Recombinant FSH in alternative doses or versus urinary gonadotrophins for ovulation induction in subfertility associated with polycystic ovary syndrome: a systematic review based on a Cochrane review

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This systematic review was performed to study the efficacy and safety of recombinant FSH (rFSH) versus urinary FSH (uFSH) and to compare different dose regimens of rFSH for ovulation induction in women with clomiphene-resistant polycystic ovary syndrome (PCOS). Six randomized controlled trials were included in the review, according to the principles of the Cochrane Menstrual Disorders and Subfertility Group. Three trials compared rFSH with uFSH and three trials compared two different treatment regimens of rFSH. Participants were women with clomiphene citrate-resistant PCOS. Main outcome measures were ovulation, clinical pregnancy, miscarriage, multiple pregnancy, ovarian stimulation syndrome (OSS), total gonadotrophin dose used and total duration of stimulation. Summary statistics were expressed as odds ratios. Data from the trials comparing rFSH and uFSH could be pooled. There was no evidence of a difference between rFSH and uFSH in any of the outcomes. Data from the trials comparing different dose regimens of rFSH could not be combined, and for each comparison there was insufficient evidence of a difference. More randomized clinical trials with sufficient power are necessary to estimate the difference, if one exists, between rFSH and uFSH and between different dose regimens of rFSH.

Key words: Cochrane review/ovulation induction/PCOS/rFSH/uFSH

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of female anovulatory infertility. To induce ovulation, clomiphene citrate (CC) is the first line of treatment. However, about 20% of women are resistant to CC and require gonadotrophin therapy (Hull, 1987). Since 1958 these women have been treated with FSH, originally extracted from pituitary glands (Gemzell et al., 1958) and later extracted from post-menopausal urine (Lunenfeld et al., 1960).

Over the last four decades, various urinary FSH (uFSH) products have been developed. Menotropin (HMGs), available since the early 1960s, contains FSH, LH and large quantities of potentially allergenic urinary proteins. Urofollitropin (FSH), available since the mid-1980s, is devoid of LH, but is still contaminated with urinary proteins. Highly purified Urofollitropin (FSH-HP), available since the mid-1990s, contains very small amounts of urinary proteins. Lack of urinary proteins diminishes adverse reactions such as local allergy or hypersensitivity (Biffoni et al., 1994; Albano et al., 1996), while the absence of LH has no negative influence on stimulation of PCOS patients (van Weissenbruch et al., 1993; Hayden et al., 1999).

To obtain higher purity, complete absence of LH and co-purified proteins, high specific bioactivity (roughly 100 times higher than for urine-derived FSH products), independence of urine collection, absolute source control and batch-to-batch consistency, recombinant FSH (rFSH) was synthesized in 1988. This was realized by transflecting Chinese hamster ovary cell lines with both FSH subunit genes (Howles, 1996; Keene et al., 1989).

At present, two preparations of rFSH are available: follitropin alpha (Gonal F®), marketed in 1995, and followed by follitropin beta (Puregon®) soon after. Both preparations are similar to pituitary FSH and uFSH, although they show minor
differences in the structure of the carbohydrate side chains and contain more basic and less acidic isohormones than the natural hormones (Hard et al., 1990; de Leeuw et al., 1996).

Ovulation induction with FSH bears the risk of multiple follicle development, multiple pregnancies and ovarian stimulation syndrome (OSS) (Wang and Gemzell, 1980; Garceca et al., 1985; Neyro et al., 1991). To reduce these complications, various dose regimen strategies have been used (Brown et al., 1969; Lunenfeld and Insler, 1974; Hamilton-Fairley et al., 1991; Shoham et al., 1991; Fauser et al., 1993; Balen et al., 1994).

At present, the most frequently used administration schedules are the low dose step-up and step-down regimens. For uFSH it was shown that a low dose step-up protocol has the advantage of a more controlled stimulation, resulting in less development of multiple follicles and therefore a decreased risk of OSS and multiple pregnancies (Homburg and Howles, 1999).

In a previous Cochrane review the effectiveness of urinary gonadotrophins in PCOS was studied (Hughes et al., 2000; Nugent et al., 2000). Urinary-derived FSH preparations did not improve pregnancy rates when compared with traditional and less expensive HMG preparations. However, the use of uFSH did result in a reduced risk of OSS.

