Can 200 IU of hCG replace recombinant FSH in the late follicular phase in a GnRH-antagonist cycle? A pilot study

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BACKGROUND: GnRH-antagonist protocols shorten the treatment period and reduce inconvenience for IVF patients. This randomised controlled trial (RCT) further explored whether low-dose hCG can be used clinically to replace recombinant FSH (rFSH) during the late follicular phase in a GnRH-antagonist protocol.

METHODS: Seventy ICSI patients undergoing controlled ovarian stimulation (COS) in a GnRH-antagonist protocol was randomized into two groups. The control group received a standard treatment with rFSH (Puregon) plus a GnRH-antagonist, daily from Day 6 of stimulation. In the study group, rFSH was discontinued when six follicles ≥12 mm were observed and estradiol levels were ≥600 ng/l; rFSH was subsequently replaced by low-dose hCG (200 IU/l daily).

RESULTS: Mean values (SD) for dose and duration of rFSH treatment in the control versus low-dose hCG group were 1617 (280) versus 1273 (260) IU rFSH [between-group difference -344, 95% confidence interval (CI) -483 to -205; P < 0.001], and 8.2 (1.6) versus 6.4 (1.3) days (-1.8, -2.6 to -1.1; P < 0.001), respectively. The mean number of metaphase II oocytes of 10.1 versus 8.9 (between-group difference -1.2, 95% CI -3.9 to 1.5) and the ongoing pregnancy rates of 10/35 (29%) versus 13/35 (37%) (between-group difference 8.6%; 95% CI -13.0 to 29.1%; P = 0.45) for control versus hCG, respectively, did not differ.

CONCLUSION: In this pilot trial, substitution of rFSH by low-dose hCG in the final days of COS leads to a reduction of FSH consumption whereas ICSI outcome, in terms of oocyte yield and ongoing pregnancy rate, remains comparable to the traditional regimen (ClinicalTrials.gov, trial number: NCT00750100).

Key words: hCG / recombinant FSH / GnRH antagonist cycle / ICSI / ongoing pregnancy rate

Introduction

Attempts to improve the outcome of assisted reproduction treatment (ART) programmes in terms of improving patient friendliness, reducing the incidence of potential complications, such as cyst formation and development of ovarian hyperstimulation syndrome (OHSS), and cutting the global cost of ART have led to a growing interest in GnRH-antagonist protocols in the past decade.

Systematic reviews and meta-analyses (Kolibianakis et al., 2006; Tarlatzis et al., 2006) have shown that GnRH-antagonist protocols significantly shorten the treatment period and reduce the inconvenience for the patient, although no clear benefit in terms of live birth rate has been attributed to one type of GnRH analogue (Al-Inany and Aboulghar, 2002; Kolibianakis et al., 2006). The question of whether GnRH antagonist based treatment cycles can be optimized therefore remains. Although concerted efforts were made to improve the outcome of GnRH-antagonist cycles through various modifications of the stimulation protocol (de Jong et al., 2000; Wikland et al., 2001; Fauser et al., 2002; Ludwig et al., 2002; Hohmann et al., 2003; Aboulghar et al., 2004; Cédrin-Durnerin et al., 2004; Escudero et al., 2004; Kolibianakis et al., 2004; Mochtar and the Dutch Ganirelix Study Group, 2004; Out et al., 2004; Griesinger et al., 2005; Humaidan et al., 2005; Kolibianakis et al., 2005), a number of research groups went on to focus on lowering the cost and improving the safety of ART cycles through a reduction of the total dose of FSH administered during controlled ovarian stimulation (COS).
Since the study by Sullivan et al. (1999) who showed that developing follicles become less dependent on FSH as they acquire LH-responsiveness, several studies have been conducted to assess the role of LH in COS. The results from a number of studies show that low levels of LH are associated with adverse reproductive outcome in GnRH antagonist cycles (Fleming et al., 1998; Westergaard et al., 2000; Esposito et al., 2001; Coppola et al., 2003), as well as in natural cycles (Verpoest et al., 2000).

Moreover, supplementation and substitution of FSH from the mid-follicular phase of GnRH-agonist cycles onwards by the long-acting LH agonist hCG yielded pregnancy rates comparable with those of conventional COS cycles (Filicori et al., 2002a, b; Lee et al., 2005; Gomes et al., 2007). A number of authors adapted a GnRH-antagonist protocol to demonstrate favourable treatment outcomes in terms of number of oocytes, embryo quality and pregnancy rates in patients who received daily low-dose hCG supplementation (Koichi et al., 2006; Serafini et al., 2006). Also, this approach led to significant treatment cost savings of an average of $600 per ART cycle (Van Horne et al., 2007).

