDougall MJ, Tan SL, Balen AH, Jacobs HS: A controlled study comparing patients with and without polycystic ovaries undergoing in-vitro fertilisation. *Human Reproduction*, 1993; **8**:233-237.
6. Hughes EG, Fedorkow DM, Daya S, Sagle MA, Van de Koppel P, Collins JA. The routine use of gonadotropin-releasing hormone agonists prior to in vitro fertilization and gamete intrafallopian transfer: a meta-analysis of randomized trials. *Fertil Steril* 1992; 58:888-96.
7. Richter KS, van Nest RL, Stillman RJ. Late presentation with severe ovarian hyperstimulation syndrome is diagnostic of clinical; IVF pregnancy. *Fertil Steril* 2004; **82**: 478-479.
8. Stewart JA, Hamilton PJ, Murdoch AP. Thromboembolic disease associated with ovarian stimulation and assisted conception techniques. *Human Reprod* 1997; **12**: 2167-73.
9. Stewart JA, Hamilton PJ, Murdoch AP. Upper limb thrombosis associated with assisted conception treatment. *Human Reprod* 1997; **12**: 2174-5.
10. Schanzer A, Rockman CB, Jacobowitz GR, Riles TS. Internal jugular vein thrombosis in association with the ovarian hyperstimulation syndrome. *J Vascular Surgery* 2000; **31**: 815-8.
11. Lamon D, Chang CK, Hruska L, Kerlakian G, Smith JM. Superior vena cava thrombosis after *in vitro* fertilization : case report and review of the literature. *Annal Vascular Surgery* 2000; **14**: 283-5.
12. Ryo E, Hagino D, Yano N, Sento M, Nagasaka T, Taketani Y. A case of ovarian hyperstimulation syndrome in which antithrombin III deficiency occurred because of its loss into ascites. *Fertil Steril* 1999; **71**: 860-2.

13. Tang OS, Ng EHY, Cheng PW, Ho PC. Cortical vein thrombosis misinterpreted as intracranial haemorrhage in severe ovarian hyperstimulation syndrome. *Hum Reprod* 2000; **15**:1913-1916.
14. Yoshii F, Ooki N, Shinohara Y, Uehara K, Mochimaru F. Multiple cerebral infarctions associated with ovarian hyperstimulation syndrome. *Neurlogy* 1999; **53**: 225-7.
15. Sadek MME, Amer MK, Fahmy M. Acute cerebrovascular accidents with severe ovarian hyperstimulation syndrome. *Hum Reprod* 1998; **13**: 1793-5.
16. Dulitzky M, Cohen SB, Inbal A, Seidman DS, Soriano D, Lidor A, Mashiach S, Rabinovici J. Increased prevalence of thrombophilia among women with severe ovarian hyperstimulation syndrome. *Fertil Steril* 2002; **77**: 463-467.
17. Daya S, Gunby J, Hughes EG, Collins JA, Sagle MA. FSH versus hMG for IVF cycles: a meta-analysis. *Fertil Steril* 1995;64:347-54.
18. Agrawal R, Holmes J, Jacobs HS. Follicle-stimulating hormone or hMG for ovarian stimulation in in vitro fertilization cycles: a meta-analysis. *Fertil Steril* 2000;73:338-43.
19. Daya S, Gunby J. Recombinant versus urinary FSH for ovarian stimulation in assisted reproduction cycles. *Cochrane Database Syst Rev* 2000;(4):CD002810. 518.
20. Al-Inany H, Aboulghar M, Mansour R, Serour G. Meta-analysis of recombinant versus urinary-derived FSH: an update. *Hum Reprod* 2003;18:305-13.
21. Van Wely M, Westergaard LG, Bossuyt PM, Van der Veen F. HMG versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. *Cochrane Database Syst Rev* 2003;(1):CD003973.
22. Al Inany H, Aboulghar M, Mansour R, Serour G. Meta-analysis of recombinant versus urinary-derived FSH: an update. *Hum Reprod* 2003;18:1.
23. Orvieto R. Can we eliminate severe ovarian hyperstimulation syndrome? *Human Reprod* 2005; **2**: 320-322.
24. Kol S. Luteolysis induced by a GnRH agonist is the key to prevention of ovarian hyperstimulation syndrome. *Fertil Steril* 2004; **81**: 1-5.
25. Practice Committee, American Society for Reproductive Medicine. Repetitive oocyte donation. *Fertility Sterility* 2004; **82**: S158-159.
26. Sauer MV, Paulson RJ, Lobo RA. Rare occurrence of ovarian hyperstimulation syndrome in oocyte donors. *Int J Gynaecol Obstet* 1996; **52**: 259-262.
27. Human Fertilisation and Embryology Authority. *The Patients' Guide to IVF Clinics*, 2002.