The objective of this review was twofold. First, to assess the efficacy and safety of rFSH for ovulation induction in women with PCOS as compared with uFSH, and secondly, to assess the efficacy and safety of different dose regimens of rFSH.

Materials and methods

This paper is based on a Cochrane review published in The Cochrane Library 2001, Issue 2 (see www.CochraneLibrary.net for information). The review has drawn on the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group as a whole. Relevant trials were identified from the Trial Register of the Review Group and the electronic databases MEDLINE and EMBASE were searched. The following keywords were used: polycystic ovary syndrome, oligomenorrhea, oligo-amenorrhea, amenorrhea, ovulation, ovulation induction, recombinant FSH and FSH.

Hand-searching of the references mentioned in the included trials was performed and citation lists of eligible studies, conference abstracts and relevant review articles were examined as well. Serono Benelux BV and NV Organon, the manufacturers of follitropin alpha (Gonal Fâ®) and follitropin beta (Puregonâ®) respectively, were asked for ongoing studies and unpublished data.

Only truly randomized controlled trials comparing rFSH and uFSH or different treatment modalities of rFSH for ovulation induction in women with PCOS, and specifying at least the clinical pregnancy rate per woman, were eligible for this review.

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. As this outcome was not evaluated in all eligible trials, clinical pregnancy rate per woman was chosen as primary outcome. Secondary outcomes included ovulation rate per cycle and ongoing pregnancy rate, live birth, miscarriage rate, incidence of OSS, incidence of multiple pregnancy, total gonadotrophin dose, total duration of stimulation, single follicle development and cancellation rate per woman.

The selection of trials for inclusion in the review was performed independently by two reviewers (M.v.W. and N.B.) after employing the search strategy described previously. The search strategy yielded six randomized controlled trials eligible for inclusion. Included studies were assessed independently for predefined quality criteria and methodological details (Table I).

Two reviewers (M.v.W. and N.B.) independently extracted the data. All data were entered into the Review Manager (RevMan 4.0.4) computer software (Update Software, Oxford, UK) and double-checked for accuracy. When crossover studies were identified, only data from the pre-crossover period were included in the review.

Additional information on trial data was sought by contacting the corresponding author when data were in a form unsuitable for meta-analysis. Statistical analysis was performed in accordance with the guidelines developed by the Cochrane Menstrual Disorders and Subfertility Group (1999). For dichotomous data, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each individual trial using the Peto modification of the Mantel–Haenszel method (Peto, 1987). For continuous data the weighted mean difference (WMD) was calculated. When median and range were given instead of mean and 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. In the absence of heterogeneity of treatment effect among trials, which was tested using the Breslow–Day χ2-test, the data were pooled. For pooled dichotomous data an overall combined OR with 95% CIs was calculated using the Peto method and for continuous data a WMD with 95% CIs was calculated using the inverse variance method. Negative values in WMD indicate a benefit of rFSH over uFSH.

Results

This review identified six trials that met the inclusion criteria (Lounaye et al., 1996; Coelingh Bennink et al., 1998; Hedon et al., 1998; Yarali et al., 1999; Balasch et al., 2000; 2001). Three trials with a total of 457 women compared rFSH with uFSH (Lounaye et al., 1996; Coelingh Bennink et al., 1998; Yarali et al., 1999). A further three trials compared different treatment regimens using rFSH. The number of included patients in these trials were 103 (Hedon et al., 1998), 15 (Balasch et al., 2000) and 26 (Balasch et al., 2001). All trials were fully published in peer-reviewed journals except for one study (Lounaye et al., 1996), which was described in a review on human gonadotrophins produced by recombinant DNA technology. Additional data on this trial were obtained by personal communication (E.Lounaye).

The participants in all six trials were CC-resistant, anovulatory women. CC resistance was generally defined as failure to ovulate on doses of CC up to 150 or 200 mg/day, or failure to conceive with the ovulatory dose of CC during three to six previous cycles (Coelingh Bennink et al., 1998; Yarali et al., 1999; Balasch et al., 2000; 2001). Two trials did not give a definition of CC resistance (Lounaye et al., 1996; Hedon et al., 1998). A detailed description of the six trials included in this review is given in Table I.

