The significance of coasting duration during ovarian stimulation for conception in assisted fertilization cycles

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BACKGROUND: Withholding gonadotrophin administration and postponing HCG injection, termed coasting, has been suggested as a treatment modality in cases of impending ovarian hyperstimulation syndrome (OHSS). It presents an opportunity to reduce the risk of OHSS and salvage the treatment, without apparent compromise to outcome. However, the duration of the coasting period, which would maintain the advantage without reducing conception rate, has not been fully established. In this retrospective study, we attempted to define the optimal interval of coasting in patients at risk of developing OHSS. METHODS: Patients were grouped according to the number of days elapsed between cessation of gonadotrophins and administration of HCG. Overall, out of 207 patients (mean age 30.76 ± 0.33 years) coasting lasted 1 day in 39 cycles (18.8%), 2 days in 61 cycles (29.4%), 3 days in 49 cycles (23.6%) and ≥4 days in the remaining 58 cycles (28.5%). RESULTS: There was no difference between the groups in patients’ age, serum estradiol concentrations at the time of HCG administration, oocyte maturity, fertilization and embryo cleavage rates. However, patients in whom coasting lasted ≥4 days had significantly reduced implantation (10.5%) and pregnancy (26.7%) rates compared with patients with a shorter coasting interval (ranges 18.4–27.9 and 41–55.7% respectively; P < 0.05). CONCLUSION: Coasting for >3 days appears to reduce implantation and pregnancy rates while in-vitro oocyte and embryo quality do not appear to be affected. We suggest that in patients who need coasting for >3 days, cryopreservation of embryos should be considered.

Key words: coasting/implantation rate/ovarian stimulation/pregnancy rate

Introduction

High estradiol (E2) concentrations measured during ovarian stimulation for assisted reproduction technology were suspected of being detrimental to embryo implantation, as well as being a marker for impending ovarian hyperstimulation syndrome (OHSS) (Delvigne et al., 1991; Simon et al., 1995). The underlying mechanism by which high estradiol concentrations may reduce pregnancy rates remains elusive. Both oocyte quality and endometrial receptivity have been addressed in this regard (Simon et al., 1995, 1996; Aboulghar et al., 1997). Beyond preliminary identification of patients at risk and modifying the treatment accordingly, several approaches have been suggested to avoid the deleterious effects of exaggerated ovarian response during ovarian stimulation. Among them are: decreasing the amount of exogenous HCG (Smitz et al., 1990) or using GnRH agonists for triggering of ovulation (Shalev et al., 1994), cancelling the cycle by aspirating follicular contents prior to HCG administration (Egbase et al., 1999), aspirating oocytes after ovulation induction but withholding embryo transfer (Ferraretti et al., 1999), and postponing injection of HCG while withdrawing gonadotrophin administration until serum E2 concentrations drop below a given threshold (Urman et al., 1992). The latter has been termed coasting and was presented as a unique way to reduce the risk of OHSS, but still rescue the cycle without any significant compromise to outcome (Sher et al., 1995). The duration of coasting, which would maintain the advantage without reducing conception rate, has not been fully established. Too short a period of coasting may not prevent OHSS, whereas too long a period may impinge upon endometrial receptivity or its synchronization with embryonic age, thus bringing embryo transfer effectively out of the alleged implantation window (Garcia et al., 1984; Ben-Nun et al., 1992).

Our retrospective analysis of assisted reproduction treatment cycles in which coasting was applied attempted to define the optimal duration for coasting in terms of conception rates.

Materials and methods

Patients

The database of all patients who underwent ovarian stimulation for assisted reproduction in Bahceci Women’s Health Care Center in
Istanbul from February 1, 1999 to February 29, 2000, was retrospectively evaluated to identify the cycles in which the method of coating for the prevention of OHSS was applied. In 257 out of 1880 (13.6%) ovarian stimulation cycles, coating was applied. Fifty cycles were performed in patients whose husbands were diagnosed with azoospermia or severe oligoasthenoteratospermia, necessitating testicular sperm extraction (TESE), and were therefore not included in the analysis. The diagnoses of the participating couples were as follows: chronic anovulation 12.5%, endometriosis 5.7%, tubal factor 10.1%, male factor 42.9% and unexplained infertility 28.5%.

A cycle was considered to have been treated by coating when administration of gonadotrophins was withheld for at least 1 day prior to triggering of ovulation by HCG while GnRH agonist was continued. The treatment cycles were grouped by the duration of coating in days. Coating lasted 1 day in 39 cycles (18.8%), 2 days in 61 cycles (29.4%), 3 days in 49 cycles (23.6%) and ≥4 days in the remaining 58 cycles (28.5%).

