Recombinant versus urinary gonadotrophins for triggering ovulation in assisted conception

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This paper is based on a Cochrane review ‘Recombinant versus urinary human chorionic gonadotrophin for ovulation induction in assisted conception’. The Cochrane Database of Systematic Reviews 2005 Issue 2 Art No CD003719 DOI 10.1002/14651858 CD003719. pub 2 (see www.CochraneLibrary.net for information) with permission from the Cochrane Collaboration - John Wiley and Sons. 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.

BACKGROUND: The objective of this systematic review was to assess the safety and efficacy of subcutaneous recombinant (r) HCG and high-dose rLH compared with intramuscular urinary (u) uHCG for inducing final oocyte maturation and triggering ovulation. METHODS: We searched the Cochrane Menstrual Disorders and Subfertility Group trials register (August 27, 2003), the Cochrane Central Register of Controlled Trials (CENTRAL on The Cochrane Library, issue 4, 2003), MEDLINE (1966 to February 2004) and EMBASE (1980 to February 2004). Searches were not limited by language. The bibliographies of included and excluded trials and abstracts of major meetings were searched for additional trials. Authors and pharmaceutical companies were contacted for missing and unpublished data. Only truly randomized controlled trials (RCTs) were included. Assessment of inclusion/exclusion, quality assessment and data extraction were performed independently by at least two reviewers. RESULTS: Seven RCTs were identified, four comparing rHCG and uHCG and three comparing rhLH and uHCG. There was no statistically significant difference between rHCG and uHCG regarding the ongoing pregnancy/live birth rate [odds ratio (OR) 0.98; 95% confidence interval (CI) 0.69–1.39], clinical pregnancy rate, miscarriage rate or incidence of ovarian hyperstimulation syndrome (OHSS). There was no statistically significant difference between rhLH and uHCG regarding the ongoing pregnancy/live birth rate (OR 0.94; 95% CI 0.50–1.76), pregnancy rate, miscarriage rate or incidence of OHSS, rHCG was associated with a reduction in the incidence of local site reactions (OR 0.47; 95% CI 0.32–0.70). CONCLUSIONS: According to these data, there is no evidence of a difference in clinical outcomes between urinary and recombinant gonadotrophins used for induction of final follicular maturation. Additional factors should be considered when choosing gonadotrophin type, including safety, cost and drug availability.

Key words: assisted conception/ovulation/randomized controlled trials/recombinant gonadotrophins/urinary gonadotrophins

Introduction

LH surge is essential in the final stages of follicular maturation for triggering follicle rupture, expelling the oocyte from the follicle and leading to its capture by the Fallopian tube. In addition, the LH surge promotes luteinization, forming an active corpus luteum. These effects of LH are essential for conception to occur.

In assisted conception, urinary (u) HCG has been used for several years to mimic the endogenous LH surge as there are considerable structural similarities between HCG and human (h) LH, and hence both hormones stimulate the same receptor (Pierce and Parsons, 1981). HCG is readily available in the urine of pregnant women, whereas only low concentrations of LH are found in the urine of post-menopausal women.

Urinary preparations, however, are associated with a number of disadvantages, including an uncontrolled source, lack of purity and batch-to-batch variation in activity leading to variable clinical results (Zegers-Hochschild et al., 1996). In addition, administration of HCG will lead to a higher and more prolonged biological signal than one induced by natural LH. Evidence suggests that this could be a possible contributing factor to the development of ovarian hyperstimulation syndrome (OHSS) (Emperaire and Ruffie, 1991), which is a potentially lethal condition when severe (Aboulghar et al., 1990; 1998).

Recombinant (r) HCG and rLH preparations are derived from genetically engineered Chinese hamster ovary cells through recombinant DNA technology. The production
Materials and methods

Types of studies
Only randomized controlled trials (RCTs) comparing rHCG or rLH preparation with uHCG for inducing final follicular maturation and early luteinization in patients undergoing assisted conception were included. The method of randomization and allocation concealment were considered.

Types of participants
Subfertile couples undergoing triggering of ovulation as part of an assisted reproductive cycle using either rHCG or rLH preparation versus uHCG in the protocol of ovulation induction.

Types of interventions
rHCG or rLH preparation versus uHCG for triggering of ovulation. Dose, route and schedule of rHCG and uHCG injected were considered.

Types of outcome measures
Primary outcomes. (i) Ongoing pregnancy rate/live birth rate (per woman or per couple). If live birth rates were not reported then ongoing pregnancy rate per woman or per couple was used. (ii) Pregnancy rate per woman or per couple. Pregnancy is defined by fetal heart activity on ultrasound assessment and trophoblastic tissue on pathologic exam at time of miscarriage or surgery for ectopic pregnancy. (iii) Incidence of OHSS and women who experienced cancelled cycles as a result of high perceived risk of OHSS (as detected in by clinical grading of OHSS, laboratory investigations such as haematocrit, haemoglobin and renal functions, and imaging techniques such as ovarian and abdominal ultrasound and chest X-ray).
Secondary outcomes. (i) Miscarriage rate per woman randomized, (ii) number of oocytes retrieved, (iii) tolerance and (iv) cost-effectiveness.

