High pregnancy rates and successful prevention of severe ovarian hyperstimulation syndrome by ‘prolonged coasting’ of very hyperstimulated patients: a multicentre study

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In a multicentre trial, 65 in-vitro fertilization (IVF)–embryo transfer cycles were severely hyperstimulated. Instead of cancelling the cycle, gonadotrophins were withheld for a ‘coasting period’ until serum oestradiol concentrations had dropped below 10 000 pmol/l (mean 4.3 days), and then human chorionic gonadotrophin was administered. Four cycles were cancelled and there were 61 oocyte aspirations. A total of 103 fresh embryos was transferred to 53 patients, resulting in a pregnancy rate of 42% per started cycle (51% per embryo transfer), with an implantation rate of 31%. Only one patient developed severe ovarian hyperstimulation syndrome (OHSS). Four patients developed moderate OHSS. In all, two patients were hospitalized for OHSS. In order to optimize the coasting procedure, it seems important that each IVF centre identifies its appropriate cut-off limits for serum oestradiol concentrations and follicle size for initiating and ending of the coasting period. Correctly handled, it seems to be a major advance in the search for improved stimulation policies for high responders.

Key words: coasting/in-vitro fertilization/ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious complication after controlled ovarian stimulation for in-vitro fertilization and embryo transfer (IVF–embryo transfer). Once the syndrome occurs, little can be done to change the course of events, other than interventions aiming at reducing the risk of serious complications.

Many methods have been tried to prevent the syndrome. The administration of i.v. human albumin solution prior to and immediately after oocyte retrieval in women at risk was first reported as a promising prophylaxis (Asch et al., 1993), but since then many others have not been able to confirm the positive effects (Ng et al., 1995, Ndukwe et al., 1997), or reported a reduction but not elimination of severe OHSS (Chen et al., 1998). Graf et al. (1997) proposed infusion of hydroxyethyl starch solution at oocyte collection and 2 days later, resulting in a slight reduction of patients with severe OHSS, and a significant decrease of patients with moderate OHSS in the treatment group. Unilateral ovarian follicular aspiration prior to the administration of human chorionic gonadotrophin (HCG) was recently reported with disappointing results (Egbase et al., 1997).

Cryopreservation of all prezygotes has no effect on the syndrome occurring in the days immediately following oocyte retrieval, but eliminates the risk of early pregnancy OHSS. It takes a good success rate at subsequent frozen–thaw transfers for the procedure to be advocated (Queenan et al., 1997). Even if that success rate is good, it would seem even better to give the patient the chance of a pregnancy at both a fresh embryo transfer and a frozen–thaw embryo transfer. Moreover, at least at our centres, far from all patients have pre-embryos well suited for freezing.

Withholding gonadotrophin administration has been employed in ovulation induction cycles to prevent excessive response (Rabinovici et al., 1987; Urman et al., 1992; Schenker, 1993), and was used in 1993 in gonadotrophin-releasing hormone analogue (GnRHa)-treated patients (Ben-Nun et al., 1993). Sher et al. (1993, 1995) introduced the concept of ‘prolonged coasting’ in cycles obviously pointing at a high risk of OHSS. Gonadotrophins were withheld until serum oestradiol fell to <3000 pg/ml (conversion factor to SI unit, 3.671), and then HCG was administered. None of the women developed severe OHSS and pregnancy rates were good, suggesting oocyte quality was not compromised even by a long ‘coasting’ period.

The purpose of this paper is to present, for a group of patients at very high risk of OHSS, the efficacy of ‘prolonged coasting’ at three IVF centres. Though each centre followed the same protocol, we are able to identify some important differences between clinical management of successful coasting in the individual IVF centres.

Materials and methods

During ovarian stimulation for IVF–embryo transfer, 65 women developed hyperstimulation to the extent that withholding HCG and cancelling the cycle was considered the only alternative to coasting. The indications for IVF–embryo transfer were: unexplained infertility 17 couples, tubal factor 16, endometriosis three, polycystic ovary syndrome four and male factor 25 couples. The percentage of each indication did not differ from the general IVF population. All indications were equally distributed between the three centres.

The women had first been downregulated according to the long protocol with GnRHα nasal spray, either buserelin (Suprecur; Hoechst, Stockholm, Sweden and Copenhagen, Denmark) or nafarelin (Synarel; Searle, Malmo, Sweden and Copenhagen, Denmark). Then, daily...
administration of pure follicle stimulating hormone (FSH) (Fertinorm or Gonal F, Serono Nordic, Stockholm, Sweden and Copenhagen, Denmark) was added.