Protocols
The ovulation induction protocol for ovarian stimulation began with pituitary desensitization by GnRH agonist (Lucrin; Abbott, France) in the mid-luteal phase of the preceding menstrual period. Administration of gonadotrophins at a dosage of 2–4 ampoules per day (Metrodin® HP, 75 IU; Serono, Aubonne, Switzerland or Humegen®, 75 IU; Organon, Oss, The Netherlands) was initiated when serum E2 concentrations fell below 50 pg/ml. The starting regimen was fixed for the first 4 days and thereafter the dose of gonadotrophins was adjusted according to the individual ovarian response. When at least two follicles reached 18 mm in diameter, HCG (Pregnyl®, Organon) 10 000 IU was administered i.m. Oocytes were retrieved 32–38 h following HCG injection and subjected to ICSI. Embryos were transferred transcervically 3 days after oocyte retrieval under ultrasound guidance. Luteal phase was supported by either 100 mg/day progesterone in oil, i.m. or 100 mg/day micronized progesterone, orally.

Coasting was applied in cycles where E2 serum concentrations were >4000 pg/ml in the presence of at least 20 follicles, each >12 mm in diameter and at least 30% of them >15 mm. Daily measurements were taken until serum E2 concentrations dropped below 4000 pg/ml, on which day HCG 10 000 IU was administered. Clinical pregnancy was defined by the demonstration of a gestational sac on ultrasonography with concomitantly rising serum HCG concentrations.

Statistical analysis
Statistical analysis used χ2 test, analysis of variance with Bonferroni post-hoc test and Kruskall–Wallis rank sum test with Dunn post-hoc test as applicable. A P-value < 0.05 was considered significant.

Results
The mean age (± SD) of all 207 participating women was 30.76 years (± 0.33). The mean duration of coating was 2.9 days (± 0.11) with mean serum E2 concentration on the day of HCG administration 2644.4 pg/ml (± 120.3). Fertilization and implantation rates in all cycles were 71 and 19.2% respectively. There were 105 clinical pregnancies (pregnancy rate of 50.7%). Overall, only four (1.9%) patients were hospitalized for OHSS during the study period, of which one was severe enough to require paracentesis.

The outcome of ovarian stimulation of cycles by days of coating is shown in Table I. There was no difference between the groups in patients’ age and E2 concentrations at the time of HCG administration. E2 concentrations on the day when gonadotrophins were withheld were different between the groups, showing an inverse relation to the duration of coating. The mean number of gonadotrophin ampoules used was related to the duration of coating, i.e. higher dosages were administered to patients who ended up coating for ≥3 days compared with those coating for 1 or 2 days. The mean number of oocytes retrieved in cycles with ≥4 days of coating was significantly lower than in the cycles with 1–3 days of coating. However, oocyte maturity, as reflected by metaphase II oocytes to total oocytes ratio in all patients, did not reveal any significant difference. Fertilization rates and cleavage of the derived zygotes were not different between the groups.

Implantation and pregnancy rates of patients in the groups by days of coating are displayed in Figures 1 and 2 respectively. Patients who coated for ≥4 days had significantly reduced implantation and conception rates compared with patients who coated for 1–3 days (P < 0.05).

Breakdown of outcome by E2 concentrations on the day of HCG administration did not reveal any difference between the groups (Table II).

The overall multiple pregnancy rate in the reported cycles was 43.1%, without significant differences between the groups (38.8, 50, 36.3 and 54.5% in 1, 2, 3 and ≥4 days coating respectively).

Discussion
OHSS is the major complication of ovarian stimulation and its most severe form can even threaten the patient’s life. During the last two decades, the availability of GnRH agonists has led to a rise in cases of exaggerated over-stimulation of the ovaries, supposedly due to lack of feedback from the down-regulated pituitary. An almost universal prerequisite to the development of OHSS is triggering of ovulation with exogenous HCG. In addition to this, endogenous HCG produced by the trophoblast of the newly established conceptus can further aggravate the condition. Few approaches, singly or in combination, can be taken in an attempt to avoid OHSS. One may avoid HCG injection or reduce its dose. It is also possible to avoid embryo transfer and freeze all embryos (Tiitinen et al., 1995). However, it should be considered that any form of cancellation is associated with emotional and financial costs to the couple involved. Another modality tested for the prevention of OHSS is withholding gonadotrophin administration and postponing the HCG injection, while continuing GnRH agonists (or relying on the effect of a depot preparation). This modality has been termed coating (Sher et al., 1993). Its alleged main advantage is prevention of OHSS without the need to cancel the cycle. Our results confirm that coating is an effective alternative to the various forms of cancellation. Fertilization, implantation and pregnancy rates in the reported cycles were comparable with the results in the relevant literature (Van Steirteghem et al., 1998). Tortoriello suggested that the coating interval may affect outcome and should be studied in this regard (Tortoriello et al., 1998). Due to our relatively large patient population, we were able to define that coating for >3 days did not have any
Numbers are mean with SEM. E2 = estradiol; NS = not significant.

