Highly purified hMG versus recombinant FSH plus recombinant LH in intrauterine insemination cycles in women ≥35 years: a RCT

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STUDY QUESTION: Is the treatment with recombinant FSH (rFSH) plus recombinant LH (rLH) more effective than highly purified (HP)-hMG in terms of ongoing pregnancy rate (PR) in women ≥35 years of age undergoing intrauterine insemination (IUI) cycles?

SUMMARY ANSWER: The ongoing PR was not significantly different in women treated with rFSH plus rLH or with HP-hMG.

WHAT IS KNOWN ALREADY: Although previous studies have shown beneficial effects of the addition of LH activity to FSH, in terms of PR in patients aged over 34 years having ovulation induction, no studies have compared two different gonadotrophin preparations containing LH activity in women ≥35 years of age in IUI cycles.

STUDY DESIGN, SIZE, DURATION: A single-centre RCT was performed between May 2012 and September 2013 with 579 women ≥35 years of age undergoing IUI cycles. The patients were randomly assigned to one of the two groups, rFSH in combination with rLH group or HP-hMG (Meropur) group, by giving them a code number from a computer generated randomization list, in order of enrolment. The randomization visit took place on the first day of ovarian stimulation.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Five hundred and seventy-nine patients with unexplained infertility or mild male factor undergoing IUI cycles were recruited in a university hospital setting. All women were enrolled in this study only for one cycle of treatment. Five hundred and seventy-nine cycles were included in the final analysis. Two hundred and ninety patients were treated with rFSH in combination with rLH and 289 patients were treated with HP-hMG. The ovarian stimulation cycle started on the third day of the menstrual cycle and the starting gonadotrophin doses used were 150 IU/day of rFSH plus 150 IU/day of rLH or 150 IU/day of HP-hMG. The drug dose was adjusted according to the individual follicular response. A single IUI per cycle was performed 34–36 h after hCG injection.

MAIN RESULTS AND THE ROLE OF CHANCE: The main outcome measures were ongoing PR and number of interrupted cycles for high risk of ovarian hyperstimulation syndrome (OHSS). Ongoing pregnancy rates were 48/290 (17.3%) in the recombinant group versus 35/289 (12.2%) in the HP-hMG group [(odds ratio (OR) 1.50, 95% CI 0.94–2.41, P = 0.09]. The number of interrupted cycles for high risk of OHSS was 13/290 (4.5%) in the rFSH plus rLH group and 2/289 (0.7%) in the HP-hMG group (OR 6.73, 95% CI 1.51–30.12, P = 0.013).

LIMITATIONS, REASONS FOR CAUTION: One of the limitations of this study was the early closure and the ongoing PR could be over-estimated. Both patient and gynaecologist were informed of the assigned treatment.

WIDER IMPLICATIONS OF THE FINDINGS: Our results demonstrated the lack of differences in terms of ongoing PR between recombinant product and HP-hMG, in women ≥35 years undergoing controlled ovarian stimulation for IUI cycles. HP-hMG was safer than recombinant gonadotrophin concerning the risk of OHSS.

† These authors shared senior authorship.

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Introduction

Intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is frequently used in couples with unexplained infertility (Hughes, 1997; Zeyneloglu et al., 1998; Guizick et al., 1999; Cohlen, 2005; van Rumste et al., 2008). Although more recently the cost-effectiveness of prescribing IUI has been questioned (Reindollar et al., 2010; Gianaroli et al., 2012), this technique remains a treatment option for people with unexplained subfertility, mild endometriosis or mild male factor infertility who are having regular unprotected sexual intercourse (NICE guideline 2013). IUI is a choice in couples who have social, cultural or religious objections to IVF, in people who are unable to, or would find it very difficult to, have vaginal intercourse.

Some authors recommended IUI cycle without COS as COS has been associated with an increased risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (Gianaroli et al., 2012). However, in a meta-analysis on couples with unexplained subfertility, COS in combination with IUI was shown to result in significantly higher pregnancy rate (PR) and live birth rate per couple when compared with IUI in the natural cycle (odds ratio (OR) 2.3, 95% confidence interval (95% CI) 1.5–3.7 for PR; OR 2.07, 95% CI 1.22–3.50 for live birth rate) (Verhulst et al., 2006).

Different treatment protocols for COS have been described but the best treatment option is not yet known. Recombinant human FSH (rFSH) has been widely, and successfully, used for ovarian stimulation in infertile women undergoing treatment for IUI (la Cour Freiesleben et al., 2009; Berker et al., 2011).

