Treatment regimens in ovulation induction and ovarian hyperstimulation

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Effectiveness of human menopausal gonadotropin versus recombinant follicle-stimulating hormone for controlled ovarian hyperstimulation in assisted reproductive cycles: a meta-analysis

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Abstract

Objective: To compare the effectiveness of hMG and recombinant FSH after down-regulation for ovulation stimulation in assisted reproductive cycles.

Design: Meta-analysis.

Setting: Infertility centers providing assisted reproductive techniques.

Patients: Two thousand thirty women undergoing IVF or ICSI.

Intervention: Ovarian hyperstimulation with hMG or recombinant FSH after down-regulation.

Main outcome measures: Clinical pregnancy rate, ongoing pregnancy/live birth rate, gonadotropin dose used, oocytes retrieved, implantation rate, miscarriage rate, and multiple pregnancy rate.

Results: Six randomized controlled trials were included. In all trials, the group of women treated with hMG had higher pregnancy rates. Pooling the five trials that used a long GnRH agonist protocol resulted in a higher clinical pregnancy rate for hMG compared with recombinant FSH (relative risk, 1.22 [95% CI, 1.03 to 1.44]). However, there was no evidence of a difference in rates of ongoing pregnancy or live birth per woman between hMG recipients and recombinant FSH recipients (relative risk, 1.20 [95% CI, 0.99 to 1.45]). No differences were found in gonadotropin dose used, oocytes retrieved, miscarriage rate, or multiple pregnancy rate.

Conclusion: Use of hMG resulted in higher clinical pregnancy rates than did use of recombinant FSH in IVF/ICSI cycles after GnRH agonist down-regulation in a long protocol.
**Introduction**

Both hMG and FSH preparations have been used successfully for controlled ovarian hyperstimulation in IVF-ET. The presumed redundancy of LH use and the desire for a more purified product prompted the conversion from hMG to urinary FSH. Subsequently, highly purified and recombinant FSH entered the market and replaced earlier FSH products. The purity, batch-to-batch consistency, and availability of recombinant FSH make it an attractive alternative to urinary FSH products.

According to the two-cell, two-gonadotropin concept, both FSH and LH are required for normal follicular development and steroidogenesis.\(^1\) In hypogonadotropic women, administration of FSH without LH results in lower estradiol and inhibin concentrations and reduced oocyte fertilization rates compared with use of hMG.\(^2,3\) More important, no term pregnancies have occurred in women treated with FSH alone.\(^4\)

Several studies in normogonadotropic women, however, have suggested that very low amounts of LH are sufficient for normal follicle and oocyte development.\(^5\) Furthermore, elevations in serum LH level during the follicular phase of the menstrual cycle have been associated with lower fertility rates and an increase in the probability of spontaneous abortion.\(^6-9\) A recent study, however, found no statistically significant differences in pregnancy outcome in women with recurrent miscarriage who have a high serum LH concentration compared with those with a normal serum LH concentration.\(^10\)

It has become common practice to combine GnRH analogue–induced pituitary suppression with FSH for controlled ovarian hyperstimulation in IVF. This combination results in concentrations of circulating LH that are much lower than in the normal menstrual cycle.\(^11\) Recent trials, however, have shown that pure FSH is effective in both ovulation induction and controlled ovarian hyperstimulation in these suppressed cycles, suggesting that the endogenous LH levels present in most women are sufficient for folliculogenesis.\(^12-15\) In a meta-analysis, the long protocol was shown to be superior over the short and ultrashort protocols for GnRH analogue use in IVF and GIFT cycles in terms of clinical pregnancy rates.\(^16\)

From a clinical perspective, the decision what kind of gonadotropin to give to a woman undergoing GnRH analogue down-regulation may be difficult. In making such a decision, the clinician's first concerns are the possible differences in effectiveness among the different gonadotropins. Two meta-analyses have compared urinary FSH with hMG.\(^17,18\) In the absence of GnRH analogue down-regulation, urinary FSH was found to be more effective than hMG in terms of clinical pregnancy rates. With down-regulation, however, no differences in pregnancy rates were observed.
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Another meta-analysis compared recombinant FSH with urinary FSH.\textsuperscript{17,19} Seventeen of the 18 trials included had used GnRH analogue down-regulation in a long protocol. After pooling the data from all trials, the odds ratios for clinical pregnancy per cycle, clinical pregnancy per embryo transfer and ongoing pregnancy per cycle were significantly higher with recombinant FSH. The overall odds ratio for clinical pregnancy per cycle started was 1.2 (95% CI, 1.04 to 1.42) for recombinant FSH compared with urinary FSH.