All six trials included were randomized controlled studies. Three were single centre (Yarali et al., 1999; Balasch et al., 2000; 2001) and the other three were multicentre studies (Lounaye et al., 1996; Coelingh Bennink et al., 1998; Hedon et al., 1998). Three studies used a randomization list that
### Table I. Details of the six trials included in the review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial characteristics</th>
<th>Baseline characteristics</th>
<th>Interventions</th>
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<tbody>
<tr>
<td>Cooling et al.</td>
<td>Randomized, assessor-blind, multicentre study, Randomization list corresponding with medication boxes. Ratio rFSH versus uFSH was 3:2. 172 patients were randomized, six women withdrew before treatment. Trial took place between June 1992 and March 1994 in 12 centres in Europe. No power calculation. Concealment of allocation adequate. Three cycles per woman. Supported by NV Organon, Oss, The Netherlands</td>
<td>CC-resistant, normogonadotropic, chronic anovulatory women. Mean age (±SD) 28.9 (4.2) years for the rFSH and 29.4 (3.9) years for the uFSH group. Body mass index (±SD) was 24.5 (3.4) and 24.3 (3.1) for rFSH and uFSH, respectively. Duration of infertility (±SD) was 3.9 (2.4) years and 4.5 (2.7) years for rFSH and uFSH respectively. Number of subjects with primary infertility was 55 (55%) for the rFSH and 51 (76%) for the uFSH group. Number of women with LH:FSH ratio &gt;2 were 35 (33%) and 19 (28%) for rFSH and uFSH, respectively.</td>
<td>rFSH (Puregon®) versus uFSH (Metrodin®). Treatment was started within 5 days after a spontaneous or induced menses. Starting dose was 75 IU FSH/day, i.m., up to 14 days in the first treatment cycle. If no follicle of &gt;12 mm or a significant rise in serum E2 levels was seen the dose was increased by half an ampoule every week to a maximum of three ampoules of 75 IU/day. Treatment was discontinued after 6 weeks. In the 2nd and 3rd cycle the dose was increased after 1 week of treatment if needed. HCG (10 000 IU, Pregnyl) was given when one follicle of &gt;18 mm or 2–3 follicles of &gt;15 mm were seen.</td>
</tr>
<tr>
<td>Bennink et al.</td>
<td>Randomized multicentre study. Randomization list corresponding with medication codes. Ratio rFSH versus uFSH was 1:1. 222 patients were randomized, nine women withdrew before treatment. Trial took place between 1992 and 1994. Sample size calculated with 90% power to detect a difference of 20% in cumulative ovulation rate using a two-sided test with alpha = 0.05. Concealment of allocation adequate. Three cycles per woman. Supported by NV Organon, Oss, The Netherlands</td>
<td>CC-resistant WHO Group II anovulatory women. Mean age, BMI, duration and type of infertility unknown.</td>
<td></td>
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<tr>
<td>Loumaye et al.</td>
<td>Randomized, multinational European study. Allocation using sealed opaque envelopes. Ratio rFSH versus uFSH was 1:1. 222 patients were randomized, nine women withdrew before treatment. Trial took place between 1992 and 1994. Sample size calculated with 90% power to detect a difference of 20% in cumulative ovulation rate using a two-sided test with alpha = 0.05. Concealment of allocation adequate. Three cycles per woman</td>
<td>Infertile women with WHO II group anovulation, resistant to CC. Mean age (±SD) of the women was 27.8 (4.8) years for the uFSH and 30.0 (5.8) years for the rFSH group. Body mass index (±SD) was 27.1 (5.5) and 27.1 (3.7) for rFSH and uFSH, respectively. Duration of infertility (±SD) was 7.0 (5.6) years and 9.0 (4.2) years for rFSH and uFSH, respectively. LH:FSH ratio was 2.4:1.3 for the uFSH and 3.4:5.5 for the rFSH group, Testosterone level (±SD) (ng/ml) was 0.9 (0.4) and 0.97 (0.9) for rFSH and uFSH, respectively.</td>
<td>rsFSH (Gonal-F®) versus urinary FSH (Metrodin®). Treatment was started within 5 days after a spontaneous or induced menses. No further details could be obtained.</td>
</tr>
<tr>
<td>Yarali et al.</td>
<td>Randomized, single-centre study. Allocation using randomization list corresponding with patient drug codes. Ratio rFSH versus uFSH was 1:2. 51 patients were randomized, no information on withdrawals. Duration and timing of trial unknown. No power calculation. Concealment of allocation adequate. Three cycles per woman. No intention-to-treat analysis was performed. Source of funding not stated.</td>
<td>Infertile women with WHO II group anovulation, resistant to CC. Mean age (±SD) of the women was 27.8 (4.8) years for the uFSH and 30.0 (5.8) years for the rFSH group. Body mass index (±SD) was 27.1 (5.5) and 27.1 (3.7) for rFSH and uFSH, respectively. Duration of infertility (±SD) was 7.0 (5.6) years and 9.0 (4.2) years for rFSH and uFSH, respectively. LH:FSH ratio was 2.4:1.3 for the uFSH and 3.4:5.5 for the rFSH group, Testosterone level (±SD) (ng/ml) was 0.9 (0.4) and 0.97 (0.9) for rFSH and uFSH, respectively.</td>