Search strategy for identification of studies
All reports that described RCTs in which triggering of ovulation was performed with rHCG or rLH versus uHCG were obtained using the following search strategy. (i) We searched the Cochrane Menstrual Disorders and Subfertility Review Group specialized register of controlled trials (August 27, 2003). See the Review Group for more details on the make-up of the register. (ii) We searched the Cochrane Central Register of Controlled Trials (Issue 4, 2003) on The Cochrane Library. (iii) We searched MEDLINE (1966 to February 2004) and EMBASE (1980 to February 2004) databases using the following key words and/or MeSH: recombinant human luteinizing hormone, recombinant HCG, choriongonadotropin alfa, Ovidrel, Luveris, LHadi, Profasi, Pregnyl, OHSS, randomized controlled trial, controlled clinical trial, Randomized Controlled Trials, Random allocation, Double-blind method, Single-Blind Method. (iv) We hand searched the reference lists of included studies, review and relevant textbooks. The search was not be restricted to language. (v) Abstracts of the American Society for Reproductive Medicine and European Society for Human Reproduction and Endocrinology meetings we searched. (vi) We contacted pharmaceutical industries in view of possibility of prospective registration of trials. When important information was lacking from the original publications, the authors or pharmaceutical companies were contacted.

Methods of the review
The selection of studies for inclusion in the review together with data extraction were undertaken by two reviewers (H.Al-Inany and R.T.Mansour), with disagreements resolved by a third reviewer (M.A.Aboulghar). The authors were contacted where papers contain insufficient information to make a decision about eligibility.

The quality of all studies eligible for the review was assessed independently by the two reviewers (H.Al-Inany and R.T.Mansour), with discrepancies resolved by discussion with a third reviewer (M.A.Aboulghar).

The checklist used to assess quality of studies included the following.

Section I: internal validity
(i) Was the assigned treatment adequately concealed prior to allocation? (ii) Were the outcomes of patients who withdrew or were excluded after allocation described and included in an ‘intention-to-treat’ analysis? (iii) Were the outcome assessors blind to assignment status? (iv) Were the treatment and control group comparable at entry (descriptive information)? (v) Were the subjects blind to assignment status following allocation? (vi) Were the treatment providers blind to assignment status? (vii) Were the care programmes, other than the trial options, identical? (viii) Were the withdrawals <10% of the study population.

Section II: external validity
(i) Were the inclusion and exclusion criteria for entry clearly defined? (ii) Were the outcome measures used clearly defined? (iii) Were the accuracy, precision and observer variation of the outcome measures adequate [meaning was the confidence interval (CI) mentioned, or can be calculated]? (iv) Was the timing of the outcome measures appropriate (follow-up to ongoing pregnancy/live birth)?

The quality of allocation concealment was graded as either adequate (A), unclear (B), or inadequate (C) following the detailed descriptions of these categories provided by the Menstrual Disorders and Subfertility Review Group. Other
aspects of study quality, including the extent of blinding (if appropriate), whether groups were comparable at baseline, the extent of losses to follow-up, participation levels, whether the outcome assessment standardized and whether an intention-to-treat analysis was undertaken, were also assessed.

For each included trial, information were collected regarding the following quality criteria and methodological details. (Where possible, missing data were sought from the authors.) (i) Method of randomization. (ii) Presence or absence of blinding to treatment allocation. (iii) Number of participants randomized, excluded or lost to follow-up. (iv) Whether an intention-to-treat analysis was done. (v) The presence of a power calculation. (vi) Duration, timing and location of the study. (vii) Study design: parallel or crossover (extract first phase data and treat as a parallel design). (viii) Sources of any funding.

**Characteristics of the study participants**

(i) Definition and duration of pre-existing subfertility in both male and female. (ii) Previously administered treatment(s). (iii) Age of participants, both male and female.

**Interventions used**

(i) Type of treatment used. (ii) Methodology of technique used. (iii) Number of interventions (iv) Number of cycles. (v) Methods of fertilization [intrauterine insemination (IUI), IVF, ICSI].

**Outcomes**

(i) Definition of clinical pregnancy used. (ii) Methods used to assess all outcomes. (iii) The number of started and completed cycles for each treatment modality. (iv) The number of clinical pregnancies (total and ongoing). (v) The number of women with OHSS or women who experienced cancelled cycles as a result of high perceived risk of OHSS. (vi) The number of miscarriages. Miscarriages include all pregnancy losses prior to a gestation of 20 completed weeks, not the reduction of multiples during fetal development.

**Analysis**

Statistical analysis was performed in accordance with the statistical guidelines developed by the Cochrane Menstrual Disorders and Subfertility Group. The heterogeneity of the studies was identified by inspecting the scatter in the data points and the overlap in the CIs and more formally by checking the results of the $\chi^2$-test. Where possible, results of trials were pooled.

For dichotomous data, $2 \times 2$ tables were be generated for each trial and expressed as an odds ratio (OR) with 95% CI. These data were combined for meta-analysis with RevMan software, using the Peto-modified Mantel–Haenszel method and a fixed effects model. Any continuous data were combined for meta-analysis with RevMan software using the weighted mean difference (WMD) with 95% CI and a fixed effects model.

In the graphical display of the meta-analyses, rHCG is considered the experimental treatment. An increase in the odds of outcome with rHCG is displayed graphically to the right of the centre line. For an outcome such as pregnancy, an increase in odds is considered a benefit of intervention, and thus a benefit would be displayed to the right of the centre line. For an outcome such as OHSS, an increase in the odds is a detrimental effect of the intervention and thus a detriment would be displayed to the right of the centre line. This should be noted when the summary graphs are viewed for the assessment of the relative beneficial and detrimental effects of each intervention.

