Early unilateral follicular aspiration compared with coasting for the prevention of severe ovarian hyperstimulation syndrome: a prospective randomized study

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Thirty women undergoing in-vitro fertilization or intracytoplasmic sperm injection considered to be at high risk of ovarian hyperstimulation syndrome (OHSS) were randomly allocated to have early unilateral follicular aspiration (EUFA) (group 1) or coasting (group 2) when the serum oestradiol concentration was ≥6000 pg/ml and there were more than 15 follicles each of ≥18 mm diameter in each ovary. EUFA was performed in group 1 at 10–12 h after the human chorionic gonadotrophin (HCG) trigger injection and human menopausal gonadotrophin (HMG) were withheld for 4.9 ± 1.6 days until serum oestradiol concentrations fell below 3000 pg/ml when HCG was administered. The mean total dose and duration of administration of HMG were similar in groups 1 and 2 (48.3 ± 17.4 and 50.2 ± 16.5 ampoules; 13.7 ± 2.2 and 14.1 ± 3.2 days respectively). The mean serum oestradiol concentrations (9911 pg/ml versus 10 055 pg/ml) and number of follicles (43.3 versus 41.4) seen in both ovaries on the day of HCG administration in group 1 and on the day of HCG administration in group 2 were also similar. After coasting, the mean serum oestradiol concentration on the day of HCG administration in group 2 was lower than in group 1 (1410 pg/ml versus 9911 pg/ml; P < 0.001). The mean serum progesterone concentrations on the day of HCG administration in both groups were similar, and fell in all women in group 2. The mean number of oocytes retrieved and percentage of oocytes retrieved per follicle punctured was significantly higher in group 1 (15.4 ± 2.1 versus 9.6 ± 3.2, P < 0.001; 91.4 ± 4.4% versus 28.3 ± 3.7%, P < 0.001 respectively). The fertilization and embryo cleavage rates were similar in both groups. Clinical pregnancy was diagnosed in 6/15 (40%) patients in group 1 and in 5/15 (33%) patients in group 2, while four women in group 1 and three in group 2 developed severe OHSS. Key words: early follicular aspiration/ovarian hyperstimulation syndrome/prolonged coasting

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening condition and probably the most serious complication of gonadotrophin stimulation. Its underlying cause is unknown, although it occurs more frequently in patients with polycystic ovarian disease (Lunenfeld and Insler, 1978; Kemmann et al., 1981). Similarly, the incidence is positively correlated with conceptual cycles and is related almost exclusively to exposure to either exogenous or endogenous human chorionic gonadotrophin (HCG) stimulation (Navot et al., 1987). Other widely accepted risk factors include high serum oestradiol concentration and the presence of multiple immature and intermediate-sized follicles (Bryce et al., 1981; Haning et al., 1984).

Given the iatrogenic nature of this condition, it is particularly important to minimize the risk of OHSS in women receiving fertility treatment. It has been suggested that follicular aspiration at the time of oocyte retrieval may provide some protection by causing intrafollicular haemorrhage leading to a decline in the ovarian production of substances responsible for the occurrence of OHSS (Navot et al., 1987; Gonen et al., 1991). Early follicular aspiration of one ovary 10–12 h after HCG was recently proposed as another option to decrease the incidence of severe OHSS (Tomazevic and Meden-Vrtovec, 1996). However, unilateral ovarian follicular aspiration, performed before HCG administration, failed to prevent the occurrence of severe OHSS (Egbase et al., 1997). The option of withholding gonadotrophin injections and delaying HCG administration, while continuing with downregulation, until the oestradiol concentrations have fallen (coasting) is currently undergoing evaluation (Sher et al., 1995; Benadiva et al., 1997; Tortoriello et al., 1998a,b).

This prospective randomized study was designed to compare two methods of preventing OHSS: early unilateral follicular aspiration (EUFA) performed 10–12 h after administering HCG, and delayed administration of HCG (coasting), in an in-vitro fertilization (IVF) programme.

