OPINION

Preventive attitude of physicians to avoid OHSS in IVF patients

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The ovarian hyperstimulation syndrome (OHSS) is a dramatic iatrogenic complication of fertility treatment. There is no consensus about its prevention strategies. We assessed whether physicians modify their preventive attitude in relation to clinical risk factors and to the oestradiol response chart. Three case scenarios with three levels of risk factors for OHSS were constructed. For each case scenario, four different charts of the oestradiol curve were described (peak serum oestradiol of 3590 or 6590 pg/ml obtained after a shorter or longer period). At random, we sent three out of the 12 artificially constructed case scenarios to 573 physicians who are members of the European Society of Human Reproduction and Embryology (ESHRE). They were asked whether they would cancel the cycle, take preventive measures or proceed to a regular IVF. A total of 389 cases from 130 different physicians was analysed. Globally, in 23% of the cases the physicians would proceed to a regular IVF. This decision varied significantly according to the risk level (between 38% in low risk to 8% in high risk cases; \( P < 0.01 \)) and in relation to the oestradiol curve (\( P < 0.01 \)). In 11% of the cases they would cancel the cycle and in 66% take some preventive measures. Among the selected preventive measures, coasting was by far the most popular choice (60%), followed by the use of i.v. albumin or hydroxyethyl starch solution (36%) and cryo-preservation of all embryos (33%). In view of the sparse data as to whether coasting is really an effective method, and on how it should be carried out, we suggest that there is an urgent need to evaluate coasting as a preventive method in a large randomized trial in order to properly assess its efficiency and to provide precise guidelines for its use.

Key words: coasting/IVF/OHSS/prevention

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a dramatic iatrogenic complication of gonadotrophin treatment, and can sometimes be fatal (Mozes et al., 1965). However, severe OHSS is rare, since it complicates no more than 0.2–0.5\% of IVF attempts (Navot et al., 1992; Abramov et al., 1999). Some conditions may predispose to its occurrence: for instance it is common knowledge that women suffering from polycystic ovarian syndrome (PCOS) are at increased risk of OHSS (Rizk and Smitz, 1992). Furthermore, it has been reported that an aggressive stimulation scheme and an exaggerated response curve in oestradiol increase the likelihood of OHSS occurring (Asch et al., 1993).

Various methods for preventing OHSS or diminishing its severity have been suggested. The oldest approach had been to abandon the cycle. In view of the increased risk of OHSS associated with pregnancy, cryo-preservation of all embryos has also been proposed (Amso et al., 1990). Some medical approaches such as i.v. albumin or hydroxyethyl starch solutions during oocyte retrieval, or administrating glucocorticoids at that time have been attempted (Tan et al., 1992; Asch et al., 1993; Graf et al., 1997). Administration of recombinant LH (rLH) instead of human chorionic gonadotrophin (HCG) has also been described as a possible preventive measure for OHSS (Rizk and Smitz, 1992). The so called coasting method has been advocated, i.e. exogenous gonadotrophin treatment is stopped and HCG is withheld until serum oestradiol concentrations decrease to ‘a safer zone’ (Sher et al., 1993). Finally, another approach has consisted in performing a follicular aspiration after HCG triggering but before oocyte retrieval (Vrtorec and Tomazevic, 1995; Egbase et al., 1999).

Currently, there is no consensus as to which method to use for avoiding OHSS and there are no data available regarding which methods are used in clinical practice at different centres.

Do physicians modify their attitude in relation to risk level?

