Severe OHSS

An ‘epidemic’ of severe OHSS: a price we have to pay?

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Induction of ovulation by gonadotrophins is one of the major developments in the treatment of infertility in the second half of the 20th century. Today, it is the treatment of choice for >40% of infertile women suffering from ovulatory failure. In addition, extracorporeal fertilization techniques, primarily in-vitro fertilization (IVF) and embryo transfer are used for mechanical problems, male factor, and unexplained infertility, and are practised widely in almost every country in the world today.

Successful induction of ovulation should ideally attain as many follicles and oocytes as possible to obtain the maximal number of embryos in a single treatment cycle. This goal is achieved by using regimens employing gonadotrophin-releasing hormone (GnRH) analogues and high dose gonadotrophins. Unfortunately, these regimens are associated with a serious and potentially life-threatening medical complication, i.e. ovarian hyperstimulation syndrome (OHSS). This syndrome is expressed by a variety of clinical symptoms and signs, the underlying mechanism for which is capillary hyperpermeability mediated by ovarian-derived vasoactive substances. Severe cases present with a clinical picture of systemic capillary leakage, including massive ascites, pleural and pericardial effusions, reduced effective blood volume, oliguria, haemoconcentration, thromboembolic phenomena and, occasionally, death (Schenker and Weinstein, 1978).

The exact incidence of severe OHSS in the world has not yet been determined, since most of the data on this subject derive from relatively small series. Available data, however, suggest an incidence of 0.2–1.0% of all assisted conception cycles (Smits et al., 1990; Asch et al., 1991; Brinsden et al., 1995; Roest et al., 1996).

In order to clarify this point, we conducted a multicentric study including 16 out of 19 tertiary medical centres in (Abramov et al., 1998). In this study, we reviewed medical records of all patients who were hospitalized for severe OHSS at these centres between January 1987 and December 1996. Cases of severe OHSS were selected according to the revised criteria (Golan et al., 1989; Navot et al., 1992). These include massive ascites or hydrothorax in conjunction with prominent dyspnoea, haemodynamic instability, oliguria, anasarca, liver dysfunction, adult respiratory distress syndrome (ARDS), acute renal failure, or thromboembolic phenomena.

During the period of this study, a total of 73 492 IVF cycles were performed, 2902 patients were admitted for moderate OHSS, and 209 for severe OHSS. Among the latter, 163 patients (78%) were undergoing IVF, while the rest received conventional ovulation induction treatments. Most patients (94%) with severe OHSS undergoing IVF received ovulation induction by the long protocol using pituitary suppression with GnRH analogues, followed by exogenous gonadotrophins; 78% with an combination of follicle stimulating hormone/luteinizing hormone (FSH/LH), and 22% with pure FSH. Of the patients 13% received albumin as a preventive measure for OHSS following oocyte retrieval.

Table I shows the main signs and symptoms recorded in the study patients. Most patients presented with ascites (99%), dyspnoea (92%), haemoconcentration (95%), and gastrointestinal disturbances (54%). Oliguria was reported in 62 patients (30%), whereas massive pleural effusion appeared in 19%. Peripheral oedema occurred in 13% and thromboembolism in 2%. Five more patients (2%) had ARDS and three (1%) exhibited acute renal failure. Of the patients, 99% required therapeutic abdominal or thoracic paracentesis for alleviation of dyspnoea or oliguria.

The annual distribution of IVF/embryo transfer cycles, and of severe OHSS is presented in Figure 1. While the number of severe OHSS cases following conventional ovulation induction treatments remained unchanged, the number of cases following IVF increased dramatically from 2 (0.06% of all IVF cycles) in 1987 to 41 (0.24% of all IVF cycles) in 1996. The total number of IVF cycles performed in Israel during this time period also increased from 2890 in 1987 to 17 283 in 1996.

Thus, during the period of the study, IVF has become the main cause of severe OHSS in Israel, and its expansion dictated a parallel rise in severe OHSS numbers. However, the increase in the incidence of severe OHSS has surmounted that of total IVF activity (20-fold versus six-fold respectively), indicating a substantial rise in the risk for severe OHSS per IVF cycle from 0.06 to >0.2% (Figure 2).

Since the prevalence of infertility and anovulation has not changed significantly during the period of the study, these results reflect two important trends: increased use of extracorporeal fertilization techniques, and a more liberal use of ovulation induction medications, both of which may be held responsible for the impressive rise in severe OHSS numbers.

The first trend may be explained by the technical improvement in laboratory facilities and the advent of micromanipula-
Table I. Clinical features of 209 patients with severe ovarian hyperstimulation syndrome (OHSS)

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>No. (%) of patients</th>
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<tbody>
<tr>
<td>Ascites</td>
<td>207 (99)</td>
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<tr>
<td>Respiratory dysfunction</td>
<td></td>
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<tr>
<td>Dyspnoea</td>
<td>193 (92)</td>
</tr>
<tr>
<td>ARDS</td>
<td>5 (2)</td>
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<tr>
<td>Massive pleural effusion</td>
<td>39 (19)</td>
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<tr>
<td>Haemoconcentration (haematocrit &gt;45%)</td>
<td>199 (95)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Oliguria</td>
<td>62 (30)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Gastrointestinal irritation</td>
<td>112 (54)</td>
</tr>
<tr>
<td>Thromboembolic phenomena</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>28 (13)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
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</table>

ARDS = adult respiratory distress syndrome.

Figure 1. The annual incidence of severe ovarian hyperstimulation syndrome (OHSS) in Israel between January 1987 and December 1996. Empty bars represent cases attributed to conventional ovulation induction treatment. Grey bars represent cases attributed to assisted reproductive treatments. Dark bars represent the annual number of in-vitro fertilization (IVF) cycles (in thousands).

Figure 2. The annual incidence of severe ovarian hyperstimulation syndrome (OHSS) in Israel per 1000 in-vitro fertilization (IVF) cycles between January 1987 and December 1996.

Another possible explanation for this phenomenon is the increasing prevalence of ovulation induction protocols which practise pituitary suppression with a GnRH analogue. These protocols have gained popularity owing to their higher conception and lower cancellation rates (Fleming et al., 1988). However, these protocols have been associated with a higher risk of OHSS (Forman et al., 1990). Of the patients with severe OHSS described in our report, 94% were treated with one of these protocols.

Since the incidence of severe OHSS in Israel as presented in this study is lower than that reported worldwide (see above), this phenomenon may be even more serious in other parts of the world. In fact, over-utilization of ovulation induction medication by IVF units worldwide has been suggested previously (Edwards et al., 1996, 1997) with respect not only to OHSS but also to other undesired consequences, such as multiple pregnancies and increased costs.

Hence, we should ask ourselves how far we are willing to go in treating infertility, and where we should draw the line so that life is not endangered. Various prophylactic methods, e.g. i.v. albumin (Orvieto and Ben-Rafael, 1998) or coasting (Lee et al., 1998), do not appear to reliably prevent OHSS in all cases. Thus, revision of the eligibility criteria for extracorporeal fertilization treatments as well as serious reconsideration of the currently used ovulation induction regimens, especially those with GnRH analogue pituitary suppression, are strongly recommended.

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