Materials and methods

Patient population

In the period from April to December 1997, 37 patients aged <39 years undergoing conventional IVF and intracytoplasmic sperm injection (ICSI) treatment at the IVF Centre, Maternity Hospital, Kuwait, who were considered to be at high risk of developing severe OHSS and undergoing embryo transfer, were recruited for this study. Approval was given by the unit’s clinical review committee. The risk features (summarized in Table I) included polycystic ovarian syndrome (PCOS; anovulation, oligomenorrhea, raised serum luteinizing hormone and testosterone concentrations and ovarian ultrasound appearance), obesity, previous cancellation of ovulation induction due to risk of severe OHSS, and previous severe OHSS. The patients were counselled in detail on the serious risk of developing OHSS. In
Ovulation induction and oocyte retrieval

until two leading follicles were increased step-wise if necessary, depending on the follicular growth, stimulation, at intervals of 2–3 days. The HMG injections were performed to monitor follicular growth, from day eight of the cycle. With each ampoule of HMG, the number of follicles was counted and the results recorded. When the number of follicles increased step-wise and the mean serum oestradiol concentration on the day of the HCG trigger injection was below 6000 pg/ml, a decision was made to proceed with the follicular aspiration. In a few cases, however, the follicular aspirate was delayed, and oocyte retrieval was performed after the mean serum oestradiol concentration had fallen to below 3000 pg/ml.

Risk factors for OHSS:

- Previous severe OHSS
- Previous cancellation of ovulation induction

Indication for assisted reproduction treatment:

- Conventional IVF
- ICSI

Type of assisted reproduction procedure:

- Tubal disease
- Male factor
- Tubal + PCOS
- Male + PCOS

Risk factors for OHSS:

- PCOS
- BMI >30
- BMI >40

Previous cancellation of ovulation induction due to risk of OHSS:

- 4
- 7

Previous severe OHSS:

- 2
- 3

BMI = body mass index; EUFA = early unilateral follicular aspiration; ICSI = intracytoplasmic sperm injection; IVF = in-vitro fertilization; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovarian syndrome.

addition, they were informed of the novelty of these strategies based on reports in peer-reviewed medical journals. Only patients who provided signed consent were enrolled in the study (n = 30); otherwise the ovulation induction cycle was cancelled (n = 7).

Ovulation induction and oocyte retrieval

The protocol for ovulation induction has been previously described in detail (Egbase et al., 1996). Briefly, after pituitary luteal phase long protocol downregulation, human menopausal gonadotrophin (HMG) injections were started, usually at 2 ampoules (75 IU per ampoule) per day except when there was a record of the patient’s previous response to ovulation induction. Transvaginal ultrasound was performed to monitor follicular growth, from day eight of stimulation, at intervals of 2–3 days. The HMG injections were increased step-wise if necessary, depending on the follicular growth, until two leading follicles were >18 mm in diameter.

Patients were randomized to EUFA (group 1) or coasting (group 2) on the day when the serum oestradiol concentration was >6000 pg/ml associated with the presence of >15 follicles per ovary of which at least two were >18 mm in diameter. Randomization was performed using serially numbered sealed envelopes, each of which contained the study group number (1 or 2) that had been allocated with reference to computer-generated random numbers.

In group 1 patients, EUFA was performed 10–12 h after administration of HCG (10 000 IU); every follicle visible in the left ovary was aspirated transvaginally. The aspirates were examined using a stereoscopic zoom microscope (Olympus, SZH110). Granulosa cells were identified, but oocyte–cumulus complexes were not seen in any of the aspirates. Oocyte retrieval was carried out in the contralateral ovary 35–36 h after HCG administration.

In group 2, HMG injections were withheld for a variable number of days (mean 4.9 ± 1.6; range 3–7 days), while the gonadotrophin releasing hormone agonist (GnRH-a) was continued until the patients received a trigger dose of HCG (10 000 IU). This was administered after serum oestradiol concentrations had fallen below 3000 pg/ml and oocyte retrieval from both ovaries was performed 35–36 h later.

EUF and oocyte retrieval were performed under conscious sedation and analgesia (Fentanyl 100 μg i.v.; Janssen, Wycombe, UK and Midazolam 5 mg i.v.; Roche, Welwyn Garden City, UK) transvaginally with ultrasound guidance.

Embryo transfer

In both groups of patients, IVF or ICSI procedures were performed according to the cause of infertility. Transcervical intrauterine embryo transfer took place 2 days after oocyte retrieval, luteal support consisting of progesterone vaginal pessaries (Cyclogest; Shire, Andover, UK), 200 mg thrice daily. All patients were seen 5 days after embryo transfer to determine if they had developed evidence of clinical OHSS and for ultrasound examination. OHSS was classified as mild, moderate or severe according to criteria described previously (Rabau et al., 1967; Schenker and Weinstein, 1978; Navot et al., 1992).