<td>uFSH (Metrodin®) versus rFSH (Gonal F®). Treatment was started between day 3 and day 5 of a spontaneous or induced menses. Low dose step-up protocol was used. Starting dose was 75 IU uFSH (i.m./day) or rFSH (0.5 IU/day) up to 14 days, unless follicle maturity was reached. If no ovarian response was noted the dose was increased by half an ampoule every week to a maximum of 225 IU/day. Treatment was discontinued after 35 days of treatment. HCG (10 000 IU, Profasi) was given when a follicle of at least 17 mm was seen.</td>
</tr>
<tr>
<td>Hedon et al.</td>
<td>Randomized multicentre trial. Randomization by computer-generated random assignment schedule for each centre. Ratio rFSH versus uFSH was 1:1. 103 patients randomized. Trial took place between January and October 1996 in six French reproductive medicine centres. No sample size with power calculation was performed. Concealment of allocation adequate. One cycle per woman. No intention-to-treat analysis was performed. Source of funding not stated.</td>
<td>CC-resistant WHO Group II anovulatory women. Mean age (±SD) of the patients was 29.4 (4.3) years in the chronic low dose and 29.7 (4.0) years in the conventional group. Body mass index (±SD) was 22.6 (4.7) and 22.7 (3.7) for chronic low dose and conventional respectively. Duration of infertility (±SD) was 3.4 (1.9) years in the chronic low dose and 2.9 (1.5) years in the conventional group. Primary infertility was 73.6 and 74%, respectively. Infertility work up consisted endocrinology (LH, FSH, progesterone), hysterosalpingography, or hysterosalpingoscopy and semen analysis.</td>
<td>Chronic low dose versus conventional stimulation of rFSH (Gonal-F®). Treatment started between day 3 and day 5 of an induced or spontaneous menses. Starting dose was 75 IU rFSH (s.c./day) up to 14 days. Chronic low dose protocol: the starting dose was maintained up to 14 days unless follicle maturity was reached. If no ovarian response was noted after this period the dose was increased with 37.5 IU/day weekly. Conventional protocol: the starting dose was increased 75 IU every 5 days from day 7 of stimulation depending on ovarian response. Treatment was discontinued after 35 days of treatment or if the patient was at risk of OSS. HCG (5000 IU, Profasi) was given when a follicle of 16 mm developed.</td>
</tr>
<tr>
<td>Balasch et al.</td>
<td>Randomized crossover study, method of randomization not stated. Duration and timing not stated. Single centre study. No sample size with power calculation was performed. 26 patients randomized. Allocation concealment unclear. One pre- and one post-crossover cycle/patient. No intention-to-treat analysis performed. Source of funding not stated.</td>
<td>CC-resistant, chronic anovulatory patients with polycystic ovaries on ultrasound scan. Baseline characteristics for whole group only. Mean age (±SD) of the patients was 34.1 (0.9) years. Body mass index (±SE) was 24.6 (0.5). Duration of infertility (±SE) was 4.4 (1.3) years. Number of subjects with primary infertility was not given. The mean (SE) LH/FSH ratio was 2.5 (0.2).</td>
<td>Chronic low dose step-up stimulation with two starting doses of rFSH (Gonal-F® or Puregon®). Treatment was started at day 3 of an induced or spontaneous menses. Starting dose was 37.5 or 75 IU rFSH (s.c./day). The starting dose was maintained up to 14 days, unless follicle maturity was reached. If no ovarian response was noted after this period the dose was increased with 37.5 IU/day and 50 IU, respectively. Further dose adjustments after 7 days if necessary. HCG (10 000 IU, Profasi) was given when a follicle &gt;17 mm developed.</td>
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</table>
corresponded with patient drug codes (Loumaye et al., 1996; Coelingh Bennink et al., 1998; Hedon et al., 1998), one used computerized allocation stratified by centre (Hedon et al., 1998) and for two studies the method of randomization is unknown (Balasch et al., 2000; 2001). Only one study performed a power calculation (Loumaye et al., 1996). None of the other five trials reported a sample size with power calculation. An intention-to-treat analysis was performed only in one trial (Coelingh Bennink et al., 1998). This trial also was assessor-blind, whereas the other three were open-label. Double-blinding should have been possible for the three trials comparing rFSH with uFSH, but this was not done as rFSH was supplied in vials and uFSH in ampoules.