We conducted a survey among a sample of physicians practising IVF. The goal of our survey was to assess whether physicians
modify their preventive attitude in relation to clinical risk factors and to the oestradiol response chart. Briefly, three case scenarios were constructed according to three different risk factor levels of OHSS. These scenarios are not representative of the general population of patients, since they were artificially constructed. A complete description of the three case scenarios is provided in Appendix I. The first case scenario entailed a high risk level. This young and lean patient suffers from PCOS and multiple allergies. These are risk factors associated with OHSS (Navot et al., 1988; Enskog et al., 1990; Delvigne et al., 1993a). In addition, she is a carrier of a Protein C deficiency and is thus at increased risk for thrombo-embolic complications (Kligman et al., 1995; Hollemaert et al., 1996). The second case-scenario (medium risk) presented some less recognized or more modest risk factors for OHSS. It has been reported that women with an LH/FSH ratio higher than two are at increased risk for this complication (Delvigne et al., 1993a). Likewise, hypothyroidism and hyper-prolactinaemia have sporadically been associated with an increased tendency to develop OHSS (Rotmensch and Scommegna, 1989; Chen et al., 1996; Nappi et al., 1998). The third case scenario (low risk) concerned a 38 year old patient who had never developed OHSS in the past, even though she had received human chorionic gonadotrophin (HCG), in conditions of elevated oestrogen concentrations during previous IVF attempts.

Apart from selecting three case scenarios with three risk levels, the peak oestradiol serum concentration that was reached during stimulation was also made to vary. Although a marked inter-institutional variability of oestradiol levels exist (Hershlag et al., 1992), many authors consider that the risk of developing OHSS is increased once the concentration of 3000 pg/ml is reached (Tortoriello et al., 1998; Flucker et al., 1999). An even higher risk logically exists once the concentration of 6000 pg/ml is reached (Sher et al., 1993). According to Ash et al. 38% of women whose oestradiol concentrations attain this latter value will develop a severe form of OHSS (Ash et al., 1991). For these reasons, we chose to select oestradiol peak concentrations in this survey, at 3590 pg/ml and at 6590 pg/ml (conversion factor to pmol/l 3.671). The final parameter which was variable was the slope of oestradiol during ovarian stimulation, since a steep slope has also been associated with an increased risk of OHSS (Delvigne et al., 1993b; Flucker et al., 1999). The peak serum oestradiol concentration of 6590 pg/ml was reached after either 16 or 19 days and the peak oestradiol concentration of 3590 pg/ml was reached after either 13 or 18 days. These four charts included the values of six to eight oestradiol measurements obtained during follicular monitoring. Other parameters linked with OHSS, such as the number of small follicles measured, before or during ovarian stimulation, have not been taken into consideration in order not to hamper the statistical power of the study (Blankstein et al., 1987; Tibi et al., 1989).

Thus, for each case-scenario we provided four different charts of the response curve of oestradiol serum concentration. Each physician was sent at random (computer generated) three case scenarios. We randomly selected with a stratification for the clinical scenario, ensuring that each physician received the three different clinical histories. This model allowed us to independently analyse the data in relation to the risk level and to the chart.

In order to obtain a sample of physicians practising IVF, we used the ESHRE file and randomly selected 573 addresses from that file ensuring that we did not have the same address twice. We hoped that at least a 20% response rate would be reached.

The physicians were asked whether they would either: (i) cancel the cycle; (ii) take some preventive measures; or (iii) proceed to a regular IVF without taking any special preventive measures. If they had chosen to take preventive measures, the following choices were offered (they could choose more than one option): (i) proceed to ‘coasting’ with HMG discontinuation; continue gonadotrophin-releasing hormone (GnRH) analogue treatment and defer HCG administration until oestradiol plasma concentration declined; (ii) perform a follicular aspiration 12 h after HCG injection and regular oocyte retrieval 24 h later; (iii) use rLH instead of HCG administration and oocyte retrieval 36 h later; (iv) give i.v. albumin or hydroxyethyl starch solution during oocyte retrieval; (v) administer glucocorticoids at the time of oocyte collection; (vi) proceed to elective cryopreservation of all embryos and (vii) suggest other measures.