Mid to late follicular phase FSH substitution by hCG, rather than supplementation, in GnRH-antagonist cycles has been reported in a small cohort study (Kenigsberg et al., 2006), but this approach has not been investigated in a randomised controlled trial (RCT). Taking into account the more profound suppression of endogenous LH levels by a GnRH-antagonist as compared with a GnRH-agonist (Gomes et al., 2007), we conducted a preliminary study to explore whether low doses of hCG (200 IU/day) have a similar potential to allow similar follicular development and ongoing pregnancy rate in the absence of FSH.

Materials and Methods

Study design

The study presented here is a prospective RCT and was conducted in 70 normogonadotrophic women seeking infertility treatment between September 2007 and October 2008. The trial was set up to compare two protocols for COS with antagonists. In one group of patients a standard antagonist protocol was applied [control recombinant FSH (rFSH) group] and patients allocated to a second group underwent a modified treatment protocol with low dose hCG as a substitute for rFSH (study hCG group). Randomization was performed at the outpatient clinic, when the results of the pretreatment hormonal analyses were discussed with the patient. A computer-generated list was used for randomization, concealed to the physician but not to the study nurse. Each patient was enrolled into the study only once. All patients gave written informed consent. We registered the study with the Clinical Trial Web site (www.clinicaltrials.gov, number NCT00750100), and it received institutional review board approval by the Ethics Committee of the Centre for Reproductive Medicine at Universitair Ziekenhuis Brussel, Belgium.

The patients included in the study were women below 36 years of age who underwent a first or second treatment cycle of IVF with ICSI. Patients were excluded from the study if they requested PGD, had an azoospermic partner or had a serum FSH level on Day 3 of the menstrual cycle of more than 12 IU/l. A single embryo transfer policy was applied in all cycles.

Of the 70 patients who participated in the trial, 61 patients (32 patients in the rFSH-group and 29 patients in the hCG-group) underwent an oocyte retrieval procedure.

Outcome measures

In this pilot study, the primary end-point is ongoing pregnancy, an event of direct clinical interest and relevance. Secondary end-points include basal hormonal serum values; number of COC, number of Mmetaphase II

Multifollicular ovarian stimulation

The GnRH-antagonist protocol with rFSH has been described elsewhere (Papanikolaou et al., 2005a, b). An outline of both protocols is presented in Fig. 1. On Day 2 of the menstrual cycle (Day 1 of the stimulation), daily injections of rFSH, follitropin beta (Puregon, NV Organon, Oss, The Netherlands) were initiated at a dose of 200 IU/day and maintained for six consecutive days. On Day 7 of the cycle (Day 6 of the stimulation), s.c. administration of the GnRH antagonist garelix (Orgalutran, NV Organon, Oss, The Netherlands) was started at a daily dose of 0.25 mg. From Day 7 of the cycle onwards, ovarian ultrasound scans to assess follicular growth and blood sampling for estradiol (E2), progesterone, FSH, LH and hCG levels, were performed on a daily basis. This decision to perform daily monitoring allowed us to adjust the dose of rFSH if necessary and to discover incipient signs of premature luteinization.

In the hCG group, the administration of rFSH was discontinued when at least six follicles of ≥12 mm were observed and E2 levels were higher than 600 ng/l. rFSH was then substituted by 200 IU hCG daily (Pregnyl, NV Organon, Oss, The Netherlands), until final oocyte maturation. Final oocyte maturation was induced by the administration of 10,000 IU hCG (Pregnyl), when at least three follicles of 17 mm diameter were visualised on ultrasonography. Cumulus–oocyte-complexes (COC) were collected 36 h after Pregnyl administration. Luteal phase support consisted of 600 mg of vaginally administered micronized natural progesterone (Utrogestan, Besins International, Paris, France) per day. To assess the treatment outcome, serum hCG was measured 14 and 17 days after oocyte retrieval. HCG levels above 20 IU/l indicated pregnancy. Clinical pregnancy was defined by the observation of foetal cardiac activity on ultrasonography at 7 weeks of gestation.

Embryo culture, evaluation and embryo transfer

Procedures for ICSI were carried out as described by Van Landuyt et al. (2005). Normal fertilization was checked on Day 1. Embryo quality was assessed daily from Day 2 onwards until the moment of transfer or cryopreservation (in the case of good-quality spare embryos), as described by Papanikolaou et al. (2005a, b). The embryo quality on Day 5 was assessed according to the criteria of Gardner and Schoolcraft (1999). All transfers were single embryo transfers on Day 5.
and 2-pronuclei oocytes; duration of stimulation and total cumulative dose of rFSH used; fertilization and implantation rates in each treatment group. It is important to note that the implantation rate equals the pregnancy rate since only one embryo was transferred.