Measurement of oestradiol and progesterone

Serum oestradiol was measured using a commercial kit (Boehringer Mannheim Immunodiagnostics, Mannheim, Germany; cat. no. 1298470), the dynamic range of which was 16–1800 pg/ml. Serum oestradiol concentrations above this range were measured in dilution. The within- and between-assay coefficients of variation were 5.5% and 6.0% respectively. Serum progesterone was measured using a commercial kit (Boehringer Mannheim Immunodiagnostics; cat no. 1204475), the dynamic range being 0.2–30 ng/ml. The within- and between-assay coefficients of variation were 4.0% and 5.2% respectively.

Statistical analysis

The results of the two groups of patients were compared using the unpaired t- and chi-squared tests. Preliminary statistical analysis indicated that a sample size of 15 in each group would give a 90% power to detect a difference of 20% in the incidence of OHSS at a significant level of 5% (Armitage and Berry, 1994).

Results

The clinical characteristics of the two groups were similar with respect to the woman’s age, body mass index (BMI), and duration and cause of infertility (Tables I and II). The mean total dose (75 IU/ampoule) and duration (days) of administration of HMG were also similar in groups 1 and 2 (Table II). The mean serum oestradiol concentrations and number of follicles seen in both ovaries on the day of HCG administration in group 1 and on the day that coasting was commenced in group 2 were not significantly different.

After coasting, the mean serum oestradiol concentration on the day of HCG administration in group 2 was statistically significantly lower than that in group 1 (1410 pg/ml versus 9911 pg/ml; P < 0.001). The mean serum progesterone concentration on the day of HCG administration in group 1 was similar to that in group 2 on the day coasting was commenced, but fell to below the assay detection limit (<0.2 ng/ml) in seven of 15 women by the third day of coasting, and in all women on the day of the HCG trigger injection. The mean number of oocytes retrieved and the percentage of oocytes retrieved per follicle punctured was statistically significantly higher in group 1 (15.4 ± 2.1 versus 9.6 ± 3.2; P < 0.001, 19.4 ± 4.4% versus 28.3 ± 3.7%; P < 0.001 respectively). The fertilization and cleavage rates and the mean numbers of embryos transferred were similar in the two patient groups. Clinical pregnancy was diagnosed.
incidence of OHSS:

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (EUFA) (n = 15)</th>
<th>Group 2 (coasting) (n = 15)</th>
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<tbody>
<tr>
<td>Body mass index</td>
<td>33.6 ± 4.7 (26.3–51)</td>
<td>34.8 ± 5.2 (26–49)</td>
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<tr>
<td>No. of HMG ampules</td>
<td>48.3 ± 17.4 (20–78)</td>
<td>50.2 ± 16.5 (15–87)</td>
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<td>Duration of HMG</td>
<td>13.7 ± 2.2 (10–17)</td>
<td>14.1 ± 3.2 (11–19)</td>
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<tr>
<td>administration (days)</td>
<td>43.3 ± 2.6</td>
<td>41.4 ± 3.7</td>
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<tr>
<td>No. of follicles</td>
<td>9911 ± 1483</td>
<td>10 055 ± 965</td>
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<tr>
<td>in both ovaries</td>
<td>2.4 ± 1.2</td>
<td>2.2 ± 1.8</td>
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<tr>
<td>on day of HCG</td>
<td>1410 ± 246 (P &lt; 0.001)*</td>
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<td>(group 1)/day of</td>
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<td>starting coasting</td>
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<tr>
<td>(group 2)</td>
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<td>Oestradiol (pg/ml)</td>
<td>6</td>
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<tr>
<td>on day of HCG</td>
<td>15.4 ± 2.1</td>
<td>9.6 ± 3.2 (P &lt; 0.001)*</td>
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<td>(groups 1 and 2)</td>
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<tr>
<td>Oestradiol (pg/ml)</td>
<td>81.5 ± 4.4</td>
<td>58.4 ± 2.1</td>
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<tr>
<td>on day of HCG</td>
<td>17.4 (26.3–51)</td>
<td>76.3 ± 5.8</td>
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<td>(group 1)/day of</td>
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<tr>
<td>starting coasting</td>
<td>3.7 (26.3–51)</td>
<td>2.7 ± 0.1</td>
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<tr>
<td>(group 2)</td>
<td></td>
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<tr>
<td>Oocytes fertilized</td>
<td>3</td>
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<tr>
<td>(%)</td>
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<td></td>
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<tr>
<td>Oocytes cleaved (%)</td>
<td>4 (26.6%)</td>
<td>3 (20%) (P = 0.66)**</td>
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<tr>
<td>No. of embryos</td>
<td></td>
<td></td>
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<tr>
<td>transferred</td>
<td>6/15 (40%)</td>
<td>5/15 (33.3%)</td>
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<tr>
<td>Incidence of OHSS:</td>
<td></td>
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<tr>
<td>Moderate</td>
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<td>Severe</td>
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<td>rate per initiated</td>
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<td>cycle</td>
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*Unpaired t-test; **χ²-test.