The meta-analyses suggest that recombinant FSH is superior to the other gonadotropins in assisted reproductive cycles and that the LH present in urinary gonadotropins is not required in suppressed cycles. Nevertheless, it has been argued that an appreciable proportion of normogonadotrophic women acquire endogenous LH levels that are too low for follicle development after GnRH analogue down-regulation.\textsuperscript{20} Most of these arguments are based on endocrinologic findings in suppressed cycles, such as a low estrogen level.

Two clinical studies produced support for this concept. Lam et al. achieved oocyte retrieval and ET by additional administration of recombinant LH to recombinant FSH in six women who had previously not responded to hyperstimulation with recombinant FSH.\textsuperscript{21} Furthermore, in a retrospective study of 200 couples, an association between profound suppression of LH and early pregnancy loss was found.\textsuperscript{22}

Because of renewed interest in LH, several investigators have performed randomized clinical trials comparing the effectiveness of hMG and recombinant FSH in IVF-ET and ICSI cycles. The objective of our meta-analysis was to compare the value of hMG and recombinant FSH in women undergoing GnRH down-regulation for ART purposes.

Materials and methods

We used the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group, which can be found in the Cochrane database. To identify relevant trials, we searched the Cochrane Menstrual Disorders and Subfertility Group trials register on January 3, 2002, and the PubMed, MEDLINE, and Web of Science databases beginning with the year 1985 until May 15, 2002. The Cochrane Menstrual Disorders and Subfertility Group trials register and Web of Science database contain abstracts of presentations at major international meetings. The following key words were used: gonadotropins, hMG, menotropins, FSH, urinary FSH, recombinant FSH, and IVF. In addition, cross-references from all identified articles were checked.

We included only randomized or quasi-randomized controlled trials that compared hMG and recombinant FSH in IVF-ET after GnRH agonist down-regulation in normogonadotropic
women and that specified at least the clinical pregnancy rate per woman. Studies that did not use GnRH analogue down-regulation were excluded because pituitary desensitization has become standard procedure in IVF. Authors of eligible trials and pharmaceutical companies were asked if they knew of unpublished studies. Additional data were obtained through correspondence with the authors. Institutional review board approval was not required for this meta-analysis of previously published and unpublished clinical trials.

The preferable primary outcome measure is live birth or ongoing pregnancy per woman. Because this outcome was not evaluated in all eligible trials, the clinical pregnancy rate per woman was chosen as primary outcome. Secondary outcomes were total gonadotropin dose used, cancellation rate, ovarian hyperstimulation syndrome (OHSS) rate, number of oocytes retrieved, implantation rate, clinical pregnancy rate per embryo transfer, ongoing pregnancy/live birth rate (per woman and per embryo transfer), miscarriage rate, and incidence of multiple pregnancy per woman. In all studies, women underwent only one IVF or ICSI cycle. Each outcome therefore expresses both the rate per cycle and woman.

Data on ongoing pregnancy/live birth were pooled with live birth rate as the outcome of choice. When data on live birth were not available, data on ongoing pregnancy were used instead. Data on ongoing pregnancy and live birth can be pooled when no relative differences in success rates are expected.

The cancellation rate was calculated as the number of started cycles not undergoing oocyte retrieval divided by the total number of cycles started. The implantation rate was calculated by dividing the total number of gestational sacs by the total number of transferred embryos. Clinical pregnancy was defined by the presence of a gestational sac on ultrasonography 4 to 7 weeks after transfer. Ongoing pregnancy was defined as a pregnancy of at least 10 weeks' gestation. Multiple pregnancy rate was expressed as number of multiple gestations per woman.

Not all trials included in the meta-analysis evaluated each of the outcome variables given. As a consequence, the number of studies in the analysis varied. Results are presented in chronological order of the IVF procedure.