It was planned to undertake sensitivity analyses if there were more than 10 trials included in the review to examine the stability of the results in relation to differences in methodological quality (inclusion of all trials compared with trials of high quality only); however, our review did not meet this criteria.

**Characteristics of excluded studies**

Fifteen studies that used rHCG or rLH for triggering ovulation, were identified and critically appraised.

**Included studies**

Eight studies were excluded from the analysis as they did not meet our inclusion criteria (Emperaire, 1994; Antoine et al., 1997; Zelinski-Wooten et al., 1997; Penarrubia et al., 1999; Balasch and Fabregues, 2003; Hreinsson et al., 2003; Litmann and Milki, 2003; Ludwig et al., 2003). The reasons for excluding these studies are described in Table I.

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<th>Study</th>
<th>Reason for exclusion</th>
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<tr>
<td>Antoine et al. (1997)</td>
<td>Not RCT</td>
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<td>Balasch and Fabregues (2003)</td>
<td>Case report (not RCT)</td>
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<td>Emperaire (1994)</td>
<td>Not RCT</td>
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<tr>
<td>Litmann and Milki (2003)</td>
<td>Used combination of urinary and rHCG (not against each other)</td>
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<tr>
<td>Ludwig et al. (2003)</td>
<td>Review article (not RCT)</td>
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<tr>
<td>Penarrubia et al. (1999)</td>
<td>Not RCT</td>
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<tr>
<td>Zelinski-Wooten et al. (1997)</td>
<td>Animal study</td>
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<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
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<td>Chang et al. (2001)</td>
<td>Multicentre, RCT, open randomization, stratified for each centre, was performed according to a computer-generated list</td>
<td>297 infertile women between 18–38 years, both ovaries present, regular cycles of 25–35 days, either &gt;2 years infertility or had tubal disease, BMI ≤30 kg/m², have undergone no more than one previous ART attempt</td>
<td>Pituitary down-regulation with leuprolide acetate (Lupron) starting 7–8 days post-ovulation at a dose of 1.0 mg daily. Once evidence of down-regulation was documented, Lupron was decreased to 0.5 mg daily (with a maximum of 20 days). Follicular stimulation was initiated with highly purified urinary FSH (3 ampoules or 225 IU daily s.c.). When one follicle had reached a diameter of ≥18 mm, and ≥ others had reached a diameter ≥16 mm, with acceptable serum E₂ concentrations, patients were randomized in the ratio 1:1:1 to receive a single dose of 250 or 500 mg of rHCG s.c. or 10 000 U USP i.m. of uHCG. Patients (only those who fulfilled the criteria for HCG administration) were randomized in groups of six. Oocytes were retrieved 34–38 h after HCG administration. ICSI was not permitted unless failure of fertilization was demonstrated on the day after insemination. No more than three embryos were replaced. Progesterone in oil, 50 mg i.m. daily, was used to provide luteal support. Patients were followed until menses, or until clinical pregnancy was demonstrated by US.</td>
<td>Primary: No. of oocytes retrieved per patient who received HCG Secondary: No. of oocytes retrieved per follicle identified on the day of HCG, No. of 2PN fertilized oocytes, No. of 2PN or cleaved embryos, implantation rate per embryo transferred, S, P and HCG concentrations on the days of oocyte retrieval, embryo transfer, and day 6–7 post-HCG, pregnancy rate, pregnancy outcome, incidence and severity of adverse events, local tolerance at injection sites, pathologic changes in clinical laboratory variables, antibodies to HCG</td>
<td>Financial support by Serono</td>
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<td>Driscoll et al. (2000)</td>
<td>Part of a large multi-trial, RCT, double-blind, double-dummy, phase III, allocation by a computer-generated randomization list</td>
<td>84 women who had undergone pituitary down-regulation and ovulation induction for ICSI or IVF. No systemic diseases. BMI &lt; 30 kg/m². No PCOS. No previous H/O severe OHSS. No medical condition that might interfere with the absorption, distribution, metabolism or the excretion of the drug. No prior or poor response to gonadotrophin</td>
