Prevention of severe ovarian hyperstimulation syndrome in IVF with or without ICSI and embryo transfer: a modified ‘coasting’ strategy based on ultrasound for identification of high-risk patients

T.Al-Shawaf1,3, A.Zosmer1, S.Hussain1, A.Tozer1, N.Panay1, C.Wilson1, A.M.Lower1 and J.G.Grudzinskas1,2

1Fertility Centre, St Bartholomew’s Hospital, West Smithfield, London, EC1A 7BE, UK and 2Department of Obstetrics and Gynaecology, St Bartholomew’s and The Royal London School of Medicine and Dentistry, Royal London Hospital, Whitechapel, London, E1 1BB, UK
3To whom correspondence should be addressed. E-mail: talhayas@aol.com

Ovarian hyperstimulation syndrome (OHSS) can be a severe and potentially life-threatening complication of ovarian stimulation for IVF. Coasting or withholding gonadotrophin stimulation relies on frequent estimation of serum oestradiol to identify patients at risk. A modified coasting protocol was developed in which identification of patients at risk of severe OHSS was based on ultrasound monitoring. Serum oestradiol concentrations were measured only in patients with >20 follicles on ultrasound (high risk). If serum oestradiol concentrations were <3000 pmol/l, the gonadotrophin dose was maintained; if concentrations were ≥3000 pmol/l but <13200 pmol/l and ≥25% of the follicles had a diameter of ≥13 mm, the gonadotrophin dose was halved; and if serum oestradiol concentrations were ≥13200 pmol/l and ≥25% of the follicles had a diameter of ≥15 mm, patients were coasted. In the latter group, human chorionic gonadotrophin (HCG) 10000 IU was administered when at least three follicles had a diameter of ≥18 mm and serum oestradiol concentrations were <10000 pmol/l. Over a 10 month period, serum oestradiol concentrations were measured in 123 out of 580 cycles (24%) and in 50 cycles, gonadotrophins were withheld. Overall, moderate OHSS occurred in three patients (0.7%) and severe OHSS in one patient (0.2%). The pregnancy rates in the cycles where the gonadotrophin dose was reduced or withheld were 39.6 and 40% per cycle respectively; corresponding implantation rates were 30.7 and 25.6%. It is concluded that the modified coasting strategy is associated with a low risk of moderate and severe OHSS to a minimum without compromising pregnancy rates. Identification of patients at risk by ultrasound reduces the number of serum oestradiol measurements and thus inconvenience to patients as well as costs and workload.

Key words: coasting/oestradiol/ovarian hyperstimulation syndrome/ovarian stimulation/ultrasound

Introduction
Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of gonadotrophin stimulation, and it has been estimated that the incidence of the severe form of OHSS in patients undergoing ovarian stimulation for IVF is about 0.5–2% (Forman et al., 1990; Medical Research International, 1992). The pathophysiology of this iatrogenic and potentially life-threatening condition (Roest, 1999) has not been fully elucidated; rather, it has been suggested that widespread increased capillary permeability is responsible for the massive shift of fluids from the vascular compartment to the third space (Polishuk and Schenker, 1969; Balasch et al., 1991). As no curative methods are available except for supportive therapy, prevention is paramount (Grudzinskas and Egbase, 1998).

High serum concentrations of oestradiol (Schenker, 1993; Enskog et al., 1999), large numbers of follicles (Haning et al., 1984; Blankstein et al., 1987; Enskog et al., 1999) and a large number of oocytes retrieved (Asch et al., 1991), are associated with increased risk of OHSS. However, none of these factors is completely reliable in predicting OHSS. Consequently, various strategies have been developed in an attempt to prevent severe OHSS, including aspiration of follicles prior to human chorionic gonadotrophin (HCG) administration (Aboughar et al., 1992; Egbase et al., 1997), repeated aspiration of ovarian cysts after oocyte retrieval (Amit et al., 1993), follicular aspiration of one ovary at, or 10–12 h after, HCG administration (Tomazevic and Meden-Vrtovec, 1996), freezing of all resulting embryos after IVF (Amso et al., 1990), administration of
Ultrasound in coasting for prevention of OHSS