For dichotomous data, relative risks with 95% CIs were calculated for each individual trial. Data were pooled using a random effects model. As summary statistics, pooled relative risks with 95% CIs were calculated by using the random effects method of DerSimonian and Laird. The presence of heterogeneity of treatment effect among trials was tested using the Breslow–Day $\chi^2$ test.

For continuous data, mean differences were calculated. The weight given to each study was the inverse of the variance of the different means for that study. When median and range were given instead of means (±SD), the mean was estimated by logarithmic transformation of the minimum and maximum values and the SD was imputed from the overall SD of the
other studies. As summary statistics, pooled weighted mean differences with 95% CIs were calculated by using the random effects method of DerSimonian and Laird.\textsuperscript{23}

Review Manager software, version 4.0 (Cochrane Collaboration, Oxford, United Kingdom) was used for statistical analysis.

## Results

We identified 10 reports of prospective studies that had compared hMG and recombinant FSH. Two studies were excluded because none of the outcome measures of interest were studied.\textsuperscript{24,25} One trial was excluded because GnRH analogue down-regulation was not used.\textsuperscript{26} One trial was excluded because the number of women in each treatment group could not be determined, even though we tried to get additional information from the authors.\textsuperscript{27} The 6 remaining randomized trials met the inclusion criteria.\textsuperscript{28-33} Details of these trials, with a total of 2030 women, can be found in Table I.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial characteristics</th>
<th>Baseline characteristics</th>
<th>Interventions</th>
<th>Definition of clinical pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(28)</td>
<td>Pseudo-randomized, open-label study. Allocation according alternating weeks. Trial took place between January 1997 and June 1999. 238 patients were randomized and received treatment. No power calculation. Concealment of allocation inadequate.</td>
<td>For hMG and rFSH respectively: Mean age: 33 and 34. Mean BMI: unknown Mean duration of infertility: unknown</td>
<td>HMG: Menogon (Ferring, Langley, UK). rFSH: Gonal-F. (Serono, Feltham, UK). Both given as 150 to 375 IU according to response to ovarian reserve test after long protocol down-regulation with buserelin nasal spray. Unknown when HCG was given.</td>
<td>Presence of gestation sac, fetal pole and heart beat at six week scan.</td>
</tr>
<tr>
<td>(29)</td>
<td>Randomized, assessor-blind, single-center study. Allocation by computerized randomization by the hospital pharmacist. Ratio hMG versus rFSH apparently 3:4. A total of 128 patients were studied of whom 29 received hMG, 39 received rFSH and 60 received urinary FSH. Timing of the trial not described. Power calculation not performed. Concealment of allocation adequate.</td>
<td>For hMG and rFSH respectively: Mean age: 33 and 32. Mean BMI: unknown Mean duration of infertility: 5 and 5 yrs</td>
<td>HMG: Humegon (NV Organon, Oss). rFSH: Follitropin beta, (Puregon, NV Organon, Oss). Both given as a fixed dose of 225 IU, subcutaneously administered for five days after down-regulation in a long protocol with buserelin nasal spray. 10000 IU HCG when ( \geq 2 ) follicles of ( \geq 18 \text{ mm} ).</td>
<td>Presence of fetal sac at ultra sound 7 weeks after embryo transfer.</td>
</tr>
</tbody>
</table>
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(30) Randomised, open-label, single-centre study. Allocation by computerized randomization. Ratio hMG versus rFSH was 1:1. Trial took place between January and September 1999, 40 patients were randomized and received treatment. Power calculation based on oocyte retrieval. Concealment of allocation adequate.

For hMG and rFSH respectively: Mean age: 33 and 34. Mean BMI: 21 and 21. Mean duration of infertility: 5 and 4.8 yrs

HMG: Pergonal (Serono, Geneva, Switzerland). rFSH: Gonal-F (Serono, Germany). Both given as 150 to 450 IU administered individually adjusted for four days after long protocol down-regulation with buserelin nasal spray. 10000 IU HCG when ≥3 follicles of ≥15 mm.

(31) Randomized, open-label, single-center study. Allocation by computerized randomization. Ratio hMG versus rFSH was 1:1. Trial took place between January 1998 and June 1999, 578 patients were randomized and received treatment. Power calculation not mentioned. Concealment of allocation adequate.