When physicians chose to use coasting as a preventive measure, we also asked them which level of oestradiol they would select for the administration of HCG. A questionnaire about demographic data was included (years of practice and type of practice: university and/or private). The physicians were assured that their participation would remain anonymous. Statistical analysis was performed using the SPSS software. Descriptive and χ² tests were used to test significant differences in attitude in relation to the risk levels and in relation to the stimulation chart, with a significance level of P < 0.05. A total of 389 cases from 130 different physicians from 33 different countries was analysed. The proportion of physicians per country was: Belgium (n = 9), The Netherlands (n = 5), Luxembourg (n = 1), Germany (n = 12), France (n = 10), Denmark (n = 1), Finland (n = 5), UK (n = 7), Italy (n = 4), Switzerland (n = 3), Greece (n = 5), Spain (n = 2), Turkey (n = 5), Russia (n = 2), Slovenia (n = 3), Estonia (n = 1), Poland (n = 2), USA (n = 9), Canada (n = 2), Australia (n = 5), Israel (n = 4), Syria (n = 1), Egypt (n = 3), Kuwait (n = 2), Singapore (n = 1), Indonesia (n = 1), India (n = 5), China (n = 3), Japan (n = 2), Taiwan (n = 1), Brazil (n = 1), Costa Rica (n = 1), Chile (n = 1), unidentified (n = 11).

In 23% of the cases, physicians would proceed to a regular IVF. For the remaining 77%, they would either cancel the cycle (11%) or take some preventive measures (66%).

In Table I we present the variation in relation to the three risk levels and in Table II in relation to the stimulation charts. The decision to proceed to a regular IVF or to take preventive measures was significantly related to the case-type presentation (respectively χ² 35; P < 0.001; χ² 14; P < 0.001). The decisions to cancel or to proceed to regular IVF were also significantly related to the peak oestradiol concentration (χ² 25; P < 0.001) but not modified by the slope of the oestradiol curve (χ² 1; not significant) (Table II).
Preventive attitude of physicians towards OHSS

Table I. Physicians’ attitude (%) is analysed in relation to the case presentation (high risk, moderate risk or low risk) regardless of the stimulation chart.

<table>
<thead>
<tr>
<th>% of physicians who take the decision to:</th>
<th>Case 1 very high risk patient</th>
<th>Case 2 moderately increased risk</th>
<th>Case 3 low risk patient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proceed to a regular IVF</td>
<td>8</td>
<td>22</td>
<td>38</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cancel the cycle</td>
<td>14</td>
<td>14</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Take some preventive measures</td>
<td>78</td>
<td>64</td>
<td>55</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table II. Physicians’ attitude (%) is analysed in relation to the chart regardless of the case presentation. Oestradiol max represents the maximal oestradiol serum concentration that is reached.

<table>
<thead>
<tr>
<th>% of physicians who take the decision to:</th>
<th>Chart 1 E2 max = 6590 after 16 days</th>
<th>Chart 2 E2 max = 6590 after 19 days</th>
<th>Chart 3 E2 max = 3590 after 13 days</th>
<th>Chart 4 E2 max = 3590 after 18 days</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proceed to a regular IVF</td>
<td>15</td>
<td>10</td>
<td>28</td>
<td>39</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Cancel the cycle</td>
<td>20</td>
<td>20</td>
<td>5</td>
<td>2</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Take some preventive measures</td>
<td>65</td>
<td>70</td>
<td>67</td>
<td>59</td>
<td>NS</td>
</tr>
</tbody>
</table>

E2 = oestradiol.

Is there a preferred preventive method?

The most effective method in preventing OHSS consists of abandoning the IVF cycle and this was chosen by 11% of the physicians. No relationship was found between the case-scenario description and the decision to cancel the cycle, although there was a relationship with the peak oestradiol concentration chart. However, even in the most severe case, for which a peak oestradiol concentration of 6590 pg/ml was rapidly reached, only about a fifth of the physicians would consider cancelling that cycle. It may be assumed, therefore, that physicians are reluctant to abandon a costly treatment in which tremendous hope has been invested by the couple.

Furthermore, some physicians commented spontaneously that in their country only a limited number of IVF treatments are reimbursed by social security or insurance schemes, whether the trials are completed or not. One may feel that it is neither ethically nor morally acceptable to have these factors influence the decision to proceed to a potentially dangerous procedure.