Values are mean (± SD) (range).

Discussion

OHSS is an iatrogenic condition resulting from supraphysiological stimulation of the ovary. OHSS may be classified as mild, moderate or severe (Rabau et al., 1967; Shenker and Weinstein, 1978; Navot et al., 1992), the incidence of the severe form of the syndrome varying from 0.5% to 2% (Forman et al., 1990; Navot et al., 1992). A decrease in successful fertilisation if the HCG trigger injection was delayed has been reported (Laufer et al., 1984). Attempts have been made to develop alternative strategies in order to decrease the incidence of OHSS. The first step in prevention is the identification of patients at risk by the recognition of risk factors, including ovarian response to previous gonadotrophin administration. In addition, there is agreement that the occurrence of severe OHSS may be minimized by either withholding the HCG injection which triggers ovulation and/or continuing the administration of GnRH-a until the ovaries regain their normal size (Forman et al., 1990). If HCG is administered, the oocytes may be collected and all resulting embryos electively cryopreserved (Wada et al., 1993). Alternatively, the dose of HCG may be modified (Abdalla et al., 1983) or substituted by GnRH-a administration (Shalev et al., 1994). If embryos are transferred in the index cycle, luteal support may be provided with progesterone, and not HCG.

Despite initial reports of the effectiveness of prophylactic intravenous albumin at the time of oocyte recovery (Asch et al., 1993), its efficacy is still being debated (Ng et al., 1995). There is, at present, no single method that allows OHSS to be reliably predicted and prevented. Various studies have demonstrated the protective value of follicular aspiration at the time of oocyte retrieval (Hazout et al., 1984). It is clear that follicular aspiration and surgically induced intrafollicular haemorrhage have a negative impact on corpus luteum function (Gonen et al., 1991). There is evidence that ovarian renin–angiotensin (Navot et al., 1987) and vascular endothelial growth factor (Lee et al., 1997) systems play a role in the pathogenesis of OHSS. The administration of HCG may trigger their production since OHSS is rare in the absence of exposure to exogenous and endogenous HCG. By contrast, many authors have claimed that follicular aspiration at the time of oocyte retrieval does not prevent OHSS (Friedman et al., 1984; Golan et al., 1988; Aboulghar et al., 1992). Recent evidence (Tomazevic and Meden-V트vcev, 1996) suggests that protection afforded by early timed EUFA may be related to its timing in relation to the administration of the trigger dose of HCG (Egbase et al., 1997). When EUFA is performed in one ovary 10–12 h after HCG administration, the withdrawal of follicular contents may significantly interfere with follicular maturation and hence modify the putative intra-ovarian mechanisms responsible for OHSS.

The cause and prevention of OHSS remains an enigma, and it is not clear whether medical strategies such as withholding daily gonadotrophin injections for a few days (coasting) in women at risk of OHSS in the index cycles (Urman et al., 1992; Sher et al., 1995; Benadiva et al., 1997) is more effective than a surgical approach such as early timed EUFA. This prospective randomized study was designed to evaluate these two strategies in women at high risk for OHSS who were undergoing long protocol downregulation and ovulation induction with HMG followed by conventional IVF or ICSI. The two groups of patients (groups 1 and 2) were similar in age, BMI, cause and duration of infertility and the dose and duration of HMG administration.

The seemingly high doses of HMG and the long duration of administration reflect the clinical characteristics of the patients enrolled in this study. Seventeen of the 30 patients (eight in group 1, nine in group 2) suffered PCOS, identified
by anovulation, oligomenorrhea, raised luteinizing hormone and testosterone concentrations, and classical ultrasound evidence, either alone or in addition to tubal and/or male factor infertility. In addition, 23 patients (10 in group 1, 13 in group 2) were obese, with BMI $>30$. The mean BMI was similar in groups 1 and 2. Thus, the higher than usual number of HMG ampoules used can, in our view, be partly explained by the obesity of the women. Five patients in group 1 and six in group 2 had a BMI $>40$ and required $>40$ ampoules of HMG for duration $>14$ days. Although the policy of our Unit is to advise women to lose weight to a BMI $<30$ before undergoing ovulation induction, the obese women in this study failed to respond to various health programmes designed to lose weight. In 11 patients (four in group 1, seven in group 2), ovulation induction cycles had been cancelled on one or more previous occasions because of the risk of OHSS. Severe OHSS occurred in five of 12 patients (two of five in group 1, three of seven in group 2) for whom previous induction cycles were completed to oocyte collection and embryo transfer. These clinical characteristics are not uncommon in the patient population of this clinic.