For hMG and rFSH respectively: Mean age: 32 and 32. Mean BMI: unknown. Mean duration of infertility not known

HMG: Menogon (Ferring, Kiel, Germany). rFSH: Gonal-F (Serono, Germany). Both given as 150 to 450 IU administered individually adjusted after short protocol down-regulation with nafarelin acetate. 5000 IU HCG when ≥1 follicle of maximally 20 and 2 of 16 mm.

(32) Randomized, open-label, single-center study. Allocation by computerized randomization into 4 groups: nasal or SC GnRHα and hMG or rFSH as 1:1:1:1. Trial took place between October 1998 and January 2000, 379 patients were randomized and received treatment. Power calculation not performed. Concealment of allocation not very secure.

For hMG and rFSH respectively: Mean age: 31 and 31. Mean BMI: 23 and 23. Mean duration of infertility: not known

HMG: Menogon (Ferring, Denmark). rFSH: Gonalf, (Serono, Nordic, Denmark). Both given as a fixed dose of 225 IU for seven days after down-regulation in a long protocol with buserelin nasal spray or sc. 10000 IU HCG when ≥3 follicles of ≥17 mm.

(33) Randomized, open-label, multicenter study in six countries. Allocation of the next available patient number from the sequence using a randomization list. Ratio hMG versus rFSH was 1:1. Trial took place between May 1999 and November 2000, 781 patients were randomized and 727 treated. Power calculation based on ongoing pregnancy rate per cycle. Concealment of allocation adequate.

For hMG and rFSH respectively: Mean age: 31 and 31. Mean BMI: 23 and 23. Mean duration of infertility: 3.7 and 3.6 yrs

HMG: Menopur, highly purified hMG (Ferring, Germany). rFSH: Follitropin beta, (Puregon, NV Organon, Oss). Given as a fixed dose of 225 IU, subcutaneously administered for five days after down-regulation in a long protocol with daily or depot injections of triptorelin, buserelin, leuproolid or goserelin. 5000-10000 IU HCG when ≥3 follicles of ≥16 mm. Presence of one or more gestation sacs on scanning.

Presence of fetal sac at ultrasound 6 weeks after embryo transfer.

Presence of fetal sac at ultrasound at least 4 weeks after embryo transfer.

Presence of fetal sac at ultrasound at least 4 weeks after embryo transfer.
Five trials had been published in peer-reviewed journals. One trial was only available as an abstract.\textsuperscript{28} The authors of this trial provided us with further information. Although the randomization procedure of this trial was inadequate—treatment allocation had been performed on an alternating-week basis—baseline characteristics appeared balanced and similar numbers of embryos were transferred. Because this quasi-randomized trial was likely to introduce heterogeneity, sensitivity analyses were performed without this trial.

In most studies, the categories of infertility were tubal disease, endometriosis, unexplained, and male factor. One study included only couples with male factor infertility.\textsuperscript{30} All trials used a maximum female age limit of 39 or 40 years. The proportion of patients who had primary infertility was provided in half of the trials and ranged from 50% to 90%. The number of previous cycles of IVF-ET was unknown for two trials\textsuperscript{28,30} and varied from none to four at most in the other trials.

Concealment of allocation appeared to be adequate in most trials.\textsuperscript{29-32} Because in one trial the block randomization per center was small (blocks of four women), concealment of allocation was not assured.\textsuperscript{33} The allocation was not concealed in the quasi-randomized study.\textsuperscript{28} All trials provided intention-to-treat analyses. The number of patients in each trial was 40\textsuperscript{30}, 68\textsuperscript{29}, 238\textsuperscript{28}, 379\textsuperscript{32}, 578\textsuperscript{31}, and 727\textsuperscript{33}.

**Ovarian stimulation**

Five trials used a long GnRH analogue protocol.\textsuperscript{28,30,32,33} One trial used a short GnRH analogue protocol.\textsuperscript{31} In the study of Westergaard et al.\textsuperscript{32}, patients were first randomized between subcutaneous injections and intranasal spray for GnRH analogue administration and subsequently randomly allocated to receive HMG or recombinant FSH. For the purpose of our meta-analysis, we combined the two GnRH analogue regimens.