The importance of LH activity supplementation has been documented in the GnRH analogues down-regulated stimulation IVF cycles (Marrs et al., 2004; Plateau et al., 2004; Ruvolo et al., 2007; Al-Inany et al., 2008). Conversely, the role of LH supplementation in the non-down-regulated stimulation IUI cycles is not clear and few studies have evaluated the LH activity in IUI cycles (Sagnella et al., 2011; Gomez et al., 2014), suggesting a benefit of co-administration of LH and FSH, in terms of PR in patients aged over 35 years. Moreover, some studies showed that the addition of LH activity reduces the number of small follicles and enhances the selection of large follicles, which could reduce the incidence of multiple pregnancies and OHSS during ovarian induction (Filocorici et al., 2001; Sagnella et al., 2011).

In addition to FSH, LH activity can be administered in different forms including association of recombinant LH (rLH) to rFSH or highly purified (HP)-hMG. HP-hMG provides FSH and exogenous LH activity mainly in the form of hCG. Some authors compared these different gonadotrophin preparations, rFSH plus rLH versus HP-hMG, in IVF/ICSI (Pacchiarotti et al., 2010; Fabregues et al., 2013); however there are no large prospective studies comparing the use of these gonadotrophins in IUI cycles.

The aim of the present study was to evaluate whether rFSH plus rLH is more effective than HP-hMG, regarding ongoing PR in women ≥35 years of age undergoing IUI cycles.

Materials and Methods

Study design

To evaluate two different gonadotrophic preparations, HP-hMG and rFSH plus rLH, in women aged 35 years or older undergoing IUI cycles, we designed a RCT at the Institute of Physiopathology of Human Reproduction, Policlinico Gemelli, Rome, from May 2012 to September 2013. The Institutional Board of the Policlinico Gemelli approved the plan of work.

All participants gave written informed consent, after having been informed on all aspects of the study and in particular about the risks of OHSS and multiple pregnancies.

All women were enrolled in this study only for one cycle of treatment and it was their first cycle of treatment.

The primary end-point was the ongoing PR. Ongoing PR was defined as a pregnancy which had completed 12 gestational weeks. The major secondary end-point was the number of cancelled cycles for low or no response and the number of interrupted cycles for high risk of OHSS and multiple pregnancies. The other secondary end-points were duration of stimulation, total gonadotrophin dose, number of midsize follicles, dominant follicles, estradiol (E2) levels, endometrial thickness on hCG day, Progesterone levels and endometrial thickness at midluteal phase.

Study population

The indications for the IUI treatment were recorded, as was age, BMI (kg/m²) and duration of infertility.

The eligibility criteria were: women in good health aged 35–41 years; regular ovulatory menstrual cycles; BMI ≤27 kg/m²; bilateral tubal patency, as defined by hysterosalpingo contrast sonography (HyCoSy) or laparoscopy and dye hydrotubation; normal or moderate-to-mild male infertility, according to World Health Organization criteria; normal Day 3 hormonal pattern: FSH (2.5–11 mIU/ml) and E2 (30–100 pg/ml). The exclusion criteria were: severe male factor (total motile sperm count of <1 million after semen preparation); mono/bilateral closed tubes; polycystic ovary syndrome or any systemic disease or endocrine or metabolic abnormalities; pelvic inflammatory disease; endometriosis; sexual organ malformations; neoplasms; breast pathology incompatible with gonadotrophin stimulation.

Intervention

Two hundred and ninety patients were treated with rFSH ( follitropin alpha; Gonal-f; Merck Serono, Geneva, Switzerland) in combination with rLH ( lutropin alpha; Luveris; Merck Serono, Geneva, Switzerland) and two hundred eighty-nine patients were treated with HP-hMG (menotropin; Meropur; Ferring Pharmaceuticals, Copenhagen, Denmark). Both gonadotrophin preparations were administered s.c.

Ovarian stimulation cycle started on the third day of the menstrual cycle, after hormonal assay and basal ultrasound examination. We evaluated the following Day 3 hormone levels: FSH (2.5–11 mIU/ml), E2 (30–100 pg/ml). The antral follicle count (AFC) was also studied on ultrasound scan.