Demographic and clinical characteristics, such as age, weight and height are also collected.

**Statistical analysis**

Data for continuous variables are summarized with the use of means and SD or SE for each group of interest. The data for categorical variables are presented as number of cases or percentages including nominator and denominator values. Comparisons among groups are presented as absolute between-group differences with corresponding 95% confidence intervals (95% CIs) and P-values for each comparison made (Altman, 1991). We also used the t-test for independent samples, and the χ² test or Fisher’s exact test to compare continuous and categorical variables, respectively. All tests were two-sided, and a P-value of <0.05 was considered to indicate statistical significance.

The purpose of our pilot trial is to provide an estimate of the probability that patients will benefit from a therapy, or have serious side effects from it. Assuming an anticipated ongoing pregnancy rate for both treatment options of at least 30%, as observed in our current day-to-day clinical practice, and referring to sample size determination procedures as described by Simon et al. (1985) for pilot trials in cancer research, a sample size of 35 patients per group can provide a 90% probability of selecting a promising treatment option that has a true response rate of 45%. (By comparison, for a randomized equivalence trial, the sample size needed to demonstrate equivalence within 10% of the standard with 90% power at the 5% significance level is 454 per arm.).

**Results**

A total of 70 patients were randomly assigned to either the study (hCG) or the control (rFSH) group. There were no significant differences between the groups with regard to demographic characteristics. As shown in Table I, the mean female age in the rFSH-group was 30.6 (SD 3.0) years, versus 29.0 (SD 3.8) years in the hCG-group (NS).

<table>
<thead>
<tr>
<th>Table I Baseline characteristics of patients undergoing ICSI*</th>
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<tr>
<td></td>
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<tr>
<td>Age, years</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Height, m</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>FSH, IU/l</td>
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<td>LH, IU/l</td>
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<tr>
<td>E₂, pg/ml</td>
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<td>Progesterone, ng/ml</td>
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rFSH: recombinant FSH, E₂: estradiol.
P-values of t-tests for independent samples: all NS, P > 0.05.
Blood values were taken on Day 3 of the cycle.
*Mean values per patient (SD).

In the rFSH-group, three patients did not get to undergo oocyte retrieval, as compared with six patients in the hCG-group. The reasons for cancelling the intended treatment cycle are shown in Fig. 2. In the rFSH-group, three patients did not reach the stage of embryo transfer due to failed blastocyst development. In the hCG-group, there was no blastocyst development in one patient and no fertilization in a further patient (Fig. 2).

Details referring to the stimulation are summarized in Table II. Overall treatment duration (days of stimulation) did not significantly differ. Obviously, the duration of rFSH administration in the hCG-group was significantly lower than in the rFSH-group. hCG was administered in the hCG-group for 2.3 ± 1.4 days. The total dose of rFSH consumed was significantly lower in the hCG-group: 1273 (SD 260) versus 1617 (SD 280), P < 0.001.

The number of COCs obtained at retrieval was similar in both groups. The fertilization rate, the implantation rate, the pregnancy rate and miscarriage rate were comparable in both groups (Table III). None of the patients developed moderate or severe forms of the OHSS. With regard to the ultrasound findings before administration of hCG, the numbers and sizes of pre-ovulatory follicles were investigated in both groups. There was no difference in the numbers of small follicles (<10 mm), intermediate follicles (10–12 mm and >12–14 mm) and large follicles (>14 mm) in both groups.

Serum hormone levels as measured immediately before final oocyte maturation were found to be similar in both treatment groups, except for the serum hCG value being significantly higher and the FSH value being significantly lower in the hCG-group. In Fig. 3, the hormone measurements across the late follicular phase are plotted. Table IV shows serum concentrations of gonadotrophins and gonadal steroids during the last day of stimulation.

**Discussion**

The LH receptor is expressed in the granulosa cells of ovarian follicles from a follicular size of 10–12 mm onwards (Zeleznik, 2001). Nearly a decade ago, Campbell et al. (1999) showed that LH not only plays...
a crucial role in the ovulation process, but is also capable of exerting virtually all the physiologic actions of FSH on granulosa cells. Based on that information, which had been gathered in natural cycles, the concept was introduced that LH can substitute for FSH in the late stages of COS. The approach to use low doses of hCG in COS protocols has been tested in the past, and several of these have been published, using a variety of protocol modifications. Using serum E₂ concentration as a marker of follicular stimulation efficacy, Sullivan et al. (1999) demonstrated that the substitution of rFSH by recombinant LH during the last 2 days of COS was as efficient as continued FSH administration in GnRH agonist cycles. Filicori et al. (2002a, b) further showed that low dose hCG (200 IU) can replace FSH during the last 3–4 days of COS in a GnRH agonist protocol and additionally demonstrated the applicability of this protocol in a routine clinical setting (Filicori et al., 2005). Their findings were confirmed by others (Lee et al., 2005; Gomes et al., 2007), who demonstrated that the hCG-protocol enables the completion of COS and is also a cost-saving method. On the other hand, studies of the influence of