All women developed >25 large follicles and a highly elevated serum oestradiol concentration pointing towards a very high risk of OHSS. According to the protocol, when the three largest follicles were >17 mm, gonadotrophin was withheld.

Blood samples were taken almost daily until serum oestradiol had dropped below 10 000 pmol/l, when hCG 5000 IU (16 patients) or 10 000 IU (49 patients) (Profasi; Serono Nordic or Pregnyl; Organon, Göteborg, Sweden and Copenhagen, Denmark) was administered s.c. or i.m.

Oocyte aspiration was performed 35–38 h later, followed by embryo transfer 2 or 3 days later. Intracytoplasmic sperm injection (ICSI) was used in cases of expected male factor. The luteal phase was supported by vaginal suppositories or i.m. injection of progesterone.

Serum oestradiol concentrations were measured at the IVF Centre of Falun (CF) by Amerleit Estradiol-60 (Johnson & Johnson, Amersham, UK), at the Ciconia Fertility Clinic (CC) and the IVF-Unit of Sophiahemmet Hospital (US) by Immulite 1000 (DPC Skafte, Los Angeles, CA, USA).

At CF, serum oestradiol concentrations were given to an upper limit of 28 500 pmol/l. Any concentrations above that limit were given as >28 500. Hence, mean values which include serum oestradiol >28 500 are presented as exceeding the values calculated from 28 500.

Of the 65 patients, 29 were coasted at CF, 16 at CC and 16 at US. The overall mean age of the patients was 31.5 years (range 23–39) (at CF 30.0, at CC 32.2 and at US 33.8).

The ‘coasting period’ is defined as the number of days from the final FSH injection to the hCG administration. Only patients with a minimum coasting period of 3 days (>72 h) were included in this study. Pregnancy was defined as the detection of a fetus by ultrasound examination. The grades of OHSS were defined as: mild (ascites estimated <300 ml, no haemoconcentration), moderate (ascites estimated >300 ml and <800 ml, no haemoconcentration) or severe (ascites >800 ml, haemoconcentration or decreased urine output).

**Results**

When coasting was commenced, the mean amount of FSH (IU) administered at the three centres was at CF 1880 IU (range 750–3075), at CC 1625 IU (range 1000–2400) and at US 2062 IU (range 1275–4950).

The mean serum oestradiol (pmol/l) on the first day of withholding gonadotrophin for the three centres was: at CF >23 800 (range 13 000–>28 500), at US 13 678 (range 10 100–15 330) and at CC 19 153 (range 10 615–38 653). Despite no more administration of gonadotrophins, in 74% of the women the serum oestradiol increased further for 1–3 days, to a mean peak concentration at CF of >25 500, at US 15 526 and at CC 24 510. The mean serum oestradiol (pmol/l) on the day of hCG administration was: at CF 6325 (range 1500–10 044), at US 4279 (range 1000–6180) and at CC 6226 (range 2898–10 714).

Four cycles were cancelled before the administration of HCG. Two patients coasted for >6 days and both were among the cancelled, one of them because of logistical problems and one because of vaginal bleeding. Two more patients were cancelled, one for each of the same reasons.

The remaining 61 patients had HCG administered on mean cycle day 17.0 (range 14–21) after a mean coasting period of 4.3 days (range 3–6 days). At the CF centre, the mean coasting period was 4.2 days (range 3–6), at CC 4.4 days (range 3–6) and at US 4.1 days (range 3–5).

The average number of retrieved eggs was 10.0 (range 3–21), with no difference between the centres. For women with a coasting period of 3 or 4 days, the mean number of retrieved oocytes was 10.8. For women with a coasting period of 5 or 6 days, a mean of 7.5 oocytes were retrieved. Five couples did not achieve fertilization, in four cases because of unexpec ted male factor and in one case for unknown reasons. For the remaining couples, the fertilization rate was 61%.

Freezing of all pre-embryos was decided in three cases to avoid the risk of OHSS in case of pregnancy. Thus, 53 women had a total of 103 embryos transferred. Two embryos were transferred in 46 women, and one woman received three. For six women, only one embryo was transferred. For four of these patients, the reason for this decision was to avoid the risk of OHSS in case of a twin pregnancy, while two patients only had one good embryo available.

There were 27 sonographically identified pregnancies for a pregnancy rate per embryo transfer of 51% and a pregnancy rate per started cycle of 42%. Singleton pregnancies numbered 22 and duplex numbered five, for an implantation rate of 31% per transferred embryo. There were seven early miscarriages, leaving 20 ongoing pregnancies (>16 weeks) or delivered for a ‘late ongoing + delivery rate’ per embryo transfer of 38%.

The pregnancy rate per embryo transfer after a coasting period of 3–4 days was 58% (23/40), compared to 31% (4/13) after a coasting period of 5–6 days ($P = 0.12$, Fisher’s exact test).