Materials and methods

Patients undergoing IVF or ICSI were treated according to a standardized protocol, namely long luteal-phase pituitary down-regulation using a commercially available gonadotrophin-releasing hormone analogue started 1 week before the expected menstrual period. Patients with oligomenorrhea were treated with long follicular-phase pituitary down-regulation starting on day 2 of spontaneous or induced periods. Pituitary down-regulation was confirmed after at least 2 weeks of gonadotrophin-releasing hormone analogue treatment by demonstrating an endometrial thickness of <4 mm on transvaginal ultrasound scan (in the absence of ovarian cysts of >12 mm in mean diameter) or a serum oestradiol concentration of <150 pmol/l. The initial gonadotrophin (purified or recombinant FSH) dose used for ovarian stimulation was individualized according to the patient’s age, baseline serum FSH concentrations on day 3 of an earlier cycle, body mass index (BMI) and previous response to ovarian stimulation. Transvaginal ultrasound monitoring was commenced on day 7–9 of ovarian stimulation and repeated every 2–3 days thereafter. Those considered to be at risk of OHSS (previous OHSS, polycystic ovaries or age <30 years) were scanned on day 6 or 7 from the start of the stimulation. Serum oestradiol concentrations were not measured routinely. The HCG (10,000 IU) trigger was administered when at least three follicles reached a mean diameter of 18 mm. Transvaginal ultrasound-guided oocyte retrieval was performed under sedation and analgesia 36–38 h after the HCG injection. Up to three embryos were transferred 2–3 days after oocyte retrieval. Embryos were selected for transfer based on their cleavage stage and the degree of fragmentation seen in the blastomeres. Luteal phase support was routinely given as progesterone pessaries for 14 days, when a urinary pregnancy test was performed. Pregnant women had an ultrasound scan at 6 and 8 weeks gestation, and were advised to continue progesterone pessaries until 10 weeks gestation. A clinical pregnancy was defined as the presence of an intrauterine fetal pole with a positive heartbeat.

If at any stage of ovarian stimulation, a total of >20 follicles (mean diameter ≥5 mm) was identified on ultrasound scan, the patient was considered to be at increased risk of developing severe OHSS, and a serum oestradiol concentration was obtained. Serum oestradiol was measured by a Bayer immuno-1 automated analyser (Bayer, Newbury, Bucks, UK) with <5% coefficient of variation in the range 75–13 200 pmol/l. If serum oestradiol concentrations were <3000 pmol/l, the dose of FSH was maintained. If serum oestradiol concentrations were ≥3000 pmol/l but <13 200 pmol/l and at least 25% of the total number of follicles had a mean diameter of ≥13 mm, the FSH dose was halved and monitoring was continued with ultrasound scans and serum oestradiol concentrations every 2–3 days. If serum oestradiol concentrations were ≥13 200 pmol/l and at least 25% of the follicles had a mean diameter of ≥15 mm, gonadotrophin injections were withheld. In the coasted group, serum oestradiol concentrations were monitored on a daily basis (except for weekends) and the HCG trigger was withheld until serum oestradiol concentrations declined to <10 000 pmol/l.

OHSS was classified into three categories based on clinical symptoms (Navot et al., 1992). Patients were encouraged to contact the centre if they experienced symptoms of OHSS or required hospitalization elsewhere. Pregnant women were followed up until 12 weeks gestation.

Statistical analysis was performed with the aid of the analysis of variation (ANOVA) and Student’s t-test for the different parameters. Fisher’s and chi-square tests were used to compare proportions; differences seen were considered to be statistically significant if P < 0.05.

Results

During the study period of March to December 1998, 580 cycles of oocyte retrieval were performed for conventional IVF with or without ICSI. Ultrasonographic monitoring identified 123 (21.2%) women who had >20 follicles (mean diameter ≥5 mm), and were considered at ‘high risk’ of severe OHSS. Based on serum oestradiol concentrations and ultrasonographic findings, the FSH dose was maintained in 20 cycles (maintenance group), was halved in 53 cycles (reduced group), and withheld in 50 cycles (coasted group). In total, 457 cycles were considered at low risk of developing OHSS based on ultrasonographic findings, and did not have oestradiol measurements (low-risk group).