Table II  Cycle outcome measures∗

<table>
<thead>
<tr>
<th></th>
<th>rFSH standard treatment group** mean (SD)</th>
<th>Low-dose hCG treatment group** mean (SD)</th>
<th>Between-group difference (95% CI)</th>
<th>P-value for between-group difference****</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of rFSH, IU***</td>
<td>1617 (280)</td>
<td>1273 (260)</td>
<td>−344 (−483 to −205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall treatment duration, days</td>
<td>8.2 (1.6)</td>
<td>8.7 (1.6)</td>
<td>0.5 (−0.3 to 1.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>rFSH duration, days</td>
<td>8.2 (1.6)</td>
<td>6.4 (1.3)</td>
<td>−1.8 (−2.6 to −1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hCG duration, days</td>
<td>0</td>
<td>2.3 (1.4)</td>
<td>2.3 (1.8–2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of COCs</td>
<td>12.3 (5.8)</td>
<td>11.1 (5.2)</td>
<td>−1.2 (−4.1 to 1.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Number of M II oocytes</td>
<td>10.1 (5.8)</td>
<td>8.9 (4.6)</td>
<td>−1.2 (−3.9 to 1.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>Number of 2-PN oocytes</td>
<td>8.1 (5.0)</td>
<td>7.4 (4.0)</td>
<td>−0.7 (−3.1 to 1.6)</td>
<td>0.55</td>
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</table>

COC, cumulus-oocyte complex; 2-PN, two pronuclei; M II, metaphase II.
∗All calculations have been carried out to full arithmetic precision, but results are shown as rounded values. Absolute between-group difference = (Low-dose hCG group value [third column]) − (rFSH group value [second column]). A negative value in the fourth column favours Low-dose hCG.
**Mean values per patient (SD).
***Primary outcome measure.
****P-values for t-test for independent samples; significant P-values, 0.05 are bold.

Table III  Clinical outcome measures∗

<table>
<thead>
<tr>
<th></th>
<th>rFSH standard treatment group* number of cases (percentage)</th>
<th>Low-dose hCG treatment group* number of cases (percentage)</th>
<th>Between-group difference (95% CI)</th>
<th>P-value for between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with positive hCG</td>
<td>19/35 (55%)</td>
<td>17/35 (49%)</td>
<td>5.7% (−16.9 to 27.5%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Per started cycle</td>
<td>19/35 (55%)</td>
<td>17/35 (49%)</td>
<td>5.7% (−16.9 to 27.5%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Per retrieval</td>
<td>19/32 (59%)</td>
<td>17/29 (59%)</td>
<td>0.8% (−22.6 to 24.2%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Per embryo transfer</td>
<td>19/29 (66%)</td>
<td>17/27 (63%)</td>
<td>2.6% (−21.3 to 26.3%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Outcome for patients with positive hCG test</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Biochemical pregnancy</td>
<td>5/19 (26%)</td>
<td>1/17 (6%)</td>
<td>−20.4% (−43.3 to 5.2%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>3/19 (16%)</td>
<td>3/17 (18%)</td>
<td>2.0% (−22.7 to 24.7%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>1/19 (5%)</td>
<td>0/17 (0%)</td>
<td>5.3% (−24.6 to 13.7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>2/19 (11%)</td>
<td>2/17 (12%)</td>
<td>1.2% (−21.3 to 25.1%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Live birth</td>
<td>8/19 (42%)</td>
<td>11/17 (65%)</td>
<td>22.6% (−9.3 to 48.7%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Number of ongoing pregnancies and live births</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Per started cycle</td>
<td>10/35 (29%)</td>
<td>13/35 (37%)</td>
<td>8.6% (−13.0 to 29.1%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Per retrieval</td>
<td>10/32 (31%)</td>
<td>13/29 (45%)</td>
<td>13.6% (−10.3 to 35.7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Per embryo transfer</td>
<td>10/29 (35%)</td>
<td>13/27 (48%)</td>
<td>13.7% (−11.5 to 36.7%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Data are presented as number of cases including nominator and denominator values (percentages between brackets). All calculations have been carried out to full arithmetic precision, but results are shown as rounded values. Absolute between-group difference = (Low-dose hCG group value [third column]) − (rFSH group value [second column]). A negative value in the fourth column favours Low-dose hCG.
low-dose hCG in mid-late follicular phase of GnRH antagonist treatment cycles are scarce. The protocols of two previously reported RCTs in GnRH-antagonist cycles bear some similarities to ours, although in these studies mid-late follicular phase FSH was supplemented, rather than substituted, by hCG (Kyono et al., 2004; Koichi et al., 2006).