Withdrawals after randomization were mentioned in all trials. In the three trials comparing rFSH with uFSH women were treated for a maximum of three cycles. For these trials no information was present on losses to follow-up after the first cycle. Only three studies gave information on duration and timing of the trial (Coelingh Bennink et al., 1998; Hedon et al., 1998; Yarali et al., 1999). Of the trials comparing different dose regimens, two were crossover trials (Balasch et al., 2000; 2001).

**Outcomes**

Figure 1 summarizes all dichotomous outcomes for rFSH versus uFSH. References are numbered: 1 = Coelingh Bennink et al. (1998), 2 = Yarali et al. (1999) and 3 = Loumaye et al. (1996).

![Figure 1. Summary data of all dichotomous outcomes for rFSH versus uFSH. References are numbered: 1 = Coelingh Bennink et al. (1998), 2 = Yarali et al. (1999) and 3 = Loumaye et al. (1996).](image)
ongoing pregnancy, ovulation, miscarriage, OSS, multiple pregnancy and cancellation rate.

Table II summarizes the continuous outcomes for the trials comparing rFSH with uFSH. The weighted means for the total FSH dose used, duration of stimulation and estradiol (E2) level on the day of HCG administration did not differ significantly between rFSH and uFSH. As different measures for number of follicles were used (i.e. 10–12, 10–14 mm) these data could not be pooled and the separate results are not conclusive.

Table II. Summary data of secondary continuous outcomes for rFSH versus uFSH (Coelingh Bennink et al., 1998; Yarali et al., 1999)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>rFSH</th>
<th>uFSH</th>
<th>WMD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation (days)</td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>10.6 (7.1)</td>
<td>102</td>
<td>13.8 (13.4)</td>
</tr>
<tr>
<td>Total dose used (IU)</td>
<td>121</td>
<td>807 (887)</td>
<td>102</td>
<td>1046 (2525)</td>
</tr>
<tr>
<td>E2 level on day of HCG (pg/ml)</td>
<td>121</td>
<td>365 (554)</td>
<td>102</td>
<td>307 (433)</td>
</tr>
</tbody>
</table>

WMD = weighted mean difference.