The starting gonadotrophin doses used were 150 IU of rFSH plus 150 IU of rLH or 150 IU of HP-hMG. The drug dose was adjusted according to the individual follicular response. Follicular development was monitored by

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Key words: highly purified HMG / recombinant FSH / recombinant LH / intrauterine insemination / ovulation induction
ultrasound and E2 plasma levels. A single i.m. injection of hCG (Gonasi; Serono; 10 000 IU) was administered in the presence of one or more follicles with a diameter ≥ 17 mm, whereas hCG was not administered in presence of ≥3 large follicles with a diameter ≥17 mm or ≥4 follicles with diameter >15 mm and/or plasma E2 levels >1500 pg/ml, in order to minimize the risk of multiple pregnancy and/or OHSS.

A single IUI per cycle was performed at 34–36 h after hCG injection. Sperm preparation was performed using a gradient technique with Percoll (Cook Medical) and a prepared sperm volume of 0.20 ml was used for insemination. Ovulation was confirmed by Progesterone assay and ultrasound evaluation. A serum beta-hCG test was performed 15–20 days after hCG administration and clinical pregnancy was documented by transvaginal ultrasound 6 weeks after the IUI.

Randomization and sample size calculation

Five hundred and seventy-nine agreed to participate to the study and they were randomly assigned to one of the two groups by giving them a code number from a computer generated randomization list, in order of enrolment. Both the patient and the gynaecologist were informed of the assigned treatment. The randomization visit took place on the first day of COS.

Our simple size was based on the primary end-point (ongoing PR). From previous reports, the estimated ongoing PR was 17.4% in the HP-hMG group in the surveyed population (Sagnella et al., 2011). To detect a difference in prevalence of 10% between the two studied groups with 90% power and with α = 0.05 (two-sided test), a total of 454 patients (227 patients per group) is required. Three hundred patients per group were recruited to compensate for possible missing data or drop-outs.

Statistical methods

Baseline characteristics of patients and clinical parameters during gonadotrophin stimulation are presented as means ± standard deviations (SD) or as percentage, as appropriate. Comparisons between the two groups were made with Student’s t-test (or Mann–Whitney test when the requirements for t-test were violated) for continuous variables and with the X² test for nominal variables. The differences between treatments in PR, ongoing PR, interrupted cycles for high risk of OHSS rate, multiple PR, were estimated using a logistic regression model. In the multiple regression models, confounders were included if they were significant at a 0.05 level or they altered the coefficient of the main variable by >10% in cases in which the main association was significant.

Data were analysed by the intent-to-treat principle to maintain randomization and statistical power. Statistical analyses were performed with Stata software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP). The significance level was set at P < 0.05.
Results

Six hundred women were recruited and 579 of them were included in the study. Two hundred and ninety patients were treated with rFSH plus rLH and 289 with HP-hMG (Fig. 1).

Table I Baseline characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment groups*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>rFSH + rLH (n = 290)</td>
<td>HP-hMG (n = 289)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.4 ± 4.0</td>
<td>37.9 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Duration of infertility (months)</td>
<td>35 ± 15.3</td>
<td>36 ± 17.5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 2.1</td>
<td>22.9 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
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<tr>
<td>Male factor (%)</td>
<td>23.3</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Male age (years)</td>
<td>41.3 ± 3.7</td>
<td>40.7 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>Unexplained (%)</td>
<td>76.7</td>
<td>77.1</td>
<td></td>
</tr>
<tr>
<td>Spermiogram characteristics with male factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration (10³/ml)</td>
<td>17907 ± 5375</td>
<td>18323 ± 4982</td>
<td></td>
</tr>
<tr>
<td>Motility</td>
<td>47 ± 10.7</td>
<td>46 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>29 ± 7.6</td>
<td>28 ± 9.0</td>
<td></td>
</tr>
<tr>
<td>Spermiogram characteristics with non-male factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration (10³/ml)</td>
<td>57647 ± 13891</td>
<td>55432 ± 14087</td>
<td></td>
</tr>
<tr>
<td>Motility</td>
<td>51 ± 13.3</td>
<td>53 ± 14.9</td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>38 ± 4.4</td>
<td>38 ± 6.1</td>
<td></td>
</tr>
<tr>
<td>Mean baseline hormone values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH day 3 (mUI/ml)</td>
<td>8.0 ± 1.7</td>
<td>8.3 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>49.2 ± 14.0</td>
<td>50.6 ± 13.6</td>
<td></td>
</tr>
<tr>
<td>Antral follicle count</td>
<td>8.6 ± 2.4</td>
<td>9.0 ± 2.8</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or percentage. 

rFSH + rLH = recombinant FSH plus recombinant LH; HP-hMG = highly purified hMG; E2 = oestradiol.