Hitherto, three patients have become pregnant after the transfer of frozen–thawed embryos, but there are still more embryos frozen.

In the days immediately following oocyte aspiration, four patients developed mild OHSS and two patients developed moderate OHSS. None of these received any specific treatment. One patient developed moderate–severe OHSS and was hospitalized with moderate haemoconcentration and ascites; she only had infusions of albumin and sodium chloride solutions and recovered. Of the 27 pregnant women, two developed mild OHSS in the early days of pregnancy, one developed moderate OHSS and one developed severe OHSS. Only the woman with severe OHSS was hospitalized, in the first weeks of a twin pregnancy. She had laparocentesis three times and pleurocent esis once, and left the hospital without any further complications.

At the CF and CC centres, the patients were given 10 000 IU of hCG for ovulation induction. At the US centre, however, 16 patients were given 5000 IU of hCG. Only two of these developed mild OHSS in the days following oocyte aspiration and none of the seven who got pregnant developed OHSS in the early days of pregnancy.

The main outcome measurements are summarized in Table I.

**Discussion**

We present a series of 65 IVF–embryo transfer cycles from three different IVF centres, where the women were hyperstimu-
lated to the degree that the responsible physician seriously considered withholding HCG and cancelling the cycle as the only option, even though all centres have the option to cryopreserve all embryos. Instead, HCG was administered and oocyte retrieval was done after a coasting period where no gonadotrophins were administered. Only one severe case of OHSS was encountered and the fresh embryo pregnancy rate per embryo transfer was 51%, despite the policy of not transferring more than two pre-embryos.

In our experience, the timing of the HCG administration to the falling serum oestradiol is crucial. There seems to be one optimal day, where serum oestradiol has fallen below the appropriate cut-off point, but not fallen too low. In two cases, where HCG administration was planned 1 day after serum oestradiol had dropped below 10 000 pmol/l, the patient experienced a vaginal bleeding and the cycle was cancelled. In three other cases, serum oestradiol was allowed to fall below 1000 pmol/l, resulting in the retrieval of only one to three oocytes of poor quality. Surprisingly though, one of these patients became pregnant and has delivered.

On the other hand, administering HCG 1 day too early seems to put the patient at a high risk of OHSS. Before this study was undertaken, in the days of trying to manage the coasting procedure, HCG was administered to four patients before serum oestradiol had dropped below 10 000 pmol/l. One of these patients developed severe OHSS directly following oocyte retrieval and one patient developed mild to moderate early pregnancy OHSS. Another patient, excluded from this study, did not follow the protocol and administered HCG when serum oestradiol was slightly above 10 000 pmol/l. She developed severe early pregnancy OHSS.

In a study recently reported by Lee et al. (1998), four out of 20 patients developed severe OHSS despite coasting, and the conclusion was that coasting was not very efficient in preventing OHSS. They administered HCG on the day when serum oestradiol started to decrease, and we would agree with the conclusion of the authors that this is too early.

This narrow cut-off point focuses on the fact that the reference levels of serum oestradiol seem to display a high variation between laboratories, probably depending on the assay used. For other purposes than this study, the CF centre has double-checked blood samples with other laboratories, and the results were widely different, especially for low and high levels of serum oestradiol. As presented in this study, the mean serum oestradiol at which the three centres either chose to withhold gonadotrophins or to administer HCG exhibited a wide range. To some extent, this may reflect individual attitudes among responsible physicians. Since serum oestradiol rises and falls rapidly in these patients, it may also vary depending on the time of the day when gonadotrophin was administered and blood samples were drawn. Whatever the reason, we believe it is necessary for each clinic to identify their optimal serum oestradiol cut-off points.

Of the 16 patients at the US centre who were administered 5000 IU of HCG, only two developed OHSS and both were mild. Values are too small for any comparison to those who were administered 10 000 IU, because serum oestradiol tended to be lower at US compared to the other centres. However, since the pregnancy rate was the same, there may be an advantage to administer the lower dose of HCG.