<td>400 µg intra-nasal nafarelin ×2/day from mid-luteal for down-regulation (till E₂ &lt; 180 pmol/l, Pg &lt; 4 nmol/l, LH &lt; 3 IU/l. If failed after 10 days, patient is withdrawn from study. Dose is reduced to 200 µg nafarelin ×2/day with start of OI (rFSH, Gonal-F standard ART protocol). When criteria for HCG are met (largest follicle ≥18 mm diameter; presence of at least two</td>
<td>Primary: No. of oocytes retrieved per patient Secondary: No. of patients with at least 1 oocyte retrieved, No. of oocytes retrieved/No. of follicles aspirated, No. of mature oocytes, No. of normally fertilized oocytes, No. of cleaved embryos, endocrine profile, US endometrial thickness, obstetric outcome, adverse events, local tolerance to injection, OHSS and severity</td>
<td>Sponsored by Ares – Serono</td>
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| ERHCG Group (2000) | Multicentre, RCT, double-blind, double-dummy, allocation by a computer-generated randomization list | 190 premenopausal women, non-pregnant, age 20–38 years, infertility due to: tubal factor, AFS stage I or II endometriosis, severe male factor (ICSI patients), or unexplained infertility. Male with acceptable semen analysis (within last 6 months) or severe male factor (ICSI patients). At least 2 previous ART attempts last at least 2 full menstrual cycles. Regular, spontaneous menstrual cycles of 25–35 days. Acceptable follicular phase serum FSH, LH, PRL and testosterone. BMI ≤ 30 kg/m². Presence of both ovaries and normal uterine cavity. No CC or gonadotrophins in the 2 months. No extrauterine pregnancy in the last 3 months. No previous IVF or GIFT failure due to poor response or failure of fertilization. No PCO. | 400 µg intra-nasal nafarelin × 2/day for 10–25 days for down-regulation (US: no evidence of ovarian activity, endometrial thickness < 10 mm, E₂ > 500 pmol/follicle). When down-regulation is OK, rFSH (Gonal-F) s.c. daily 2–6 × 75 IU ampoules, 150–450 IU/day according to centre practice with max. dose 450 IU/day (or total of 7500 IU). Dose adjusted by US and plasma E₂. When criteria for HCG are met (largest follicle ≥ 18 mm diameter; presence of at least two other follicles with a mean diameter ≥ 16 mm; E₂ > 150 pg/ml, i.e. 540 pmol/ml per follicle) (patient were given either s.c. 250 µg rHCG (vial) plus uHCG placebo (ampoule) or 5000 IU uHCG (ampoule) plus rHCG placebo (vial)). Ovum pickup 34–38 h after HCG administration. Cumulus oophorus maturity was assessed, cumulus removed, oocyte nuclear maturity assessed, IVF done and the numbers of IPN, 2PN and multi-pronucleate eggs on day 1 after retrieval were recorded. On days 2–3, the number of blastomeres, embryo grading and the outcome of each embryo were recorded and up to 3 embryos were replaced. | 400 µg intra-nasal nafarelin × 2/day for 10–25 days for down-regulation (US: no evidence of ovarian activity, endometrial thickness < 10 mm, E₂ > 500 pmol/follicle). When down-regulation is OK, rFSH (Gonal-F) s.c. daily 2–6 × 75 IU ampoules, 150–450 IU/day according to centre practice with max. dose 450 IU/day (or total of 7500 IU). Dose adjusted by US and plasma E₂. When criteria for HCG are met (largest follicle ≥ 18 mm diameter; presence of at least two other follicles with a mean diameter ≥ 16 mm; E₂ > 150 pg/ml, i.e. 540 pmol/ml per follicle) (patient were given either s.c. 250 µg rHCG (vial) plus uHCG placebo (ampoule) or 5000 IU uHCG (ampoule) plus rHCG placebo (vial)). Ovum pickup 34–38 h after HCG administration. Cumulus oophorus maturity was assessed, cumulus removed, oocyte nuclear maturity assessed, IVF done and the numbers of IPN, 2PN and multi-pronucleate eggs on day 1 after retrieval were recorded. On days 2–3, the number of blastomeres, embryo grading and the outcome of each embryo were recorded and up to 3 embryos were replaced. | 400 µg intra-nasal nafarelin × 2/day for 10–25 days for down-regulation (US: no evidence of ovarian activity, endometrial thickness < 10 mm, E₂ > 500 pmol/follicle). When down-regulation is OK, rFSH (Gonal-F) s.c. daily 2–6 × 75 IU ampoules, 150–450 IU/day according to centre practice with max. dose 450 IU/day (or total of 7500 IU). Dose adjusted by US and plasma E₂. When criteria for HCG are met (largest follicle ≥ 18 mm diameter; presence of at least two other follicles with a mean diameter ≥ 16 mm; E₂ > 150 pg/ml, i.e. 540 pmol/ml per follicle) (patient were given either s.c. 250 µg rHCG (vial) plus uHCG placebo (ampoule) or 5000 IU uHCG (ampoule) plus rHCG placebo (vial)). Ovum pickup 34–38 h after HCG administration. Cumulus oophorus maturity was assessed, cumulus removed, oocyte nuclear maturity assessed, IVF done and the numbers of IPN, 2PN and multi-pronucleate eggs on day 1 after retrieval were recorded. On days 2–3, the number of blastomeres, embryo grading and the outcome of each embryo were recorded and up to 3 embryos were replaced. | Supported by Ares-Serono. \n| | | ERHCG or rHCG for triggering ovulation | ERHCG or rHCG for triggering ovulation | ERHCG or rHCG for triggering ovulation | ERHCG or rHCG for triggering ovulation | ERHCG or rHCG for triggering ovulation | ERHCG or rHCG for triggering ovulation | 2065