Table III. Summary data of primary and secondary dichotomous outcomes in comparing different dose regimens

<table>
<thead>
<tr>
<th>CLD vs conventionala (Hedon et al., 1998)</th>
<th>CLD n/N (%)</th>
<th>Conventional n/N (%)</th>
<th>Peto OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation (per cycle)</td>
<td>30/53 (57)</td>
<td>29/50 (85)</td>
<td>0.95</td>
<td>0.43–2.06</td>
</tr>
<tr>
<td>Clinical pregnancy (per woman)</td>
<td>14/53 (26)</td>
<td>9/50 (18)</td>
<td>1.62</td>
<td>0.64–4.07</td>
</tr>
<tr>
<td>Miscarriage (per woman)</td>
<td>1/14 (7.1)</td>
<td>1/9 (11)</td>
<td>0.62</td>
<td>0.03–11.34</td>
</tr>
<tr>
<td>OSS (per woman)</td>
<td>1/53 (1.9)</td>
<td>1/50 (2)</td>
<td>0.94</td>
<td>0.06–15.03</td>
</tr>
<tr>
<td>Multiple pregnancy (per woman)</td>
<td>2/14 (14)</td>
<td>2/9 (22)</td>
<td>0.59</td>
<td>0.07–5.12</td>
</tr>
</tbody>
</table>

CLD starting dose 37.5 versus 50 IU (Balasch et al., 2000)

<table>
<thead>
<tr>
<th>CLD n/N (%)</th>
<th>Conventional n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.5 IU</td>
<td>30/53 (57)</td>
</tr>
<tr>
<td>50 IU</td>
<td>29/50 (85)</td>
</tr>
</tbody>
</table>

Clinical pregnancy (per woman) 0.79 0.12–4.96

Modified step-down versus CLD (Balasch et al., 2001)

<table>
<thead>
<tr>
<th>CLD n/N (%)</th>
<th>Conventional n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step-down</td>
<td>30/53 (57)</td>
</tr>
<tr>
<td>CLD</td>
<td>29/50 (85)</td>
</tr>
</tbody>
</table>

Clinical pregnancy (per woman) 1.90 0.18–19.98

For the three trials that compared different treatment regimes of rFSH no trial results could be combined, as each trial compared a different treatment regime. Table III summarizes the dichotomous outcomes for these trials. One trial compared chronic low dose step-up with conventional rFSH stimulation (Hedon et al., 1998). There was insufficient evidence of a difference in ovulation, clinical pregnancy, live birth, miscarriage, OSS, multiple pregnancy, FSH dose and duration of stimulation for chronic low dose step-up versus conventional.
protocol rFSH stimulation. The OR for clinical pregnancy per woman was 1.62 (95% CI 0.64–4.07) for chronic low dose versus conventional rFSH stimulation. However, in women treated with a chronic low dose, this trial found significantly less follicles >10 mm and a lower level of E₂ on the day of HCG administration compared with women treated with the conventional regimen (Table IV).

Another trial (Balasch et al., 2001) compared a modified step-down with a chronic low dose step-up protocol for rFSH stimulation. Pre-crossover data could only be recovered for ovulation and clinical pregnancy. All women ovulated in the first cycle before actual crossover. The OR for clinical pregnancy per woman was 1.9 (95% CI 0.18–19.98) for the modified step-down versus chronic low dose step-up protocol.

The third trial (Balasch et al., 2000) compared a starting dose of 37.5 IU with 50 IU in a chronic low dose step-up protocol for rFSH stimulation. Pre-crossover data could only be recovered for ovulation and clinical pregnancy. All women ovulated in the first cycle before actual crossover. The OR for clinical pregnancy per woman was 0.79 (95% CI 0.12–4.96) for 37.5 versus 50 IU.

Discussion
In this systematic review of randomized controlled trials there was no evidence of a difference in efficacy and safety between rFSH and uFSH. Gonadotrophins used in these studies were follicitropin beta (Puregon®) versus Urofollitropin (Metrodin®); Coelingh Bennink et al., 1998; and follicitropin alpha (Gonal F®) versus Urofollitropin (Metrodin®); Loumaye et al., 1996; Yarali et al., 1999). Pooling the data from these three studies was only possible for pregnancy rate (OR 0.95, 95% CI 0.64–1.41), multiple pregnancy rate (OR 0.44, 95% CI 0.16–1.21), miscarriage rate (OR 1.26, 95% CI 0.59–2.70) and OSS (OR 1.55, 95% CI 0.50–4.84). For the following outcomes only two studies (Coelingh Bennink et al., 1998; Yarali et al., 1999) could be pooled: ovulation rate per cycle (OR 1.19, 95% CI 0.78–1.80), mean total FSH dose (IU) used (WMD = −171, 95% CI −650, 308), mean duration of stimulation (WMD = −1.99 days, 95% CI −4.51, 0.54) and mean E₂ level used on day of HCG administration (WMD = −9.1, 95% CI −110.6, 92.5). All trials comparing rFSH with uFSH used a chronic low dose scheme.