The demographic characteristics of the three high-risk groups and the low-risk group are described in Table I. The mean age, baseline FSH concentrations, aetiology of infertility and distribution of primary or secondary infertility (data not shown) were similar in all high-risk groups. The mean BMI was significantly higher in the maintenance group (27.4 ± 6.9 kg/m²) and in the reduced group (25.9 ± 4.7 kg/m²) compared with the coasted group (23.9 ± 4.3 kg/m²; P = 0.03). In the study group (123 cycles), a total of 81 patients were having their first IVF with or without ICSI cycle (15 in the maintenance group, 32 in the reduced group, and 34 in the coasted group). In total, 245 low-risk cycles were in patients having their first IVF with or without ICSI treatment cycle. Seven patients (16.3%) were identified who had previous severe OHSS despite...
Table I. Characteristics of patients considered at risk of severe ovarian hyperstimulation syndrome

<table>
<thead>
<tr>
<th>Aetiology of infertility (%)</th>
<th>Low-risk group</th>
<th>Maintenance group</th>
<th>Reduced group</th>
<th>Coasted group</th>
<th>P^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>33.3 ± 4.3 (21–43)</td>
<td>31.7 ± 4.2 (23–40)</td>
<td>31.3 ± 3.8 (24–39)</td>
<td>32.5 ± 4.5 (23–41)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI*</td>
<td>–</td>
<td>27.4 ± 6.9 (21–43)</td>
<td>25.9 ± 4.7 (19–34)</td>
<td>23.9 ± 4.3 (18–37)</td>
<td>0.03^c</td>
</tr>
<tr>
<td>Basal FSH^b</td>
<td>7.6 ± 3.2 (2.0–35.2)</td>
<td>6.0 ± 1.8 (2.0–8.5)</td>
<td>6.2 ± 1.7 (2.3–12.5)</td>
<td>5.9 ± 1.6 (2.0–9.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

A*Values are mean ± SD (range).
BAnalysis of variance (ANOVA) with Bonferoni correction (excluding the low-risk group).
CMaintainance and reduced groups versus coasted group.
BMI = body mass index; NS = not significant; PCOS = polycystic ovarian syndrome.

Table II. Numbers of women undergoing their first IVF with or without ICSI and details of outcome of previous ovarian stimulation and completed IVF with or without ICSI cycles

<table>
<thead>
<tr>
<th>Outcome of previous ovarian stimulation:</th>
<th>Maintenance group</th>
<th>Reduced group</th>
<th>Coasted group</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cycle</td>
<td>15</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>One or more cycles previously</td>
<td>5</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Freeze all embryos</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Abandoned cycles</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

OHSS = ovarian hyperstimulation syndrome.

preventative measures, such as freezing all embryos (four patients) and intravenous albumin (all patients). In addition, four further patients had had their cycles abandoned (Table II).

The mean (± SD) starting dose of FSH (ampoules of 75 IU) was lower in the maintenance group (2.2 ± 0.6; P = 0.02), but similar to the reduced group (2.5 ± 0.8) when compared with the coasted group (2.8 ± 1.0), while the total dose was similar in all three groups (Table III). The number of follicles <14 mm in mean diameter observed during the last ultrasound scan before the HCG injection was lower in the maintenance group (9.2 ± 3.1) and the reduced group (12.6 ± 3.1) compared with the coasted group (18.6 ± 5.8; P < 0.0001). However, there were more mature follicles (>14 mm) in the maintenance group (20.5 ± 12.3; P = 0.01) than in the reduced group (13.3 ± 5.7) or the coasted group (13.9 ± 8.2). The mean number of days from starting FSH stimulation to the HCG trigger day was longer in the maintenance group (14.5 ± 3.2; P < 0.05) than the reduced group (13.0 ± 1.6) and the coasted group (14.9 ± 2.1), but was not different between the latter two groups. The mean number of oocytes retrieved was significantly higher in the maintenance group (15.7 ± 7.4; P = 0.005) and the reduced group (13.5 ± 5.6; P = 0.03) when compared with the coasted group (11.0 ± 5.5), but was similar in the first two groups. The fertilization rate was significantly lower in the maintenance (44.7%) or the reduced (49.3%) groups than the coasted group (55.1%, P < 0.01).