The IVF procedure included ICSI in no cycle in the study of Gordon et al.\textsuperscript{29}, 25% of cycles in the study of Westergaard et al.\textsuperscript{32}, 50% of cycles in the study of Serhal et al.\textsuperscript{28}, 64% of cycles in the study of the European and Israeli Study Group\textsuperscript{33}, 63% of cycles in the study of Strehler et al.\textsuperscript{31}, and 100% of cycles of the study of Ng et al.\textsuperscript{30} All studies included the secondary outcomes of administered gonadotropin dose, cancellation rate, OHSS rate, and oocyte retrieval.

The pooled weighted mean difference for administered gonadotropin dose was similar for both gonadotropins ($-28$ IU [95% CI, $-330$ to $275$ IU]). The direction of this effect varied among studies. Pooling the data of the truly randomized trials that used a long protocol resulted in a weighted mean difference of $25$ IU (95% CI, $-40$ to 90 IU) for hMG versus recombinant FSH. Two of these trials had reported median and extreme values and were excluded in a sensitivity analysis to study whether inclusion of the imputed mean
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(±SD) affected the outcome; however, the results remained unchanged (weighted mean difference, 22 IU [95% CI, −44 to 90 IU]).

The cancellation rate varied from 1% to 20% among studies, but the relative differences were small (relative risk, 0.82 [95% CI, 0.56 to 1.20]). Exclusion of the trial that used a short protocol and of the quasi-randomized trial did not affect the results.

No differences in occurrence of OHSS were found. Of the women treated after down-regulation using the long GnRH analogue protocol, 1.5% developed OHSS after hMG use and 1% after recombinant FSH use (relative risk, 1.45 [95% CI, 0.56 to 3.73]).

The pooled weighted mean difference in retrieved oocytes was similar for both gonadotropins (−0.84 oocytes [95% CI, −2.02 to 0.34]). The direction of this effect varied between studies. Pooling only the data of the truly randomized trials that used a long protocol resulted in a weighted mean difference of minus 0.53 oocytes (95% CI, −1.53 to 0.49) for hMG versus recombinant FSH. Two of these trials had reported median and extreme values and were excluded from a sensitivity analysis of whether inclusion of the imputed mean had affected the outcome. Results, however, remained unchanged (weighted mean difference, −0.45 IU [95% CI, −1.59 to 0.69]).

Table 2. The study specific and pooled relative risks for clinical pregnancy per woman

<table>
<thead>
<tr>
<th>Reference</th>
<th>GnRHa Protocol</th>
<th>Clinical pregnancy per woman</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HMG</td>
<td>rFSH</td>
</tr>
<tr>
<td>(28)</td>
<td>Long protocol</td>
<td>37/144</td>
<td>15/94</td>
</tr>
<tr>
<td>(29)</td>
<td>Long protocol</td>
<td>11/29</td>
<td>11/39</td>
</tr>
<tr>
<td>(30)</td>
<td>Long protocol</td>
<td>5/20</td>
<td>4/20</td>
</tr>
<tr>
<td>(32)</td>
<td>Long protocol</td>
<td>75/189</td>
<td>65/190</td>
</tr>
<tr>
<td>(33)</td>
<td>Long protocol</td>
<td>98/373</td>
<td>78/354</td>
</tr>
<tr>
<td><strong>Pooled results for the long protocols</strong></td>
<td>226/755 (30%)</td>
<td>173/697 (25%)</td>
<td>1.22 (1.03-1.44)</td>
</tr>
<tr>
<td>(32)</td>
<td>Short protocol</td>
<td>89/282</td>
<td>78/296</td>
</tr>
<tr>
<td><strong>Pooled results for all GnRHa protocols</strong></td>
<td>306/1037 (30%)</td>
<td>251/993 (25%)</td>
<td>1.18 (1.02-1.36)</td>
</tr>
</tbody>
</table>

Pregnancy outcome measures

Clinical pregnancy rates per woman ranged from 20% to 28% in all studies except both arms in the study of Westergaard et al.32 and the hMG arm in the study of Gordon et al.29, in which clinical pregnancy rates were 10% higher.