28. European IVF-monitoring programme for ESHRE. Assisted reproductive technology in Europe, 2000. Results generated from European registers by ESHRE. *Human Reprod* 2004; **19**: 490-503.
29. Society for Assisted Reproductive Technology, The American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 2000 results. *Fertil Steril* 2004; **81**: 1207-2000.
30. Hugues JN. Ovarian stimulation for assisted reproductive technologies. In Vayena E, Rowe PJ and Griffin PD (eds). *Current Practices and Controversies in Assisted Reproduction*, World Health Organisation, Geneva, Switzerland, 2002; pp 102-125.
31. Venn A, Hemminki E, Watson L, Bruinsma F, Healy D. Mortality in a cohort of IVF patients. *Hum Reprod* 2001; **16**: 2691-6.
32. Practice Committee, American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome . *Fertility Sterility* 2004; **82**: S81-86.
33. Practice Committee, American Society for Reproductive Medicine. 2004 Compendium of ASRM Practice Committee and Ethics Committee Reports. *Fertility Sterility* 2004; **82**: Supplement 1.

Personal selected references relevant to the subject of ovarian hyperstimulation syndrome.

BOOKS

Infertility in Practice, Second Edition; Balen AH and Jacobs HS. Churchill Livingstone/Harcourt Brace, London, 2003.

Clinical Management of Polycystic Ovary Syndrome. Balen AH – Editor-in-chief, with co-editors: G. Conway, R. Homburg, R. Legro. Parthenon Press, 2005.

Chapters

Balen AH, Balen FG, Tan SL: The ovary and assisted reproduction. In Kurjak A (editor): Ultrasound and the Ovary, Parthenon Press, Carnforth, Lancashire, 1994, pages 83-98

Balen AH: PCOS – Medical or surgical treatment? Evidence-based Fertility Treatment, RCOG Study Group. Templeton A, Cooke I & O'Brien PMS (eds), RCOG Press, 1998, pp 157-177.

Balen AH, MacDougall J, Jacobs HS: Polycystic ovaries and assisted conception. In Bourn Hall Textbook of IVF, P Brinsden (ed), Parthenon Press, Carnforth, Lancashire, 1999 pp 109-130.

Balen AH, Jacobs HS: Polycystic ovaries and assisted conception. In The Polycystic Ovary Syndrome, editor G Kovacs 2000, Cambridge University Press, pp 159-181.

Balen AH. GnRH agonists and superovulation for assisted conception. Infertility and Reproductive Medicine Clinics of North America, ed P Devroey, WB Saunders Co, Philadelphia, 2001; 12: 89-104.

Balen AH. Strategies for Superovulation for IVF. In: Good Clinical Practice in Assisted Reproduction, Editors Paul Serhal and Caroline Overton. Cambridge University Press, 2004 pp 112-128.

Tang T, Balen AH: The polycystic ovary and IVF. Textbook of Assisted Reproductive Techniques, 2nd Edition, editors: DK Gardner, A Weissman, C Howles, Z Shoham. Taylor & Francis, London, 2004, pp 771-780.

Balen AH: Pathophysiology – trying to understand polycystic ovary syndrome and its endocrinology. Polycystic Ovary Syndrome, editors: IS Fraser & GT Kovacs, Bailliere's Best Practice in Research and Clinical Obstetrics and Gynaecology, 2004; 18: 685-706.

Balen AH: Polycystic ovaries and their relevance to assisted conception. A Textbook of *in vitro* fertilization and assisted conception, 3rd Edition, editor Peter Brinsden, Parthenon Press 2005 (in press).

Papers

Tan SL, Balen AH, Hussein EE, Campbell S, Jacobs HS: The administration of steroids for the prevention of ovarian hyperstimulation syndrome in IVF. A prospective randomised study. Fertility and Sterility, 1992; 58: 378-383.

MacDougall MJ, Tan SL, Balen AH, Jacobs HS: A controlled study comparing patients with and without polycystic ovaries undergoing in-vitro fertilisation. *Human Reproduction*, 1993; 8:233-237.

Balen AH, Braat DDM, West C, Patel A, Jacobs HS: Cumulative conception and live birth rates after the treatment of anovulatory infertility. An analysis of the safety and efficacy of ovulation induction in 200 patients. *Human Reproduction*, 1994 9: 1563-1570.

Balen AH: Anovulatory infertility and ovulation induction - Recommendations for good practice. *Journal of the BFS, Human Reproduction*, 12: supp, 2:2, 1997; 83-87.

Brinsden P, Balen AH, Wada I, Tan S.L., Jacobs HS: Diagnosis, prevention and management of ovarian hyperstimulation syndrome. *British Journal of Obstetrics and Gynaecology*, 1995; 102: 767-772.

Balen AH, Hayden C, Rutherford AJ: What are the value of the recombinant gonadotropins? *Human Reproduction* 1999; 14: 1411-1417.

Balen AH: Ovarian hyperstimulation syndrome. *Human Reproduction* 1999; 14: 1138.

Salha O, Balen AH: New concepts in superovulation strategies for assisted conception treatments. *Current Opinion in Obstetrics & Gynaecology*, 2000; 12: 201-206.

Balen AH. Thromboembolism in women with ovarian hyperstimulation syndrome. *Reproductive Vascular Medicine*, 2001; 1: 120-124.

Balen AH. Ovulation induction – optimizing results and minimizing risks. *Human Fertility*, 2003; 6: S42-51.

Balen AH The current understanding of polycystic ovary syndrome. *The Obstetrician and Gynaecologist*, 2004; 6: 66-74.