On average, 10 oocytes were recruited, which is much fewer than expected if we had carried out the oocyte aspiration without a coasting period. This was also noticed by Benadiva et al. (1997), who suggested that smaller follicles may undergo maturation arrest and/or atresia following gonadotrophin withdrawal. However, in our study, most follicles were ≥16–17 mm when gonadotrophin was withheld and these follicles usually went on growing to the mature size of 18–19 mm. Since FSH upregulates the number of luteinizing hormone (LH) receptors of the follicle, we have speculated that the decreased serum FSH concentrations may downregulate the LH receptors of the follicles, thus making fewer oocytes available for maturation by HCG. At ovarian puncture, oocytes which fail to undergo the final maturation presumably stick to the follicle wall and are not retrieved. At oocyte retrieval in a coasted patient, it is quite obvious that many follicles, though mature by size, are punctured without any oocyte being retrieved. It may be that the same process reduces the number of granulosa cells available for luteinization, which, as proposed by Sher et al. (1995), could explain its efficacy in the prevention of OHSS development. Tortoriello et al. (1998) also suggest that the falling FSH concentration induces increased apoptosis of granulosa cells. The end result may be a reduction of chemical mediators or precursors that augment fluid extravasation.

Sher et al. (1995) described a series of 51 women where the coasting period was initiated when at least 30% of the follicles attained a mean diameter of 15 mm. Before this study was undertaken, we followed that protocol, but often encountered a rapid drop in serum oestradiol, resulting in small follicles and very few oocytes. Sher et al. (1995) found that waiting until most of the follicles were >15 mm left them with cystic follicles and poor quality oocytes. In this study, we initiated coasting when at least three follicles had attained a mean diameter of ≥17 mm, and many patients exhibited follicles ≥19 mm. We did encounter some cystic follicles, but generally we had good quality oocytes with a fertilization rate equivalent to the average in our programmes. We believe it is important that each centre should identify their optimal follicle measurements for the initiation of coasting.

Tortoriello et al. (1998) compared two subsets of coasted patients and concluded that a coast interval beyond a critical

### Table 1. Main outcome measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Started cycles (n)</td>
<td>65</td>
</tr>
<tr>
<td>Peak oestradiol, mean (pmol/l)</td>
<td>22 785</td>
</tr>
<tr>
<td>Coasting days, mean (n)</td>
<td>4.3</td>
</tr>
<tr>
<td>Oocyte aspirations (n)</td>
<td>61</td>
</tr>
<tr>
<td>Embryo transfers (n)</td>
<td>53</td>
</tr>
<tr>
<td>PR/started cycle (%)</td>
<td>42</td>
</tr>
<tr>
<td>PR/embryo transfer (%)</td>
<td>51</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>31</td>
</tr>
<tr>
<td>Mild OHSS (n)</td>
<td>6</td>
</tr>
<tr>
<td>Moderate OHSS (n)</td>
<td>4</td>
</tr>
<tr>
<td>Severe OHSS (n)</td>
<td>1</td>
</tr>
</tbody>
</table>

PR = Pregnancy rate. Pregnancy = fetus seen sonographically. OHSS = ovarian hyperstimulation syndrome.
threshold may exert a detrimental effect on cycle outcome. In our series, it seems that a coasting period ≤ 4 days does not compromise cycle outcome. If anything, the pregnancy rate suggests that it may be beneficial. However, the number of retrieved oocytes and pregnancy rate tended to be lower for patients coasted >4 days compared to patients coasted for 3–4 days. The larger the follicles are and the higher the serum oestradiol is when coasting is initiated, the longer will the coasting period be before serum oestradiol drops below 10 000 pmol/l. Consequently, if we had initiated coasting one day earlier, i.e. when the largest follicles were no more than 17–18 mm, we might have avoided the long coasting periods of >4 days.

Benadiva et al. (1997) coasted their patients for 1.9 ± 0.9 days after serum oestradiol levels had reached an average of 3803 pg/ml (conversion factor to SI unit, 3.671). After that relatively short coasting period, serum oestradiol had dropped to a mean level of 2206 pg/ml. We confirmed what has previously been described by Sher et al. (1995), i.e. almost all of our patients displayed a rising serum oestradiol for the first days after the final gonadotrophin injection, leaving us with a coasting period of mean 4.3 days before dropping below 10 000 pmol/l. Presumably, our patients were already more hyperstimulated when gonadotrophins were withheld, than those presented by Benadiva et al. (1997). The high pregnancy rates in both series imply that coasting is effective both for mildly and for severely hyperstimulated patients.

In conclusion, ‘prolonged coasting’ of severely hyperstimulated patients results in good pregnancy rates with a low risk of severe OHSS. In the hands of great person experience, it may almost eliminate the risk of severe OHSS. Coasting should not be initiated too early or too late. Serum oestradiol must be allowed to fall appropriately before HCG is administered, but conversely HCG must be administered before serum oestradiol drops too low. A coasting period >4 days may be suboptimal for the oocytes and cycle outcome. We believe it is of major importance that each IVF centre identifies its own cut-off limits for serum oestradiol and follicle size in order to optimize the coasting procedure in their hands. Correctly handled, we believe it is a major advance in the search for improved stimulation policies for high-responders.

Acknowledgements
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