DEBATE continued

Severe OHSS

Severe OHSS—an acceptable price?

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Burgeoning literature over the past decade has well documented the complication of severe ovarian hyperstimulation syndrome (OHSS). All clinicians involved in the management of infertile women should be expected to know the presentation and management of this serious condition. The contribution by Abramov et al. is useful as it presents a large retrospective analysis of virtually an entire country’s worth of data from tertiary referral centres over a 10 year period (Abramov et al., 1999). However, I would disagree with several of the conclusions drawn by the authors and I would regard their data as being reassuring rather than a cause for concern. They describe an ‘epidemic’ of OHSS. An epidemic would be defined as a widespread occurrence, or spread, of a disease. Even if the authors’ estimation of a tripling of the number of tertiary referral centres over a 10 year period (Abramov et al., 1999) is correct, this could hardly be considered an ‘epidemic’.

Previous studies cited by Abramov et al. have suggested an incidence of severe OHSS of 0.2–1%. Their own data comes in at the low end of this estimate (0.28%) which, in such a large series of cycles, is very reassuring.

They also highlight an increased incidence of severe OHSS in in-vitro fertilization (IVF) cycles over the past decade citing a change from 0.06% of all IVF cycles in 1987 to 0.24% in 1996. One of my concerns with their data is that they have selected entry criteria to their study as cases of severe OHSS presenting according to previously published criteria (Golan et al., 1989; Navot et al., 1992). Once criteria are published it is more likely that clinicians will report patients’ findings according to these criteria; hence, there may be a selection bias as there appears to be numerically a leap in the number of cases in 1994 compared to the previous years of data charted in Figure 1 of their paper which referred to the years 1987, 1990 and 1992.

We have previously suggested that the use of GnRH agonist protocols in conjunction with ovulation stimulation may increase the risk of OHSS (Forman et al., 1990) and Abramov et al. also raise this possibility as an explanation for their rise in OHSS cases. However, it might have been anticipated that this trend would have been apparent prior to 1994 as these protocols have been used with increasing frequency since 1987. It is possible that the so-called ‘dramatic increase’ in OHSS between 1987 and 1996 could actually represent an under-reporting of these cases in the earlier years. Certainly, the quoted incidence of 0.06% in the early years of the series would be considered as remarkably low compared to other published series.

To put the data into perspective, severe OHSS has to be considered as one of the complications of ovulation stimulation and, in particular, of IVF treatment. Other potential life-threatening complications occur with similar frequency. Perhaps the most serious of these is ectopic pregnancy. SART (1999) has recently reported an incidence of ectopic pregnancy in 1996 of 0.4% of all pregnancies (corresponding to ~0.1% of all IVF cycles). A 1.9% ectopic rate per pregnancy cycle corresponding to ~0.6% per initiated IVF cycle has been described recently (Serour et al., 1998). Another serious IVF complication is multiple pregnancy. Triplet pregnancies, in particular, carry a considerable maternal morbidity. The incidence of high order multiple pregnancy is increasing. A recent report of the French FIVNAT group from 1986–1993 shows that 7.3% of all IVF conceptions between 1986 and 1993 were triplets or higher order multiple gestation (Cohen, 1998).

I have reservations about the contention of Abramov et al. that ‘successful induction of ovulation should ideally attain as many follicles and oocytes as possible to obtain the maximum number of embryos in a single treatment cycle’. This philosophy of care is potentially responsible for many cases of OHSS. I would regard the aim of successful induction of ovulation to obtain the minimum possible number of oocytes conducive with establishing a pregnancy. Ideally, as has already been suggested, the best option would be to collect a single oocyte from a natural cycle, develop it into a blastocyst and maximize pregnancy potential (Edwards et al., 1996; Olivennes et al., 1998). Whilst this is currently not feasible with a sufficient degree of success, I believe that there is no advantage in over-stimulating patients to obtain 20 or 30 oocytes. If a more moderate response can be achieved using a low dose stimulation, there is evidence that this is associated with just as good a pregnancy rate as in very high responders (Forman et al., 1991).

Finally, thought needs to be given to the prevention of OHSS. Whilst no technique is 100% effective, severe hyper-stimulation can be almost totally excluded by withholding the ovulation-inducing trigger of human chorionic gonadotrophin (HCG) in patients at high risk. Low dose stimulation to achieve a moderate number of follicles and the use of embryo cryopreservation to avoid conception in the index cycle may offer some degree of protection against hyperstimulation.

Prophylactic albumin administration, while initially thought to be promising (Asch et al., 1993; Shalev et al., 1995), is controversial and several groups have reported finding no benefits (Chen et al., 1997; Ndukwe et al., 1997). Potentially
more worrying is the recent evidence that human albumin may increase mortality in critically ill patients (Cochrane Injuries Group Albumin Reviews, 1998). The Committee on Safety of Medicines expert working party has concluded that ‘special care should be taken when administering albumin in pathological states which effect capillary integrity’ (Committee on Safety of Medicines, 1999). Severe OHSS would fall into this category.

The use of ‘coasting’, deliberately withholding gonadotrophin stimulation and delaying HCG administration in women with an excess response to superovulation, was first reported in 1995 (Sher et al., 1995). Since then several studies have confirmed that this technique can reduce the incidence of severe OHSS in patients at risk (Fluker et al., 1999; Waldenstrom et al., 1999), although other authors (Lee et al., 1998) have reported severe OHSS still developing in 20% of patients at risk of OHSS in whom the coating technique was used. This technique appears to be the most promising of the currently available methods for reducing the incidence of severe OHSS without cancelling the cycles. The timing of the delayed HCG injection in relation to the reduction in oestradiol concentrations appears to be critical to the efficacy of coating.

Clinicians’ desire to help their patients achieve a successful pregnancy should be tempered by their responsibility to reduce the risk of potentially life-threatening conditions, such as severe OHSS and multiple pregnancy. Very few medical interventions are risk-free and severe OHSS will remain a complication of IVF cycles despite all attempts at prevention. Patients need to be advised of the risk and incidence of severe OHSS prior to embarking on ovulation stimulation therapy to enable them to give informed consent for assisted conception treatment.

References