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<td>ERLH Group (2001)</td>
<td>RCT, Double-blind, randomization by a computer in balanced blocks of four</td>
<td>259 premenopausal women between 18 and 39 years, BMI ≥ 32, have a menstrual cycle lasting between 21 and 35 days, have serum hormone levels of FSH 12 IU/l or less, PRL 1040 mIU/l or less and TSH within the normal range of 0.3–4.1 mIU/l; and show normal results in pretreatment haematology, clinical chemistry or urinalysis parameters. Infertility due to at least one of the following causes: tubal factor, mild endometriosis (AFS classification stage I or II), unexplained (with a history of at least 3 years of infertility, and a postcoital test showing at least one forward progressive sperm/HPF), male factor (only if an oocyte fertilization rate of &gt; 50% had been observed during a previous IVF attempt, or if donor sperm was used), severe male factor (only if ICSI was performed). Both ovaries present. Patients have undergone no more than 3 previous ART cycles. No CC treatment or gonadotropins for at least 1 month before screening, and a normal uterine cavity confirmed by hysteroscopy, or hysterosalpingography or a US scan performed within the past 5 years.</td>
<td>(e.g. neuroleptics) were to be avoided. Patients requiring these medications were only permitted to continue in the trial at the investigator’s discretion. Support with 600 mg Pg pessaries from pick-up day for 3 weeks after diagnosis of pregnancy or till menses. 200 mg/day s.c. self-administered GnRH agonist (Suprefact; Buserelin) for down-regulation starting in the mid-luteal phase (for a minimum of 10 days and a max of 25 days) and continuing until 24 h before rhLH or uHCG. Down-regulation was confirmed by US (no evidence of ovarian activity) and plasma E2 levels (&lt;150 pmol/l or 40 pg/ml). If after 25 days no desensitization, the patient is removed from study. After down-regulation, s.c. rFSH is started and dose is adjusted by US monitoring and E2 levels (max. dose 450 IU/day). FSH dose is reduced or stopped if woman is at risk of developing OHSS. US was performed at least once between days 10 and 25 of pituitary suppression, on the day of rhLH or uHCG administration (day 0), and at least once between days 6 and 9. LH, P4, E2, HCG, inhibin, testosterone and androstenedione were determined once between days 10 and 25 of pituitary suppression (except for HCG), on the day of rhLH or uHCG administration (day 0), and on days 1–3, day 6 or 7, and day 8 or 9. In addition, E2 was also determined on all days the patient came in for US. Anti-FSH and anti-LH antibodies were determined on the first day of rhFSH treatment, and total renin was determined on the day of rhLH or uHCG administration. Serum HCG was also determined on day 15 and 18 or 19. rhLH or uHCG was given in the evening, within 24 h of the last rhFSH and GnRH agonist administration (the largest follicle ≥ 18 mm, at least</td>
<td>Primary: the No. of oocytes retrieved in the different study arms Secondary: follicular and oocyte development, No. of embryos, implantation rate, pregnancy rates, No. of cryopreserved embryos and their fate, the course of different hormone levels</td>
<td>Supported by Serono International</td>
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one other follicle had a mean diameter of 16 mm, and serum E2 levels were within an acceptable range for the number of follicles present. Patients in treatment arms 1, 2 and 3 received an i.m. injection of uHCG (5000 IU or placebo) in the buttock and an s.c. injection of rhLH (either 5000 IU, 15 000 IU, 30 000 IU, or placebo) in the abdomen. Patients in arm 4 received a single i.m. injection of uHCG (5000 IU or placebo) and two s.c. injections of rhLH. The first rhLH injection (15 000 IU or placebo) was given on the same day as HCG, and the second (10 000 IU or placebo) was administered 3 days later. Oocytes were retrieved by regular follicle aspiration 34–38 h after rhLH or uHCG injection. Up to 3 embryos were replaced in the uterine cavity on day 2 or 3 after OPU. Luteal support was done by vaginal pessaries of 200 mg micronized P4 three times a day, starting after oocyte collection and continued up to menstruation or for at least the first 3 weeks of pregnancy if the patient became pregnant.