Table IV  Serum hormone levels on last day of stimulation before final oocyte maturation*

<table>
<thead>
<tr>
<th></th>
<th>rFSH standard treatment group** mean (SD)</th>
<th>Low-dose hCG treatment group** mean (SD)</th>
<th>Between-group difference (95% CI)</th>
<th>P-value for between-group difference***</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU/l)</td>
<td>14.6 (3.3)</td>
<td>8.2 (4.2)</td>
<td>−6.4 (−8.4 to −4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>2.5 (4.3)</td>
<td>1.4 (1.4)</td>
<td>−1.1 (−2.8 to 0.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>2044 (1204)</td>
<td>2250 (1739)</td>
<td>206 (−555 to 966)</td>
<td>0.59</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.8)</td>
<td>−0.1 (−0.4 to 0.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>hCG (IU/l)</td>
<td>0.1 (0)</td>
<td>8.8 (10)</td>
<td>8.7 (5.2−12.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All calculations have been carried out to full arithmetic precision, but results are shown as rounded values. Absolute between-group difference = (Low-dose hCG group value [third column]) − (rFSH group value [second column]). A negative value in the fourth column favours Low-dose hCG.

**Mean values per patient (SD).

***P-values for t-test for independent samples; significant P-values < 0.05 are bold.

Figure 3  Daily serum concentrations (mean and SE) of LH, FSH, HCG, progesterone (Prog) and estradiol (E2) during the last 4 days of COS.
With regard to the consumption of gonadotrophins

We observed a significant reduction of the total dose of FSH administered in the hCG-group. This yields a significant reduction of the total cost of the treatment. In contradiction to the results of Filicori’s study (2005), where a more estrogenic environment seemed to be created with low dose hCG, the serum E2 levels on the day of final oocyte maturation did not differ significantly in both arms of our study. Nevertheless, E2 serum levels on the day of final oocyte maturation trigger has no predictive value in terms of pregnancy outcome (Kosmas et al., 2004). On the other hand, serum levels of FSH and hCG were significantly different between groups, as expected. Finally, serum progesterone levels at the final day of ovarian stimulation were similar in the study and control groups, which indicates that there were no signs of premature luteinization in the study group. This finding illustrates that premature luteinization is not an LH-related phenomenon (Filicori et al., 2005).

With regard to the number of retrieved oocytes

We observed no differences between groups, in spite of the reduced total dose of gonadotrophins used in the study group. The same finding was observed in a GnRH agonist protocol (Filicori et al., 2005). Moreover, in the present study the number of oocytes and the pregnancy figures meet the standards of current care at our centre (Tables II and III). The pregnancy rate at our centre in the same period for patients <36 years old was 38.8% (835 out of 2150 ICSI patients).

Even though Filicori et al. (2005) suggested that the use of LH in the late-follicular phase led to a preferential stimulation of larger follicles, thereby restraining the development of small pre-ovulatory follicles, this observation could not be confirmed in our study. The heterogeneity of follicular cohorts appeared not to be influenced by the presence of hCG, and therefore, we are unable to propose that the low dose hCG protocol is associated with a reduced risk of OHSS.

With regard to pregnancy rates

No difference was noted between groups, although we admit that the study was not powered with a sufficiently high number of cases to demonstrate superiority of the low-dose hCG protocol in terms of the pregnancy rate.

In conclusion, our study demonstrates that the administration of 200 IU/day of hCG can be safely applied in patients undergoing ART to substitute for rFSH in the final days of ovarian stimulation in an antagonist protocol. There was a positive impact of low-dose hCG administration, with respect to the decreased consumption of gonadotrophins, and also regarding the number of oocytes retrieved and the pregnancy outcome in patients allocated to receive this treatment. The protocol is generally applicable and the use of hCG confers a dramatic reduction on the treatment cost, as compared with FSH-containing preparations, like rFSH or highly purified hMG.

To investigate whether this approach is suitable in the majority of ART candidate patients, the results obtained in this pilot study will need confirmation in additional larger studies with less age-restrictive inclusion criteria.

Acknowledgements

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