Another trial compared chronic low dose with a conventional regimen using follicitropin alfa (Gonal F®) (Hedon et al., 1998). In this comparison a difference in favour of chronic low dose regimen was found for clinical pregnancy rate (OR 1.62, 95% CI 0.64–4.07), miscarriage rate (OR 0.62, 95% CI 0.03–11.34) and multiple pregnancy rate (OR 0.59, 95% CI 0.07–5.12), although these differences did not reach statistical significance, which might be because of the fact that these results are based upon a small population size of 103 women. Ovulation rate was similar (OR 0.95, 95% CI 0.43–2.06) in both groups.

This stimulation regimen with a low starting dose and small stepwise increments in dosage has been introduced to prevent the development of multiple follicles and therefore of multiple pregnancies and OSS. Indeed, in women treated with a chronic low dose, significantly less follicles >10 mm and a lower level of E₂ on the day of HCG administration were found compared with women treated with the conventional regimen (Hedon et al., 1998). Similar findings were observed in a review that included 11 studies comparing chronic low dose with conventional regimens of uFSH (Homburg and Howles, 1999). Therefore, chronic low dose regimens appear to be preferable above the conventional regimens for both uFSH and rFSH.

The two further trials that compared, respectively, a modified step-down with a chronic low dose step-up protocol and two starting doses of rFSH in a chronic low dose step-up protocol were very small crossover studies that do not permit any conclusions to be drawn (Balasch et al., 2000; 2001).

When comparing the effectiveness of rFSH and uFSH the bioactivity of these gonadotrophins is of interest. The glycoform distribution of rFSH is most basic. In that sense, Urofollitropin resembles FSH more closely than highly purified Urofollitropin, as the last is more acidic (Lambert et al., 1995). The more basic preparations would have a higher biopotency (Lambert et al., 1995).

Several parameters are commonly used as indicators for the bioactivity of FSH: number of follicles >12 mm, E₂ level on the day of hCG administration, total dose of FSH required to induce follicular development and the duration of stimulation. Indeed, one of the included studies found significantly more follicles in the range of 12–14 mm in the rFSH group, although this was not found for follicles >15 mm (Coelingh Bennink et al., 1998). Furthermore, rFSH required a significantly shorter treatment period to induce ovulation in the first cycle. There was no proof of a difference in mean E₂ level and total dose required between rFSH and uFSH. One other trial also studied the indicators for bioactivity mentioned above (Yarali et al., 1999). This trial, however, found no difference in number of follicles in the range of 10–14 mm, but did find significantly less follicles >14 mm in the rFSH group. No differences were observed in E₂ level, total FSH dose and treatment period required to induce ovulation. Based on these two studies it therefore cannot be determined whether rFSH has a higher bioactivity than uFSH in ovulation induction.

In ovulation induction the main goal is to achieve maturation and ovulation of a minimal number of follicles, preferable one, to obtain a singleton pregnancy without OSS. A higher bioactivity of rFSH in ovulation induction is therefore only beneficial when this is translated into a lower total dose and a shorter duration of stimulation.

If the use of rFSH would lead to a low dosage requirement and short stimulation duration in ovulation induction, it is still questionable whether rFSH is also more cost effective, as rFSH is more expensive than uFSH. In summary, there is as yet insufficient evidence to conclude that rFSH is more effective than uFSH for ovulation induction in women with CC-resistant PCOS. More randomized clinical trials with sufficient power are necessary to estimate the difference between hMG and rFSH, if one exists. Evaluations of the outcomes should relate to efficacy parameters, as well as to adverse effects and cost-effectiveness analyses.
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Note
Cochrane reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and The Cochrane Library should be consulted for the most recent version of the review. The results of a Cochrane Review can be interpreted differently, depending on people’s perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of review authors, and are not necessarily shared by the Cochrane Collaboration.

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