### Table I. A breakdown of outcome by interval of coasting in a group of 207 women undergoing ovarian stimulation with coasting, applied for the prevention of impending ovarian hyperstimulation syndrome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Days of coasting</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>29.42 ± 0.84</td>
</tr>
<tr>
<td>Ampoules of gonadotrophins</td>
<td>34.64 ± 3.1</td>
<td>33.19 ± 1.5</td>
</tr>
<tr>
<td>E2 concentration on the day of coasting start day</td>
<td>4228.8 ± 43.8</td>
<td>4503.1 ± 83.0</td>
</tr>
<tr>
<td>E2 concentration on HCG injection day</td>
<td>2655.7 ± 139.0</td>
<td>2655.1 ± 133.0</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>19.15 ± 1.1</td>
<td>18.88 ± 0.8</td>
</tr>
<tr>
<td>Metaphase II/oocytes</td>
<td>0.81 ± 0.04</td>
<td>0.77 ± 0.02</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>74 ± 3</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Cleavage rate (%)</td>
<td>87 ± 4</td>
<td>90 ± 4</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>4.02 ± 0.17</td>
<td>4.16 ± 0.11</td>
</tr>
</tbody>
</table>

**Figure 1.** Implantation rates by days of coasting in a group of patients who underwent ovarian stimulation for assisted reproduction. Patients who coasted for ≥4 days had significantly reduced implantation rates compared with patients who coasted for 1–3 days.

**Figure 2.** Pregnancy rates per embryo transfer by days of coasting in a group of patients who underwent ovarian stimulation for assisted reproduction. Patients who coasted for ≥4 days had significantly reduced pregnancy rates compared with patients who coasted for 1–3 days.

Adverse effect on oocyte quality and subsequent fertilization. It is therefore of significance that a coasting interval >3 days can affect embryo implantation. Since the threshold of E2 at which we administered HCG was uniform, we found no difference in E2 concentrations on the day of HCG administration among the various interval groups. It has been suggested that exposure to very high concentrations of E2 on the day of HCG administration may adversely affect the endometrium rather than oocyte quality (Simon et al., 1995). On the other hand, Aboulghar showed that high E2 concentrations are associated with low oocyte quality (Aboulghar et al., 1997). In our study we could not directly address this issue. However, in view of the following: (i) similar concentrations of E2 on the day of HCG administration; (ii) the lack of association between the different E2 concentrations and outcome (Table II); and (iii) the comparable fertilization and cleavage rates among the various groups, it is likely that the interval of coasting mainly affected endometrial receptivity.

The data available about coasting in ovarian stimulation cycles are not abundant, and results from different studies do not fully agree in many aspects. Nevertheless, prevention of OHSS seems to succeed with this method. Several reports have detailed the interval of coasting, but did not analyse results accordingly. Sher et al. treated 17 patients with a mean coasting interval of 4.8 days, with 72% fertilization and 35.2% pregnancy (Sher et al., 1993). In a later report on 51 patients, a mean coasting interval of 6.1 days allowed 69% fertilization and 41% pregnancy (Sher et al., 1995). Others (Benadiva et al., 1997) compared 22 coasting cycles with a mean interval of 1.9 days with cycles with embryo transfer of cryopreserved embryos. They did not detect any significant difference in outcome between these groups. Dhont compared 120 coasting cycles with a mean interval of 1.9 days with regular control cycles and did not find any difference in fertilization and pregnancy rates (Dhont et al., 1998). Tortoriello evaluated patients who underwent ovarian stimulation with coasting and grouped them by the pre-ovulatory serum E2 concentration at the time of HCG injection (Tortoriello et al., 1998). They reported reduced implantation rates in those patients whose serum E2 concentration was >4000 pg/ml when they met the criteria for HCG injection. Interestingly, in their subset of patients with a mean interval of 2.6 coasting days they found...
Duration of cooling in ovarian stimulation

Table II. A breakdown of outcome by concentration of E₂ on the day of HCG administration in a group of 207 women undergoing ovarian stimulation with coasting

<table>
<thead>
<tr>
<th>E₂ concentrations pg/ml</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>&lt;1999</td>
<td>2000–2999</td>
</tr>
<tr>
<td>(n = 58)</td>
<td>(n = 89)</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>(n = 58)</td>
<td>(n = 89)</td>
</tr>
<tr>
<td>Implantation rate in %</td>
<td>22.8 (51/223)</td>
</tr>
<tr>
<td>(n = 58)</td>
<td>(n = 89)</td>
</tr>
<tr>
<td>Pregnancy rate in %</td>
<td>58.6 (34/58)</td>
</tr>
</tbody>
</table>

Numbers are mean ± SEM.
NS = not significant.

a 19% implantation rate, while in those with 3.5 coasting days it was only 6.7%.

Our results, like those of Tortoriello and colleagues (Tortoriello et al. 1998), suggest that coating for >3 days reduces the implantation and pregnancy rates, whilst oocyte quality does not appear to be affected. Although exact timing of the endometrial implantation window has not been clearly identified, it is likely that in order to obtain a successful outcome, the synchronization of endometrial phase to embryonic developmental phase should be achieved. It is possible that the receptivity of the endometrium is not merely hormonally-dependent, but also time-dependent.

In a retrospective judgement of the frequency of high E₂ concentrations reached during the reported study period, we are now practising more cautious protocols with less daily gonadotrophin. A practical guideline from our results may be to consider cancellation of embryo transfer in patients who needed coating for >3 days during their ovarian stimulation. This cancellation enables cryopreservation of good embryos, which in turn can be transferred to an ideally prepared endometrium in a subsequent frozen–thawed cycle.

References


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