Egbase et al. have correctly said that we cannot prevent OHSS entirely, unless the treatment is cancelled, and that the pathology of the condition is poorly understood (Egbase et al., 1999). Furthermore, they have taken the usual course of trying to find methods to prevent this complication and of course ‘prevention is always better than cure.’ A possible strategy which has been overlooked in this and most other reports is that we may be able to prevent OHSS from progressing to the life-threatening severe situation. If this can be achieved, the need to cancel treatments is removed, together with the ethical problems such actions cause.

Ovarian enlargement, nausea and vomiting are common in all women undergoing successful ovulation stimulation, and probably do not represent a significant pathology. Ascites is more rarely seen and is thought to be a result of increased vascular permeability (Balasch et al., 1998). Haemoconcentration is the consequence of this fluid loss. It is these features which seem to represent a distinct clinical entity recognized as OHSS. ‘Severe’ OHSS is characterized by the additional features of thromboembolic events, respiratory or renal failure. It is suggested here that severe OHSS may be the natural progression of untreated OHSS and its occurrence represents a failure to adequately manage a patient who presents with OHSS. We should perhaps consider more proactive management of high-risk patients to prevent OHSS becoming severe.

What do we know of the natural history of the condition? Without this knowledge, we cannot hope to understand prevention of progression of the syndrome. Published clinical data relating to OHSS usually consists of reports of unusually severe cases. In most papers, patients are identified because of hospital admission following the self-identification of relevant symptoms. This practice causes several problems. Details of treatment up to embryo transfer are often given, but information about the subsequent development of the syndrome from then until hospital admission is rare. Investigations carried out at the time of hospital admission result in the information being obtained at varying times in the pathological process. At this late stage of the established process it is difficult to separate changes related to the underlying pathology from those which occur as a result of homeostatic adaptations. Furthermore, the only suitable control subjects for OHSS are women undergoing ovulation stimulation and who do not develop OHSS. Despite this, it is usual to relate the measured parameter to values in women with normal ovarian function. More recently, some studies have attempted to correct this by studying high-risk subjects throughout the ovulation stimulation process and during the acute and recovery phase of the condition (Kodama et al., 1996; Agrawal et al., 1998). Such studies have provided valuable information about changes of a specific parameter as OHSS develops. These investigators have produced some promising information and have initiated an understanding of the time-course of this pathology. An awareness of OHSS as a variable process over a set period is an essential step forward in our understanding of both its pathology and clinical management.

We have reviewed 17 cases of patients with OHSS in this unit over 3 years to identify the time scale of the pathological process, five of whom were studied from the start of ovulation stimulation. Ascites is the constant feature of OHSS and it begins to develop early. We have recently presented data (Evbuomwan and Murdoch, 1998) showing that there is a loss of ~30% of circulating plasma volume between days 2 and 4 after administration of human chorionic gonadotrophin (HCG). Those who were at high risk, but who did not develop OHSS, showed no alteration in plasma volume. Ascites was difficult to detect clinically at this stage because large volumes are necessary before this sign is apparent. Ultrasound can detect small volumes of peritoneal fluid but since it is not uncommon to have significant i.p. bleeding after oocyte retrieval, this could not be a definitive diagnostic tool. The use of haematological markers to detect haemoconcentration was useful, but not diagnostic of OHSS, because some women severely reduce their fluid intake due to nausea and thus became dehydrated.
Our observation of such patients was that, unlike those who developed OHSS, they had normal urea and electrolyte concentrations and their serum osmolality remained normal. Weight gain and increase in abdominal girth were reliable indicators of fluid accumulation in those who developed OHSS.

Early clinical symptoms of developing OHSS became apparent at least 48 h after HCG administration. These symptoms of nausea, vomiting, dizziness and abdominal pain usually developed rapidly within a few days of oocyte retrieval and our experience was that they were most severe between days 7–10 after HCG. The development of clinical symptoms related to ascites (abdominal discomfort due to distension) was very uncommon before day 7 after HCG. Symptoms then slowly improved with a rapid diuresis within 48 h of the onset of menses if pregnancy did not occur. The slow initial improvement was also seen in those women who conceived. However, coincidentally with the rising B-HCG of pregnancy, ascites continued to develop and paracentesis was carried out as soon as a clear pool was detected on abdominal ultrasound. It is our experience that this was rarely needed unless the woman was pregnant and was usually needed about 14 days after HCG with an mean volume of 5 ± 2 l. An instant clinical improvement was typical although milder symptoms of OHSS persisted and merged with the usual pregnancy symptoms by 6 weeks gestation. Repeat paracentesis was sometimes required.

It has been suggested that there are distinct early- and late-onset types of OHSS (Lyons et al., 1994) but our experience suggests that it is more likely that there are two phases of a self-limiting condition. These phases coincide with the initial pre-ovulatory HCG and the second rise in HCG due to pregnancy.

The discomfort experienced by women who have these symptoms should not be considered lightly. Nausea and abdominal pain related to large ovaries can be severely debilitating. However, none of these women developed the life-threatening consequences which are characteristic of severe OHSS, i.e. thromboembolism, respiratory and renal failure. Were we lucky or did we prevent these occurring?

Thromboembolism has been shown to be associated with ovulation stimulation (Stewart et al., 1997; Aboulghar et al., 1998; El Sadek et al., 1998) and the unusual feature of predominantly upper body thombosis is unexplained. There is no evidence to support the view that all women undergoing ovulation stimulation should have antithrombotic treatment. However, women with OHSS are at higher risk because they are haemoconcentrated and often immobile. Prophylactic heparin and antithrombotic stockings were given to women admitted to hospital with OHSS. Thrombosis is probably not entirely preventable but the risk should be reduced.

Renal failure in OHSS is a result of poor renal perfusion secondary to haemoconcentration (Balsch et al., 1998). To prevent it, adequate circulation was maintained by encouraging oral fluids. i.v. expanders were used if indicated by decreased urine output, rising urea, creatinine and potassium. Metabolic attention to fluid balance was carried out with daily serum monitoring of renal function. Renal failure is a preventable complication.

A recent review of respiratory problems in OHSS showed that they are invariably associated with massive ascites (Abramov et al., 1999). These symptoms may all have been prevented by restricting i.v. crystalloid solutions and performing early paracentesis. Respiratory failure is a preventable complication.

If severe OHSS is preventable, why are so many cases reported? Published studies reflect the usual practice of allowing patients to monitor their own progress after ovulation stimulation and report for help only when symptoms develop. As a result, reported experience is often of severe complicated cases with a late presentation.

Consider an obstetric analogy. Have we learnt anything about the pre-eclamptic process by studying eclamptics? Will we understand the pathogenesis of OHSS by studying women with severe late consequences of OHSS? We do not prevent women at high risk of pre-eclampsia becoming pregnant; we offer intensive monitoring with appropriate intervention. Perhaps we should offer the same strategy for those at high risk of OHSS. We will not prevent OHSS but we may significantly reduce the life-threatening consequences of severe OHSS. The ethical problems associated with cancelling treatments would then be avoided.

References


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