Clinical pregnancy rates per woman and per ET were higher with hMG use in all trials. Pooling the five trials that used a long GnRH analogue protocol resulted in a relative risk for
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Clinical pregnancy per woman of 1.22 (95% CI, 1.03 to 1.44). When the quasi-randomized trial was excluded, the pooled relative risk for clinical pregnancy was 1.19 (95% CI, 1.00 to 1.42). When all studies were pooled, including the one study that used a short GnRH analogue protocol, the summary relative risk was 1.18 (95% CI, 1.02 to 1.36). Table 2 shows the study-specific and pooled relative risks for clinical pregnancy per woman.

Four truly randomized trials that used a long GnRH analogue protocol reported ongoing pregnancy rates or live birth rates. Ongoing pregnancy was reported in one trial, and live birth was provided in three trials. Pooling the data resulted in a relative risk for ongoing pregnancy/live birth per woman of 1.20 (95% CI, 0.99 to 1.45).

A miscarriage rate was reported only by the four truly randomized trials that used a long GnRH analogue protocol. The pooled relative risk was 1.15 (95% CI, 0.61 to 2.18) for hMG versus recombinant FSH. Multiple pregnancy was reported by three of the truly randomized trials that used a long protocol, resulting in a relative risk of 1.43 (95% CI, 0.87 to 2.35). When the trial that used a short protocol was included, the relative risk was 1.38 (95% CI, 0.99 to 1.92). Figure 1 summarizes all dichotomous outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>References</th>
<th>hMG</th>
<th>rFSH</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy per woman</td>
<td>(28-33)</td>
<td>306/1037</td>
<td>251/993</td>
<td>1.18 (1.02-1.36)</td>
</tr>
<tr>
<td>Clinical pregnancy per ET</td>
<td>(28-33)</td>
<td>306/934</td>
<td>251/682</td>
<td>1.17 (1.02-1.34)</td>
</tr>
<tr>
<td>Ongoing/delivery per woman</td>
<td>(29,30,32,33)</td>
<td>68/611</td>
<td>139/603</td>
<td>1.20 (0.99-1.45)</td>
</tr>
<tr>
<td>Ongoing/delivery per ET</td>
<td>(29,30,32,33)</td>
<td>168/546</td>
<td>139/533</td>
<td>1.20 (0.99-1.44)</td>
</tr>
<tr>
<td>Miscarriage per woman</td>
<td>(29,30,32,33)</td>
<td>22/189</td>
<td>19/158</td>
<td>0.15 (0.61-2.18)</td>
</tr>
<tr>
<td>Multiple pregnancy per woman</td>
<td>(30-33)</td>
<td>79/269</td>
<td>56/236</td>
<td>1.38 (0.99-1.92)</td>
</tr>
<tr>
<td>Cancellation rate per woman</td>
<td>(28-33)</td>
<td>47/1037</td>
<td>57/993</td>
<td>0.84 (0.57-1.24)</td>
</tr>
<tr>
<td>OHSS rate per woman</td>
<td>(28-31,32,33)</td>
<td>11/755</td>
<td>7/697</td>
<td>1.45 (0.56-3.73)</td>
</tr>
</tbody>
</table>

Figure 1. Summary data of all dichotomous outcomes.
Because implantation is expressed per implanted embryo and not per woman, only rates can be given for this outcome. In the four trials for which data on the implantation rate were available, the treatment direction was in favor of hMG. In these trials, the implantation rate ranged from 12% to 34% in the hMG group and 11% to 27% in the recombinant FSH group.

Discussion

In this systematic review, we selected studies that compared hMG with recombinant FSH in down-regulated ART cycles. Clinical pregnancy rates per woman and per embryo transfer favored hMG in all trials. Our analysis shows a relative increase of 22% in clinical pregnancy rate for women treated with hMG compared with those treated with recombinant FSH (relative risk, 1.22) after down-regulation using a long protocol.

However, evidence was insufficient of a difference between hMG and recombinant FSH in terms of ongoing pregnancy or live birth in women down-regulated by using a long protocol. A sample size of more than 2,184 would be needed to detect a difference in ongoing pregnancy/live birth rate of at least 5 percentage points over a control rate of 20% with a power of .8 at a significance level of .05. In our review, four truly randomized trials that included a total of 1,312 women could be pooled. After the one quasi-randomized trial was included, the sample size was 1,550. More trials are needed to prove a difference in treatment success.