As shown in Table I, the main demographic and baseline characteristics of the patients in both treatment groups, including age, BMI, duration of infertility, indication for IUI, spermiogram characteristics, basal hormonal assay and antral follicle count were similar. This supports the validity of the comparison process.

Data regarding gonadotrophin treatment and ovarian response in two groups are presented in Table II.

There were no differences between groups with respect to the total dose used in the cycle and days of stimulation. However, the number of follicles 14–16 mm and ≥ 17 mm diameter on hCG day was significantly higher in the rFSH plus rLH group (Table II).

We obtained 59 (21.2%) clinical PR in the 290 rFSH plus rLH cycles and 40 (13.9%) in 289 HP-hMG cycles (P = 0.024). Ongoing PRs were 48/290 (17.3%) in the recombinant group versus 35/289 (12.2%) in the HP-hMG group (P = 0.09) (Table III). A multiple pregnancy was observed in 4/289 (1.4%) HP-hMG cycles and in 6/290 (2.1%) rFSH plus rLH cycles (P = 0.53). All of the multiple pregnancies were twin pregnancies. This study was not sufficiently powered to exclude a difference between treatments regarding multiple pregnancies. No case of extrauterine pregnancy was observed.

The number of interrupted cycles for high risk of OHSS was 13/290 (4.5%) in the rFSH plus rLH group and 2/289 (0.7%) in the HP-hMG group (ORs 6.73, 95% CI 1.51–30.12) (Table III).

After adjustment for age, follicles of 14–16 mm, follicles ≥ 17 mm and E2 levels on hCG day, the OR for clinical PR was 1.41 (95% CI 0.84–2.37) and the OR for ongoing PR was 1.33 (95% CI 0.76–2.32).

Discussion

rFSH and hMG are the gonadotrophin products used most widely to induce follicle development in IUI cycles as in patients undergoing assisted reproductive techniques (ART) (la Cour Freiesleben et al., 2009; Berker et al., 2011; Sagnella et al., 2011; Fábregues et al., 2013).

Several studies demonstrated that LH activity in addition to FSH in COS protocols increases ovarian sensitivity to FSH and provides an adequately oestrogenized environment to achieve normal follicular development, oocytes maturation, good-quality zygotes and embryos, and endometrial growth and higher implantation rates when compared with stimulation with FSH alone (Tarlatzis et al., 2006; Balasch et al., 2009; Franco et al., 2009). In a RCT comparing rFSH and HP-hMG in

Table II Clinical parameters evaluated during ovarian stimulation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment groups</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rFSH + rLH (n = 290)</td>
<td>HP-hMG (n = 289)</td>
<td>P-value</td>
</tr>
<tr>
<td>Total dose of FSH for cycle (IU)</td>
<td>906.1 ± 176.3</td>
<td>876.6 ± 198.0</td>
<td>0.059</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>6.2 ± 1.4</td>
<td>6.0 ± 1.3</td>
<td>0.075</td>
</tr>
<tr>
<td>Endometrial thickness on hCG day (mm)</td>
<td>9.8 ± 2.1</td>
<td>9.5 ± 1.8</td>
<td>0.066</td>
</tr>
<tr>
<td>Follicles of 14–16 mm on hCG day</td>
<td>1.7 ± 1.5</td>
<td>1.1 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follicles ≥ 17 mm on hCG day</td>
<td>2.1 ± 0.9</td>
<td>1.4 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E2 on hCG day (pg/ml)</td>
<td>703.7 ± 364.6</td>
<td>448.2 ± 209.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endometrial thickness in midluteal phase (mm)</td>
<td>11.4 ± 2.5</td>
<td>11.0 ± 2.5</td>
<td>0.055</td>
</tr>
<tr>
<td>Progesterone in midluteal phase (ng/ml)</td>
<td>32.9 ± 23.5</td>
<td>34.9 ± 21.8</td>
<td>0.089</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
Comparing different gonadotrophin preparations containing LH in ART

data in IVF cycles (Ferraretti et al., 2004) showed that in older women, the addition of LH/hCG activity could positively affect oocyte quality and steroidogenesis, as supported by previous studies (Sagnella et al., 2009; Lisi et al., 2001).

To the best of our knowledge, there are only a few previous studies comparing different gonadotrophin preparations containing LH in ART patients (Pacchiarotti et al., 2010; Fabregues et al., 2013).

The present study is the first to compare rFSH plus rLH versus HP-hMG in IUI cycles in women ≥34 years. We demonstrated similar results in terms of ongoing PR between recombinant products and HP-hMG. Our findings are in agreement with those reported in ART cycles (Fabregues et al., 2013).