The mean number of days that the FSH dosage was halved (reduced group) was 2.5 ± 1.4 (median 3, range 2–5 days). The mean number of coasting days was 3.4 ± 1.6 (median 3, range 2–9 days). Fifteen (30%) of the patients in the coasted group were coasted for longer than 4 days.

There were no cases of moderate or severe OHSS in the 457 cycles that were not considered to be at high risk. Table IV summarizes the incidence of OHSS in the different high-risk groups. Overall, four patients developed moderate OHSS and one patient developed severe OHSS, all being early-onset OHSS (3.3% and 0.8% of the high-risk population and 0.7% and 0.2% of the total cycles respectively). The woman who developed severe OHSS was triggered when the serum oestradiol concentration was >13 200 pmol/l, only made known after the HCG trigger injection; thus the HCG was given in violation of the protocol. This was her first cycle of ovarian stimulation for ICSI because of male factor infertility, and the patient was hospitalized for 10 days and required paracentesis and supportive therapy. She did not conceive. There were two women with moderate OHSS in the coasted group, the diagnosis being tubal infertility in one and polycystic ovarian syndrome (PCOS) in the other. There was one case of moderate OHSS in the maintenance group (tubal), and one in the reduced group (male factor and PCOS).

Eight women of the 123 cycles studied (6.5%) did not have an embryo transfer procedure (Table IV). Two cycles were abandoned before oocyte collection, one for administrative reasons and the other because of a sharp drop in serum oestradiol concentrations to 371 pmol/l after being coasted for 3 days, indicating that oocyte collection would be unsuccessful. In one cycle, no oocytes were retrieved because of poor access to the ovaries due to fibroids. In two cycles, all the embryos were frozen, in one for an oocyte recipient, while in the other cycle the patient had developed moderate OHSS requiring hospitalization on the expected day of embryo transfer, 72 h after the retrieval of 21 oocytes. Failed fertilization occurred in three women, two in the reduced group and one in the
in preventing severe OHSS in high-risk patients, without coasting to be achieved.

Discussion

Several studies have demonstrated the value of coasting in preventing severe OHSS in high-risk patients, without compromising pregnancy rates (Table V). One difference among these studies is the serum oestradiol concentrations at which HCG was administered. The rates of severe OHSS vary in these studies, possibly due to the different threshold levels of oestradiol at which the HCG was given, as well as possible differences in case mix. The crucial importance of when to administer HCG in coasted patients has been stressed (Waldenström et al., 1999), it being just as important to start coasting when serum oestradiol concentrations are not excessively high. Others (Tortoriello et al., 1998a) observed patients who developed severe OHSS, despite coasting, when gonadotrophins were withheld when serum oestradiol concentrations were >14 700 pmol/l. Similarly, a higher than expected incidence of severe OHSS (33%) was encountered when coasting was started with serum oestradiol concentrations >29 400 pmol/l and a large number of follicles with diameter >18 mm (Egbase et al., 1999). In these cases, the granulosa cell mass may have become too large for the full effect of coasting to be achieved.

Table III. Outcome of ovarian stimulation and IVF with or without ICSI in 123 women identified to be at risk of OHSS. Values are mean ± SD (range)