Approximately two-thirds of the physicians preferred to apply some preventive measures. This decision was related to the severity of cases but not to the oestradiol level characterizing the ovarian response to stimulation. Some physicians selected only one preventive method while others considered more than one. Among the different preventive measures, coasting clearly represents the most popular choice. It was the preferred technique for about 60% of the physicians when they had decided to use preventive measures. The advantage of this technique is that the cycle is not abandoned, and that no additional procedure is needed. In addition, coasting can be carried out in all countries, which is not the case for cryopreservation and use of rLH. We were able to review 12 papers which evaluated coasting, totaling 443 patients (Sher et al., 1993, 1995; Benavida et al., 1997; Dhont et al., 1998; Lee et al., 1998; Tortoriello et al., 1998; Egbase et al., 1999; Fluker et al., 1999; Waldenström et al., 1999; Aboulghar et al., 2000; Dechaud et al., 2000; Ohata et al., 2000). Some of these studies present encouraging results, suggesting that the chances of pregnancy remain unaffected, while the risk of severe OHSS is diminished. However, all except one of these studies were retrospective ones and used various protocols. The only prospective study, which evaluated coasting versus early unilateral follicular aspiration, included a limited number of patients (15 per arm) (Egbase et al., 1999). Thus no current consensus exists as to whether coasting is really an effective method nor as to how it should be carried out. Most of the surveyed physicians who would use coasting, selected an oestradiol concentration of 3000 pg/ml (Figure 1) as a safe value for the administration of HCG when applying coasting as a preventive measure.

![Figure 1: Frequency histogram of the oestradiol value (pg/ml) which was chosen by the physicians (n = 141) as a value for the administration of HCG when applying coasting as a preventive measure.](image-url)
About one-third of the physicians surveyed answered that they would administer macro-molecules such as i.v. albumin or hydroxyethyl starch as a preventive method. Albumin administration has been reported to reduce OHSS risk (Asch et al., 1993), but these results were not confirmed by others (Ng et al., 1995). Shoham et al. observed, in a randomized trial, a significant reduction of the number of severe OHSS cases (Shoham et al., 1994). One study has also reported that the administration of hydroxyethyl starch solutions during and after retrieval significantly reduces the risk of moderate OHSS forms, but the reduction in severe forms did not reach statistical significance (Graf et al., 1997). Our survey suggests that about a third of the physicians who selected preventive measures were convinced by the efficacy of i.v. albumin or hydroxyethyl starch as a preventive method. About a third of them would also shift to cryopreservation of the embryos. Cryopreservation avoids the risk of pregnancy and of endogenous production of HCG, a well-known promoting factor of severe OHSS. This method has been reported to reduce the risk of severe OHSS without totally eliminating it (Amso et al., 1990; Queenan et al., 1997). Benavida et al. estimated the reduction of the risk of OHSS by using cryo-preservation to be similar to that obtained by coating and Shaker et al. to that of albumin administration (Shaker et al., 1996; Benavida et al., 1997). It is possible that cryo-preservation was less often selected because of its negative psychological impact and the prevailing opinion that the chances of pregnancy are reduced when thawed embryos rather than fresh ones are transferred. However, Queenan et al. obtained very favourable implantation rates in a series of cases with cryopreserved embryos for OHSS prevention (Queenan et al., 1997). One should note that cryopreservation not available in all countries.

Only 13% of the physicians advocated the administration of rLH instead of HCG. This rather low percentage is probably due to the fact that in many countries rLH is not commercialized, as was commented upon by several respondents.