There was no significant difference in the mean serum oestradiol concentrations or the total number of follicles each $>12$ mm in diameter on the day of administration of HCG in group 1 and the day coasting was started in group 2. After coasting for 3–7 days (mean 4.9 ± 1.6 days), the mean serum oestradiol concentration on the day of HCG administration was statistically significantly lower. Despite performing early follicular aspiration in the left ovary, the mean number of oocytes retrieved and the percentage of oocytes retrieved per follicle punctured was significantly higher in group 1 patients compared with those in group 2 where gonadotrophins were withheld (coasting) and oocyte retrieval performed routinely from both ovaries (Table II). Although follicles of a threshold size may continue to grow without gonadotrophin administration for a variable interval, the lower number of oocytes retrieved in group 2 suggests that smaller follicles may undergo maturation arrest and/or atresia following gonadotrophin withdrawal (Sher et al., 1995; Benadiva et al., 1997). The fertilization and cleavage rates and embryo quality were similar in both groups, confirming previous reports that EUFA or coasting did not affect these events (Tomazevic and Meden-Vrtovec, 1996; Benadiva et al., 1997). However, the significant reduction in the number of oocytes retrieved after coasting would limit the number of embryos available for cryopreservation. By contrast, the mean number of oocytes retrieved in group 1 was similar to the number retrieved from patients responding appropriately (non-excessive ovarian response) to ovarian stimulation in our IVF programme (Egbase et al., 1996).

Contrary to a previous report (Tomazevic and Meden-Vrtovec, 1996), EUFA did not completely prevent the occurrence of severe OHSS in our high-risk patients, since four women in group 1 developed severe OHSS. This may be explained by the different criteria used to identify the high-risk patients. In this study, patients were identified as high risk when the serum oestradiol concentration on the day of HCG administration was $>6000$ pg/ml, while a value of $>3000$ pg/ml was used in the previous study (Tomazevic and Meden-Vrtovec, 1996). Similarly, withholding gonadotrophin injections while continuing GnRH-a until the serum oestradiol concentration was $<3000$ pg/ml (coasting) did not prevent severe OHSS in three high-risk patients in group 2. Whereas the mean serum progesterone concentration on the day of HCG administration in group 1 was similar to that in group 2 on the day coasting commenced, a fall in serum progesterone concentration was common to all patients, being unassociated with either the occurrence of OHSS or pregnancy. The withholding of gonadotrophin injections and the corresponding fall in oestradiol and progesterone concentrations have previously been shown not to affect clinical pregnancy and miscarriage rates (Sher et al., 1995; Benadiva et al., 1997). This was confirmed by the similar pregnancy rates in the two groups in our study.

There are currently no clinical criteria that accurately predict the development of OHSS. The only preventive strategy, including the elective cryopreservation of all embryos (Wada et al., 1993), able completely to prevent this serious iatrogenic life-threatening complication of gonadotrophin stimulation appears to be cancellation of the cycle, which is associated with a significant financial and emotional toll. The potential benefits of electrocautery or laser vaporization of one or both ovaries in at-risk women in the index cycle before gonadotrophin stimulation (Fukaya et al., 1995; Rimington et al., 1997; Egbase et al., 1998) have been described, but require further evaluation.

The incidence of severe OHSS in this study was similar in the two groups. We acknowledge that the small sample size limited by the duration of the project could mask any moderate differences between the two study groups. The high incidence of OHSS was probably related to the clinical characteristics of the patients and the criteria for inclusion in the study. A similarly high incidence of severe OHSS (20%) in four of 20 patients in whom HMG injections were withheld for the purpose of coasting, has been reported it was concluded that the risk of developing severe OHSS was multifactorial (Lee et al., 1998). However, the use of these two preventive strategies allowed oocyte collection and embryo transfer to be performed in all 30 patients, with a clinical pregnancy rate of 33–40%.

In the light of the high incidence of severe OHSS in both groups of patients, further prospective randomised studies are needed to justify the routine use of EUFA or prolonged coasting. However, either strategy may be offered to patients at serious risk of developing severe OHSS identified at advanced stages of ovulation induction, whose cycles would otherwise be cancelled. This is particularly the case if such patients have consistently experienced excessive ovarian follicular response despite low threshold doses of gonadotrophin injections, previous ovulation induction cycle cancellation, or previous severe OHSS.

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References


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Unilateral follicular aspiration or coasting to prevent OHSS