**Table II. Continued**

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<th>Study</th>
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<tr>
<td>IRHCG Group (2001)</td>
<td>Multicentre, RCT, double-blind, Double-dummy, phase III, method of randomization not stated</td>
<td>198 women-anovulatory or oligo-ovulatory (average cycle length ≥40 days or amenorrhea), aged 20–38 years. Infertility due to ovulatory dysfunction, with spontaneous menses, menses induced by CC, or a positive Pg-induced withdrawal within the previous year, no more than 10 previous cycles of gonadotropins or CC, the last cycle of which ≥2 months before the study. Acceptable hormones within 3 months of start</td>
<td>rhFSH (Gonal-F) was used to induce follicular maturation in a chronic low dose protocol. rhFSH was initiated on days 3–5 of a spontaneous or progesterone/oral contraceptive-induced menstrual bleed, at a starting dose of 75 IU, once daily s.c. The 75 IU dose was maintained for 14 days unless the patient showed a response requiring ovulation to be induced. Ovarian response was monitored by US and serum hormone measurement to ensure follicular growth and maturation.</td>
<td>Primary: ovulation evidenced by midluteal serum Pg ≥ 30 nmol/l (9.4 ng/ml), or a clinical pregnancy regardless of the midluteal phase Pg level</td>
<td>Monitored by Serono CRA Department</td>
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<td>Manau et al. (2002)</td>
<td>RCT, single centre, open, randomization was done according to a computer-generated table, allocation was done using sealed envelopes</td>
<td>30 patients, primary infertility, aged 27 to 37 years, basal FSH concentration of &lt;12 IU/L, no patient had polycystic ovary disease or had undergone more than two previous IVF/ICSI attempts</td>
<td>rhFSH was administered according to a step-down regimen consisting of 450 IU on day 1, 300 IU on day 2, and 150 IU on days 3 and 4. From day 5 onward, rhFSH was administered according to the ovarian response as assessed by transvaginal ultrasonography and serum E2 measurements when two or more follicles were &gt;18 mm in diameter, HCG (5000 IU i.m. in the buttock; Profasi; Serono) or rhLH [5000 IU (250 g) s.c. in the abdomen] was administered.</td>
<td>Primary: No. of oocytes retrieved-haemodynamic changes Secondary: pregnancy, OHSS</td>
<td>Supported by grants from the Fondo de Investigacion Sanitaria</td>
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<tr>
<td>Study 21447</td>
<td>Multicentre, international, RCT, double-blind, double-dummy, allocation by a computer-generated randomization list</td>
<td>190 premenopausal women between 18 and 39 years, have menstrual cycle lasting between 21 and 35 days, have serum hormone levels of FSH 12 IU/l or less, PRL 1040 mIU/l or less, and TSH within the normal range of 0.3–4.1 mIU/l; and show normal results in pretreatment haematology, clinical chemistry or urinalysis parameters. Infertility due to at least one of the following causes: tubal factor, mild endometriosis (AFS classification stage I or II), unexplained (with a history of at least 3 years of infertility, and a postcoital test showing at least one forward progressive sperm/HPF), male factor (only if an oocyte fertilization rate of &gt; 50% had been observed during a previous IVF attempt, or if donor sperm was used), severe male factor (only if ICSI was performed). Both ovaries present. Patients have undergone no more than 3 previous ART cycles. No CC treatment or gonadotropins for at least 1 month before screening, and a normal uterine cavity confirmed by hysteroscopy, or hysterosalpingography or a US scan performed within the past 5 years.</td>
<td>GnRH agonist for down-regulation starting in the mid-luteal phase (for a minimum of 10 days and a max. of 25 days) and continuing until 24h before rhLH or uHCG. Down-regulation was confirmed by US (no evidence of ovarian activity) and plasma E2 levels (&lt; 150 pmol/l or 40 pg/ml). After down-regulation, s.c. rFSH is started and dose is adjusted by US monitoring and E2 levels (max. dose 450 IU/day). FSH dose is reduced or stopped if woman is at risk of developing OHSS. US was performed at least once between days 10 and 25 of pituitary suppression, on the day of rhLH or uHCG administration (day 0), and at least once between days 6 and 9. LH, P4, E2, HCG, testosterone and androstenedione were determined once between days 10 and 25 of pituitary suppression (except for HCG), on the day of rhLH or uHCG administration (day 0), and on days 1–3, day 6 or 7, and day 8 or 9. In addition, E2 was also determined on all days the patient came in for US. Serum HCG was also determined on day 15 and days 18 or 19. rhLH or uHCG was given in the evening, within 24 h of the last rhFSH and GnRH agonist administration (the largest follicle &gt; 18 mm, at least one other follicle had a mean diameter of 16 mm. Patients in treatment arms received either (uHCG or placebo) and the other arm received either (rLH or rHCG or rh versus uHCG for triggering ovulation)</td>
<td>Primary: pregnancy rate/woman Secondary: No. of oocytes., No. of embryos, No. of cryopreserved embryos and their fate</td>
<td>Sponsored by Serono International</td>
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except for Manau et al. (2002), which was supported by grants from the Fondo de Investigaci Sanitaria.

In all trials healthy female partners from subfertile couples were included and the inclusion and exclusion criteria were very similar. Main common inclusion criteria were: age ≥ 18 but ≤ 39 years, regular menstrual cycle ranging from 24 to 35 days and FSH < 12 IU/l during the early follicular phase, with no history of previous OHSS. All trials involved IVF/ICSI cycles except IRHCG Group (2001), which used IUI or timed intercourse.

The categories of infertility usually included tubal disease, endometriosis, unexplained infertility and male factor infertility.

Most trials were multicentre, with the exception of Manau et al. (2002). Six trials used long protocol of GnRH agonist for pituitary down-regulation. GnRH agonist was started in the mid-luteal phase (cycle day 21–24) by either daily intranasal or subcutaneous administration. Ovarian stimulation was started after 2 weeks if pituitary down-regulation was established (serum estradiol level < 50 pg/ml). In both treatment groups, ovarian stimulation was started with a daily dose of 75–450 IU rFSH (Gonal-F; Serono) for the first five stimulation days. Thereafter, the dose of gonadotrophin was adapted depending on the ovarian response as monitored via ultrasonography. rFSH (Gonal-F) was used in all trials. Pituitary down-regulation using long protocol GnRH agonist was done in all except one trial (IRHCG Group, 2001).

Patients were given either 250 μg rHCG or rLH subcutaneously and intramuscular placebo, or 5000 IU uHCG intramuscularly and intramuscular placebo in five trials to ensure blinding (Driscoll et al., 2000; ERHCG Group, 2000; ERLH Group, 2001; IRHCG Group, 2001; Study 21447). The uHCG used was Profasi (Serono). Thirty to thirty-six hours after triggering, oocyte pick-up was performed in all trials except IRHCG Group (2001) (which was focused on ovulation induction). IVF or ICSI was performed in all trials except IRHCG Group (2001), and no more than three embryos were to be replaced 2–5 days thereafter. Luteal phase support was given as per each individual clinic’s routine practice and was started no later than the day of embryo transfer. Pregnancy test was done 18–21 days after HCG if no menstruation, followed by ultrasound on day 42. All trials reported clinical pregnancy rates and ongoing pregnancy/live birth rate were obtained by contacting the authors.

Methodological quality of included studies

Seven trials were included with publication dates ranging from 2000 to 2003. Six trials were published as peer-reviewed papers (Driscoll et al., 2000; ERHCG Group, 2000; Chang et al., 2001; ERLH Group, 2001; IRHCG Group, 2001; Manau et al., 2002). Limited data from the last trial were obtained by contacting the pharmaceutical company (Study 21447).