<table>
<thead>
<tr>
<th></th>
<th>Maintenance group (n = 20)</th>
<th>Reduced group (n = 53)</th>
<th>Coasted group (n = 50)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dosea (ampoules 75 IU)</td>
<td>2.2 ± 0.6 (1.5–4)</td>
<td>2.5 ± 0.8 (1.5–6)</td>
<td>2.8 ± 1.0 (1.5–6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total dose (ampoules 75 IU)</td>
<td>32.3 ± 13.4 (15–54)</td>
<td>26.3 ± 10.4 (16–57)</td>
<td>26.3 ± 10.1 (14–61)</td>
<td>NS</td>
</tr>
<tr>
<td>Follicles &lt;14 mm³</td>
<td>9.2 ± 3.1 (4–15)</td>
<td>12.6 ± 3.1 (6–20)</td>
<td>18.6 ± 5.8 (6–36)</td>
<td>0.001</td>
</tr>
<tr>
<td>Follicles ≥14 mm³</td>
<td>20.5 ± 12.3 (2–52)</td>
<td>13.3 ± 5.7 (4–28)</td>
<td>13.9 ± 8.2 (2–36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Eggs retrievedd,e</td>
<td>15.7 ± 7.4 (6–30)</td>
<td>13.5 ± 5.6 (2–30)</td>
<td>11.0 ± 5.5 (0–22)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>140/313 (44.7)</td>
<td>339/688 (49.3)</td>
<td>285/517 (55.1)</td>
<td>0.01**</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>2.2 ± 2.2 (0–3)</td>
<td>2.1 ± 0.6 (0–3)</td>
<td>2.1 ± 0.6 (0–3)</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate OHSS</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Severe OHSS</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>1***</td>
</tr>
</tbody>
</table>

*Analysis of variance (ANOVA) with Bonferroni correction.
**χ²-test.
***Protocol violation.

aMaintenance group versus reduced and coasted groups (P = 0.02).
bReduced group versus maintenance and reduced groups (P = 0.0001).
cMaintenance group versus reduced group (P = 0.001).
dMaintenance group versus reduced and coasted groups (P = 0.0001).
eMaintenance group versus coasted group (P = 0.005).
fReduced group versus coasted group (P = 0.03).

table IV. Outcome of treatment: number (%)

<table>
<thead>
<tr>
<th></th>
<th>Maintenance group (n = 20)</th>
<th>Reduced group (n = 53)</th>
<th>Coasted group (n = 50)</th>
<th>All (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pregnant</td>
<td>12</td>
<td>21</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Pregnancy rate/cycle</td>
<td>12/20 (60)</td>
<td>21/53 (39.6)</td>
<td>20/50 (40)</td>
<td>53/123 (43.9)</td>
</tr>
<tr>
<td>Pregnancy rate/embryo transfer</td>
<td>12/20 (60)</td>
<td>21/49 (42.9)</td>
<td>20/43 (46.5)</td>
<td>53/112 (47.3)</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>17/41 (41.5)</td>
<td>31/101 (30.7)</td>
<td>23/90 (25.5)</td>
<td>71/232 (30.6)</td>
</tr>
<tr>
<td>Moderate OHSS</td>
<td>1 (5)</td>
<td>1 (1.8)</td>
<td>2 (4)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Severe OHSS</td>
<td>–</td>
<td>–</td>
<td>1 (2)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>1 (8)</td>
<td>3 (14.3)</td>
<td>4 (20)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Twin pregnancies</td>
<td>5/12 (41)</td>
<td>10/21 (47.6)</td>
<td>3/20 (15)</td>
<td>18/53 (34)</td>
</tr>
</tbody>
</table>