Although some negative effects—local allergic reactions and batch-to-batch inconsistencies—have been previously reported for hMG due to possible protein contamination (Hill et al., 2012), at present the highly purified urinary preparations are comparable in purity as well as in safety and tolerability to the recombinant preparations (The European study group on Highly Purified hMG vs. recombinant FSH, 2001; The European and Israeli Study Group on Highly Purified hMG vs. recombinant Follicle-Stimulating Hormone, 2002).

In the present study the difference in terms of cost per ongoing pregnancy between the two gonadotrophin preparations has been not calculated. However, the majority of the previous studies showed that purified preparations are more cost effective than recombinant products in terms of ongoing PR (Wechowski et al., 2007; Gibreel and Bhattacharya, 2010).

In agreement with previous data on IVF cycles (Pacchiarotti et al., 2010), we observed that the number of interrupted cycles for high risk of OHSS was lower in the HP-hMG than in the recombinant group. These results could be explained by the different effects on follicle development and circulating E2 levels on hCG day between the gonadotrophin formulations. Multifollicular development and E2 concentrations were significantly higher in the recombinant compared with the HP-hMG group.

Urinary highly purified urofollitropin shows similar activity compared with rFSH (Loumaye et al., 1997; Strowitzki, 1997), which in turn has a shorter half-life (Bishop et al., 1995; Gordon, 2002). However, differences in the gene expression profile of granulosa cells from pre-ovulatory follicles after COS with recombinant versus urinary FSH have been reported (Grøndahl et al., 2009). Compared with the FSH isoforms in hMG, the higher potency of rFSH in inducing LH/hCG receptors (Grøndahl et al., 2009) could explain the higher number of interrupted cycles for high risk of OHSS obtained in the recombinant group.

In conclusion, our results demonstrated no differences in terms of ongoing PR between recombinant product and HP-hMG, in women ≥35 years undergoing COS for IUI cycles. HP-hMG was however shown to be safer than the recombinant FSH plus LH treatment in terms of OHSS risk.

### Authors’ roles

Each author of this original paper contributed to the work in the following ways: F.M. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, revising the article. E.S. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition, analysis and interpretation of data. R.A. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to statistical analysis and interpretation of data. F.R. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition and analysis of data. F.R. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition and analysis of data. A.F. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition and analysis of data. A.T. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition and analysis of data. A.F. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition and analysis of data.

### Funding

None.

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### Table III: Primary and major secondary outcome measures.

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted* OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFSH + rLH (n = 290)</td>
<td>1.66 (1.07, 2.58)</td>
<td>0.024</td>
<td>1.41 (0.84, 2.37)</td>
<td>0.137</td>
</tr>
<tr>
<td>HP-hMG (n = 289)</td>
<td>1.50 (0.94, 2.41)</td>
<td>0.090</td>
<td>1.33 (0.76, 2.32)</td>
<td>0.276</td>
</tr>
</tbody>
</table>

*Adjusted for age, follicles 14–16 mm, or ≥17 mm diameter and E2 levels on hCG day.

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IUI cycles, Sagnella et al. showed that the mean age of pregnant women was higher in the HP-hMG group (Sagnella et al., 2011). They hypothesized that in older women, the addition of LH/hCG activity could positively affect oocyte quality and steroidogenesis, as supported by previous data in IVF cycles (Ferraretti et al., 2004; Lisi et al., 2001).

Values are expressed as percentage. Odd ratio (OR), 95% confidence interval (CI). OHSS, ovarian hyperstimulation syndrome.

A.L. (OASI Institute for Research, Troina, Italy): revising the article critically for important intellectual content. A.L. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to statistical analysis and interpretation of data. E.L. (Institute of Public Health, Section of Hygiene, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition, analysis and interpretation of data. E.S. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to acquisition and analysis of data. A.T. (Institute of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy): contributions to analysis and interpretation of data. A.L. (OASI Institute for Research, Troina, Italy): revising the article critically for important intellectual content and final approval of the version to be published.
Conflict of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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The European Study Group on Highly Purified hMG vs. recombinant FSH. A phase III trial to study the efficacy and safety of highly purified menotrophin (Menopur)” versus recombinant FSH (folliotropin alpha) in female patients in an IVF/ICSI programme. In: Program and abstracts of the 2nd World Congress on Controversies in Obstetrics, Gynecology and Infertility, 2001.