Trial design

All seven trials were designed as non-inferiority trials to show that the efficacy of recombinant drug is not clinically
inferior to the current care, i.e. urinary gonadotrophins. All trials had a parallel design and six were multicentre trials. All trials provided intention-to-treat analyses. Each couple contributed data from only the first cycle of treatment.

**Randomization, allocation concealment and blinding**

Six trials used a computer-generated randomization list to allocate participants. Randomization was done in blocks of four in one trial (ERLH Group, 2001). In one trial the method of randomization was not stated (IRHCG Group, 2001).

Allocation concealment refers to whether the randomization sequence was adequately concealed until interventions were assigned. In the multicentre trials that used a central computer to generate randomization allocation, concealment appeared to be adequate (Driscoll et al., 2000; ERHCG Group, 2000; Chang et al., 2001; ERLH Group, 2001; Study 21447). In the remaining two trials there was not enough information in the trial to determine whether allocation concealment was adequate. Five trials used double blinding (Driscoll et al., 2000; ERHCG Group, 2000; ERLH Group, 2001; IRHCG Group, 2001; Study 21447); the remaining two were open trials.

None of these trials reported power calculation for equivalence or to detect differences in pregnancy rates. Methodologically sound and adequately powered clinical trials are needed to be able to withdraw firm conclusions, but this usually requires a large number of participants.

**Baseline similarity of groups**

In all trials, healthy female partners from subfertile couples were included and the inclusion and exclusion criteria were very similar. In each trial, the two treatment groups were similar with respect to age, height, weight and body mass index (BMI). Participants of these trials had different types of subfertility (see ‘Included studies’). Heterogeneity between the trials could be introduced by differences between the studies in ICSI use, means of GnRH agonist administration (nasal or by injections) and reason for infertility. However, subgroup analysis to compare the outcomes within the various categories of subfertility was not possible, because such detailed data were not available. There was no indication of co-intervention in any of the trials.

**Results**

Seven trials were identified and included in the review (Driscoll et al., 2000; ERHCG Group, 2000; Chang et al., 2001; ERLH Group, 2001; IRHCG Group, 2001; Study 21447).

**rHCG versus uHCG**

Four trials were included, enrolling 747 participants (Driscoll et al., 2000; ERHCG Group, 2000; Chang et al., 2001; IRHCG Group, 2001).

**Ongoing/delivered pregnancy rate per woman.** Pooling the data of the ongoing pregnancy/live birth rate from the four trials resulted in no statistically significant difference between both drugs (ongoing/delivered pregnancy rate per woman of 24.1% in the rHCG group and 22.8% in the urinary HCG group; OR 0.98; 95% CI 0.69–1.39) (see Figure 1).

**Clinical pregnancy rate per woman.** Pooling the results from the four trials showed no statistically significant difference between both drugs (clinical pregnancy rate of 29.6% in the recombinant group and 29.3% in the urinary group; OR 0.98; 95% CI 0.71–1.36).

**Severe OHSS.** Pooling the results from the four trials showed no statistically significant difference between both drugs regarding the occurrence of severe OHSS (3.3% in the recombinant group versus 1.9 in the urinary group; OR 1.89; 95% CI 0.74–4.82). Use of the dose of 500 μg rHCG resulted in more cases of severe OHSS; 3.4% of women compared with 1.1% in those given 250 μg of rHCG and no cases in those receiving uHCG, although this difference was reported as not statistically significant (P = 0.124, Fisher’s exact test) (Chang et al., 2001).

**Miscarriage rate per clinical pregnancy.** There was no statistically significant difference between both drugs regarding the miscarriage rate (16% in the recombinant group versus 17.4% in the urinary group; OR 1.89; 95% CI 0.74–4.82).
**Number of oocytes retrieved.** There was no statistically significant difference regarding the number of oocytes retrieved (WMD 0.78; 95% CI −0.60 to 2.16).

**Tolerability.** The three, randomized, placebo-controlled, double-blind and double-dummy studies (Driscoll et al., 2000; ERHCG Group, 2000; IRHCG Group, 2001) found a reduction in the incidence of local site reactions in favour of rHCG (OR 0.47; 95% CI 0.32–0.70). One trial recorded 12/44 mild or moderate adverse events (such as pain in the injection site) in the rHCG group compared with 17/40 in the uHCG group (Driscoll et al., 2000) (OR 0.64 95% CI 0.25–1.63). In another trial, 22/97 women receiving rHCG reported adverse events compared with 42/93 in the uHCG group (ERHCG Group, 2000) (OR 0.50; 95% CI 0.26–0.93). Twenty-six out of 85 women receiving rHCG in the IRHCG Group (2001) trial reported at least one adverse event compared with 39/92 in the uHCG group (OR 0.72; 95% CI 0.38–1.33). Chang et al. (2001), an open RCT, reported no difference between both drugs in terms of tolerability of the injections. Adverse events were reported by 46.3%, 57.3% and 38.5% of women in the 250 μg rHCG, 500 μg rHCG and 200 μg uHCG groups, respectively.

**Cost-effectiveness.** This outcome was not reported by any of the included studies.

**rhLH versus uHCG**

Three trials enrolling 472 women were identified (ERLH Group, 2001; Manau et al., 2002; Study 21447). One trial did not report any data that could be pooled with the other trials (Study 21447).