OHSS = ovarian hyperstimulation syndrome.
It has been noted that prematurely reducing or withholding gonadotrophins prior to follicular maturation may lead to arrest of follicular growth (Ben-Nun et al., 1993; Sher et al., 1995; Benadiva et al., 1997; Dhont et al., 1998; Waldenström et al., 1999). It has also been reported that the drop in serum oestradiol could be very marked and unexpected, and longer coating periods are associated with a markedly lower oocyte yield and pregnancy rate (Dhont et al., 1998; Egbase et al., 1999; Waldenström et al., 1999). In the current study, two patients did not have an embryo transfer as a consequence of coating due to the lack of access to daily serum oestradiol measurements and a presumed error of judgement on when to administer the HCG injection. One woman had a sharp drop in serum oestradiol concentration from >13 200 pmol/l to 371 pmol/l in 3 days of coating, and the cycle was abandoned. In the other woman, only one oocyte was collected, which did not fertilize. Although serum oestradiol concentrations were not obtained on the day of HCG administration, this was probably due to a sharp decline in serum oestradiol concentrations. Both the high and the low serum oestradiol threshold levels for coating to commence and for administration of HCG will require daily serum oestradiol measurements and continuous refinement to protocols to eliminate severe OHSS and maintain a high pregnancy rate (Fluker et al., 1999) without decreasing the number of cycles that reach the fresh embryo transfer stage.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. coasted</th>
<th>Oestradiol conc. at coatinga</th>
<th>Oestradiol conc. at HCGa</th>
<th>Severe OHSS</th>
<th>Pregnancy rate/cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sher et al. (1995)</td>
<td>51</td>
<td>22 572</td>
<td>&lt;11 016</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Benadiva et al. (1997)</td>
<td>22</td>
<td>=11 016</td>
<td>=11 016</td>
<td>0</td>
<td>63.6</td>
</tr>
<tr>
<td>Tortoriello et al. (1998b)</td>
<td>44</td>
<td>&gt;11 016</td>
<td>–</td>
<td>3 (13.6)</td>
<td>–</td>
</tr>
<tr>
<td>Dhont et al. (1998)</td>
<td>120</td>
<td>&gt;9180</td>
<td>&lt;9180</td>
<td>1 (0.83)</td>
<td>37.5</td>
</tr>
<tr>
<td>Lee et al. (1998)</td>
<td>20</td>
<td>&gt;10 000</td>
<td>declining</td>
<td>4 (20)</td>
<td>40</td>
</tr>
<tr>
<td>Egbase et al. (1999)</td>
<td>15</td>
<td>&gt;22 560</td>
<td>&lt;11 000</td>
<td>3 (20)</td>
<td>33</td>
</tr>
<tr>
<td>Waldenström et al. (1999)</td>
<td>65</td>
<td>Not fixed</td>
<td>&lt;11 000</td>
<td>2 (3.1)</td>
<td>42</td>
</tr>
<tr>
<td>Fluker et al. (1999)</td>
<td>63</td>
<td>&gt;11 016</td>
<td>25% decline</td>
<td>0</td>
<td>36.5</td>
</tr>
<tr>
<td>This study</td>
<td>50</td>
<td>&gt;13 200</td>
<td>&lt;10 000</td>
<td>1 (2)b</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>450</td>
<td></td>
<td></td>
<td>14 (3.1)</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Table V. Comparison of the outcome of various coating regimes: number (%)

αpmol/l.

βHCG administered at oestradiol concentration >13 200 pmol/l.

That each centre should establish its own threshold level for serum oestradiol.

The duration of coating that is effective in reducing the incidence of severe OHSS without a significant reduction in the number of oocytes retrieved and without affecting pregnancy rate is still to be determined, and has been debated extensively. It has been suggested (Waldenström et al., 1999) that a coasting period of ≤4 days does not compromise outcome, but longer periods may. It has been suggested that the coating duration is inversely related to the clinical pregnancy rate (Tortoriello et al., 1998b), but a ‘safe’ duration of coating has not been determined. A window for collecting fertilizable oocytes of up to 6 days has been reported (Dhont et al., 1998). In the current study it was observed that women in the coasted group who conceived were coasted between 2 to 6 days. The coating interval depends on the serum oestradiol threshold level used for withholding gonadotrophins, and it is notable that others (Benadiva et al., 1997), using a step-down protocol, withheld gonadotrophins for a mean duration of 1.9 ± 0.9 days but still had to cancel five cycles because of a >20% drop in serum oestradiol after HCG administration.

As more follicles are recruited in response to FSH stimulation, the mass of the granulosa cells increases and the cells gain functional maturation. These two factors, acting synergistically, cause a concomitant increase in serum oestradiol and in, as yet poorly defined, vasoactive substances (Agrawal et al., 1999). Although oestradiol does not cause OHSS, its serum concentrations are currently the best endocrine, albeit surrogate, marker available to estimate the maturing granulosa cell mass function. In the current study, the number of small follicles (<14 mm) was significantly higher in the coasted patients compared with the non-coasted groups, but the number of larger follicles (>14 mm) was lower in this group. This suggests that it is the small and medium (<14 mm) size follicles that are mostly responsible for the high serum oestradiol concentrations (and vasoactive compounds) (Enskog et al., 1999).