A few physicians (9%) elected to proceed to two follicular aspirations during the same IVF cycle, a method which has been previously published (Vrtovec and Tomazevic, 1995; Egbase et al., 1997; Egbase, 1999). In a randomized prospective study, Egbase (1999) obtained similar rates of fertilization, of embryo cleavage, pregnancies and OHSS incidences when using coating (Egbase, 1999). Nevertheless, using early follicular aspiration, they were able to retrieve more oocytes. It is possible that in our survey the method of follicular aspiration followed by retrieval was not selected by many physicians because it was considered to be too invasive. Seven percent of the physicians chose to use corticoids despite the fact that this method was shown to be useless in a randomized prospective study (Tan et al., 1992). Finally, 8% suggested using other methods than those proposed in our survey. The most often advocated were heparin administration, halving of the HCG dose and the use of bromocriptin.

The need for prospective studies

In conclusion, this is to our knowledge the first survey evaluating the attitude of physicians towards the risk of OHSS. These results were obtained from a wide international participation. Nevertheless, the heterogeneity which characterises the clinical setting of the participating physicians and the low number of responders may limit the conclusions which can be drawn from this study. Still, it appears that physicians adapt their attitude in relation to the presence of risk factors and in relation to the ovarian stimulation response as measured by the maximum oestradiol concentration, but not by the number of days it takes to reach the maximal oestradiol level.

When physicians are confronted with a high risk situation they prefer to use preventive methods rather than to cancel the cycle, the most popular approach being coating. In view of these results, we suggest that there is an urgent need to evaluate coating as a preventive method in a large randomized trial in order to properly assess its efficiency and to provide precise guidelines for its use.

References


Queenan, Jr, J.T., Veeck, L.L., Toner, J.P. et al. (1997) Cryopreservation of all prezygotes in patients at risk of severe hyperstimulation does not eliminate the syndrome, but the chances of pregnancy are excellent with subsequent frozen-thaw transfers. *Hum. Reprod.*, 12, 1573–1576.


**Appendix I**

<table>
<thead>
<tr>
<th>Duration of HMG administration (days)</th>
<th>Total number of HMG (ampoules)</th>
<th>Oestradiol max (pg/ml)</th>
<th>Number oocytes retrieval/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>30</td>
<td>3870</td>
<td>10 no pregnancy—no OHSS</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>4210</td>
<td>12 no pregnancy—no OHSS</td>
</tr>
</tbody>
</table>

**First case.** A 25 year old woman with a body mass index (BMI) of 23 (lean) undergoes, for the first time, ovarian stimulation in view of an intracytoplasmic sperm injection (ICSI) procedure in relation to severe male infertility (density <1 million/ml and mobility <10%). She suffers from PCOS (characteristic ultrasonographic signs, hyperandrogenism and LH/FSH ratio >2). She is a known carrier of protein C deficiency and presents multiple allergies. We used a short GnRH agonist desensitization with buserelin and ovarian stimulation with 150 IU of human menopausal gonadotrophin (HMG) from day 5 of her cycle. Her stimulation chart is shown. Echography elicited the presence of 20 follicles (10 >16 mm and 10 <16 mm).

**Second case.** A 34 year old woman with a BMI of 28 (obese) undergoes, for the first time, ovarian stimulation in view of ICSI treatment for mixed infertility: male and endometriosis. Female hormonal analyses show an LH/FSH ratio of four, normal androgen concentrations, hypothyroidism and hyperprolactinaemia. Sperm analysis shows azoospermia. Clinical, hormonal and genetic analyses suggest an excretory pathology and TESE (testicular sperm extraction) was programmed. We used a short GnRH agonist desensitization with buserelin and ovarian stimulation with 150 IU of human menopausal gonadotrophin (HMG) from day 5 of the cycle. Her stimulation chart is shown. Echography elicited the presence of 20 follicles (10 >16 mm and 10 <16 mm).

**Third case:** A 38 year old woman undergoes, for the third time, IVF treatment for tubal infertility. The hormonal profile, uterine cavity, sperm analyses were normal. The previous trials are summarized as follows:

We used a short GnRH analogue desensitization with buserelin and ovarian stimulation with 150 IU of HMG from day 5 of the cycle. Her stimulation chart is shown. Echography showed the presence of 20 follicles (10 >16 mm and 10 <16 mm).