The other secondary outcomes were similar for both gonadotropins. In terms of the incidence of OHSS and miscarriage, hMG and recombinant FSH appear to be equally safe, although more studies are needed to prove this definitively. However, the consistently higher implantation rate after hMG treatment could result in more multiple pregnancies.

As in every systematic review, the possibility of publication bias exists. Studies whose results achieve statistical significance are more likely to be published than are those whose results are nonsignificant. To minimize publication bias, we did not search for trials in peer-reviewed journals only but also included trials presented at international meetings. Furthermore, authors of eligible trials and pharmaceutical companies were asked if they knew of unpublished studies.

Another important matter in meta-analyses is heterogeneity. Heterogeneity between the trials could have been introduced by differences in percentage of ICSI, method of GnRH analogue administration (nasal spray or injection), hMG preparation, and number of previous treatment cycles. Despite probable clinical heterogeneity, we found no sign of statistical
heterogeneity. The quasi-randomized trial was most likely to introduce heterogeneity. This study is likely to overestimate effects because of its lack of allocation concealment. Exclusion of this trial in sensitivity analyses did not change the results.

Within the trials, most baseline characteristics appeared balanced over the treatment groups. An exception was the trial that used a short GnRH analogue protocol, in which randomization resulted in an imbalance in mean number of previous cycles because the hMG group had undergone significantly fewer previous cycles than did the recombinant FSH group. Although the difference was small (mean, 0.77 ± 0.91 in the hMG group versus 1.15 ± 0.93 in the recombinant FSH group) this imbalance could have negatively affected the results in the recombinant FSH group.

We included only trials that used GnRH analogue suppression because pituitary desensitization has become the standard procedure in IVF. We therefore had to exclude one trial that compared hMG and recombinant FSH in cycles without GnRH analogue suppression. Although this trial found no significant difference between treatments, the treatment effect was in favor of recombinant FSH.

Randomized trials comparing urinary FSH and hMG in the long GnRH analogue protocol have shown that severe suppression of mid-follicular serum LH levels (<1 IU/L) occur in a substantial number of normogonadotropic women treated with FSH, resulting in significantly depressed levels of circulating estradiol as well as a poorer outcome of IVF compared with women treated with hMG. This was also found in a retrospective study and in one of the trials in our meta-analysis. Hence, the clinical outcome of IVF/ICSI in normogonadotropic women who undergo the standard long-protocol GnRH analogue down-regulation may be influenced by the levels of circulation LH activity and estradiol production during ovarian stimulation. Taken together, evidence suggests the existence of a subgroup of normogonadotropic women who, when treated with standard long-protocol GnRH analogue down-regulation, may benefit from supplementation with gonadotropin preparations containing LH, hMG, or recombinant LH, during ovarian stimulation.

In the available unpurified HMG preparations, gonadotropins form less than 5% of the total protein content. Thus, during a typical ovarian stimulation cycle with hMG, several milligrams of nonrelevant proteins are administered that can result in unwanted side effects, including allergic or other hypersensitivity reactions. Therefore, the recombinant FSH represents a significant advance in gonadotropin preparations. The supply is potentially unlimited, the substance lacks copurified proteins, and batch-to-batch consistency is excellent. Furthermore, the reduced occurrence of local side effects and the fact that recombinant FSH can be self-injected make it desirable for clinical use. Most of these advantages, however, also apply to highly purified hMG products with batch-to-batch
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consistency. Highly purified hMG contains exactly 75 IU of both FSH and LH and can be self-administered subcutaneously.

In our meta-analysis, hMG resulted in more clinical pregnancies per woman than did recombinant FSH in IVF or ICSI cycles after down-regulation in a long protocol. However, evidence was insufficient of a difference in ongoing pregnancy or live birth rates. More large randomized trials are needed to more precisely estimate the difference in outcome between hMG and recombinant FSH. Such trials should preferably use a consistent long GnRH analogue protocol and a fixed dose of gonadotropin to prevent subjective decisions of the clinician in dosing and should use live birth as primary end point.
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References


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