A large number of follicles has been associated with a high risk of developing severe OHSS (Blankstein et al., 1987; Enskog et al., 1999). In patients who developed a severe form of the syndrome, 95% of pre-ovulatory follicles were <16
mm and most were <9 mm (Enskog et al., 1999), while others (Navot et al., 1988) found that patients who developed OHSS had an increased number of follicles measuring 12–16 mm and >18 mm.

It has been postulated that follicles of varying sizes have a different threshold to gonadotrophins, with smaller follicles having a higher threshold than larger follicles (Fluker et al., 1999). Therefore, withholding gonadotrophins will initially cause apoptosis of the granulosa cells and atresia of a large number of small follicles. Longer periods of coating will cause a further reduction in FSH concentrations, followed by atresia of medium-sized follicles. It is plausible that if the FSH concentration falls further, mature follicles (>15 mm) will also undergo atresia, resulting in large follicular cysts with poor-quality oocytes and lower number. We have noticed this phenomenon where, in one case, only one oocyte was collected.

There are other mechanisms that can explain the reduced incidence of severe OHSS in coated cycles. FSH is known to induce LH receptors on the granulosa cells. Withholding gonadotrophin with the resultant drop in FSH concentrations leads to down-regulation of the LH receptors (Waldenström et al., 1999). This will reduce the number of granulosa cells available for luteinization, hence a reduction in the concentration of vasoactive substances thought to be responsible for OHSS (Sher et al., 1995). Furthermore, granulosa cell growth is dependent on FSH, and a sharp decline in the FSH concentration may increase the rate of granulosa cell apoptosis (Tortoriello et al., 1998b) adding to the reduction in vasoactive substances considered to be the initiators of the increased capillary permeability. This may also explain the lower number of oocytes retrieved in coated patients in the present study.

Various strategies for eliminating or reducing OHSS have been introduced recently, and apart from withholding HCG (with its cost and psychological implications), they have only partially reduced the incidence of severe OHSS. The most widely used strategy of freezing all embryos (Amso et al., 1990) has not been found to prevent OHSS (Salat-Baroux et al., 1990; Shaker et al., 1996; Chen et al., 1997; Queenan et al., 1997). Furthermore, not all patients have embryos suitable for freezing (Waldenström et al., 1999). Administering concentrated albumin (Asch et al., 1993; Shoham et al., 1994) has also had variable outcome (Mukherjee et al., 1995; Ng et al., 1995; Shaker et al., 1996; Ndukwu et al., 1997). To determine if coating is a strategy that will become established as a viable, cost-effective option may require larger, prospective randomized studies. The difficulties in conducting a controlled study in this area (Fluker et al., 1999) should not preclude centres from reporting on their experience.

In conclusion, the strategy of individualizing ovarian stimulation, vigilance in identifying patients at risk of developing OHSS by ultrasound, and reducing or withholding gonadotrophins depending on serum oestradiol concentrations and ultrasound findings, resulted in a low incidence of moderate (0.7%) and severe (0.2%) OHSS. However, four cases of moderate OHSS were still encountered in the study group (n = 123), indicating the need for further vigilance. The only case that developed severe OHSS was one of the coated patients and was managed in violation of the protocol without information about serum oestradiol measurements, highlighting the importance of this parameter. Nevertheless, the strategy of coating has not compromised the clinical pregnancy rate (40.0% per cycle) or the implantation rates (25.6%) in coated patients, and appears to have reduced inconvenience to patients, costs and workload. Moreover, strict adherence to a defined and simple protocol will enable easier comparison and more meaningful interpretation of results in coated patients, thus permitting further opportunities to reduce the incidence of severe OHSS.

References
during superovulation and in vitro fertilization-embryo transfer cycles. 


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