**Ongoing/delivered pregnancy rate per woman.** Pooling the data of the ongoing pregnancy/live birth rate from the two trials with available data resulted in no statistically significant difference between both drugs, with an ongoing/delivered pregnancy rate per woman of 18.6% in the rhLH group and 19.7% in the uHCG group (OR 0.94; 95% CI 0.50–1.76).

One of the studies comparing rhLH and uHCG (Study 21447) reported that pregnancy rates and clinical pregnancy rates were significantly lower in the rhLH group than in the uHCG group (P = 0.018 and P = 0.023, respectively). This information was sent by the pharmaceutical company who was conducting the trial after contacting them for additional data.

**Clinical pregnancy rate per woman.** Pooling the results from the two trials with available data showed no statistically significant difference between both drugs, with clinical pregnancy rate of 24.8% in the rhLH group and 26.3% in the urinary group (OR 0.93; 95% CI 0.53–1.63).

**Severe OHSS.** Pooling the results from the two trials with available data showed no statistically significant difference between both drugs regarding the occurrence of severe OHSS (10.3% in the recombinant group versus 12.4% in the urinary group; OR 0.82; 95% CI 0.39–1.69).

**Miscarriage rate per clinical pregnancy.** There was no statistically significant difference between both drugs regarding the miscarriage rate (24.3% in the recombinant group versus 23.7% in the urinary group; OR 0.82; 95% CI 0.39–1.69).

**Number of oocytes retrieved.** One trial reported a mean number of oocytes retrieved of 11.56 in the rHCG group and 11.44 in the uHCG group (ERLH Group, 2001).

**Tolerability.** Only one trial reported tolerability data (ERLH Group, 2001). The most frequent non-serious adverse events were abdominal enlargement (29 cases), abdominal pain (19 cases), injection site pain (14 cases), diarrhea (10 cases) and nausea (seven cases). Over the course of the trial, 158 events occurred in 77 women treated with rhLH (55%) and 171 events in 77 women treated with uHCG (63.6%) (OR 0.70; 95% CI 0.42–1.16). Three serious adverse events requiring hospitalization (excluding OHSS) occurred in the uHCG treatment group: back pain, missed abortion and an ectopic pregnancy. In the rhLH group six patients experienced serious adverse events requiring hospitalization: retention of fetal placenta, abdominal pain, suspected ovarian torsion, diarrhea (two women) and pre-eclampsia.

**Cost-effectiveness.** This outcome was not reported by any of the included studies.

**Discussion**

In infertile women undergoing ovulation induction, the use of HCGs to achieve final follicular maturation and triggering follicular rupture is well established. uHCG has been used for several years, but recombinant technology allowed for the production of rHCG with high purity and batch-to-batch consistency.

The present systematic review included seven RCTs of high quality with almost similar inclusion and exclusion criteria, similar design and methodology. We included one trial that did not use down-regulation (IRHCG Group, 2001), but this did not affect the homogeneity of the studies.

The patient profiles in the trials included in this systematic review were almost similar and the IVF and ICSI procedures used were standard; moreover, there was no difference in the type of gonadotropin preparation administered. These factors have eliminated heterogeneity to a large extent, as seen in the graphs.

None of the individual trials demonstrated a statistically significant difference in clinical outcomes especially live-birth/ongoing pregnancy rate and OHSS incidence between recombinant and urinary drugs except Study 21447. Pooling the results of these trials showed similar outcome except that local injection site adverse effects were significantly less frequent with rHCG than with uHCG (less than onethird).

Results of the two published trials and the unpublished trial comparing rhLH and uHCG showed no statistically significant difference in clinical outcomes. Owing to the results of the unpublished trial (Study 21447), Serono (the pharmaceutical company producing rhLH) has decided not to register high-dose rLH for clinical use (dose range tested 37.5 μg, 825 IU to 1000 μg, 22 000 IU rHLD). The results of this trial demonstrated to the company that to prevent OHSS, the dose of recombinant drug needed to be increased to a level that resulted in a decrease of pregnancy rate (personal contact with company).
Results of one trial showed that increasing the dose of rHCG (single 500 μg dose of rHCG) may lead to a higher rate of OHSS compared with a 250 μg dose (this difference was not statistically significant), with no significant improvement in pregnancy rate. As both safety and efficacy are required for any medication, the dose of 250 μg seems the dose of choice for triggering ovulation.

The problem of high BMI and response in obese patients to a standard amount of HCG may be an inherent problem of obesity, and there are no data available yet on the use of rHCG in obese patients. It may not be solved by a recombinant product as with uHCG.

**Conclusions**

There is no evidence of a difference in the clinical outcomes of life birth/ongoing pregnancy, pregnancy, miscarriage and OHSS between urinary and recombinant gonadotrophins for induction of final follicular maturation. The dose of 250 μg of rHCG provides the optimal dose of rHCG for final follicular maturation in treatment cycles for timed intercourse and IUI, as well as IVF and IVF/ICSI.

Minor adverse reactions such as skin irritation at injection site were more likely to occur after treatment with the uHCG. Additional factors should be considered when choosing a gonadotrophin type, including cost and drug availability.

**Implications for research**

Cost-effectiveness analysis is needed between urinary and rHCG. The role of rHCG in bringing oocyte maturation should extend to the field of in-vitro maturation in order to avoid the possibility of OHSS in women at risk.

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**Potential conflict of interest**

M.A.A. and H.A.-I. contributed to one of the trials included in this review (Study 21447).

**References**


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