Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 5

Recombinant versus urinary gonadotrophins for triggering ovulation in assisted conception

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Abstract

Objectives: to assess the safety and efficacy of s.c. rHCG and the high dose r-LH compared with i.m. uHCG for inducing final oocyte maturation and triggering ovulation

Methods: Electronic search strategies were developed for the Cochrane Controlled Trials Register (searched to issue 4, 2003), MEDLINE and EMBASE (up to February 2004). Searches were not limited by language. The bibliographies of included, excluded trials and abstracts of major meetings were searched for additional trials. Authors and pharmaceutical companies were contacted for missing and unpublished data. Two reviewers independently scanned titles and abstracts, and selected those that appeared relevant for collection of the full paper. Only truly randomised controlled trials comparing rhCG or high dose r-LH with urinary hCG for triggering ovulation in assisted conception for treatment of infertility in normogonadotrophic women were included. Assessment of inclusion/exclusion, quality assessment and data extraction were performed independently by at least two reviewers. Discrepancies were discussed in the presence of a third reviewer and a consensus reached. Quality assessment included method of randomisation, allocation concealment, blinding of participants and assessors, reporting of a power calculation, intention to treat analysis, and handling of dropouts. Data extraction included characteristics of participants, the intervention and control procedures, and outcomes.

Results: High dose recombinant LH was found to be associated with statistically significant lower pregnancy rate and the manufacturer decided not to further develop it. There was no statistically significant difference between rhCG vs uhCG regarding the ongoing pregnancy/live birth rate or incidence of OHSS. There was no statistically significant difference between both drugs regarding clinical pregnancy rate or miscarriage rate. rhCG was associated with statistically significant reduction in the incidence of local site reactions.

Conclusions: there is no difference in clinical outcomes between urinary and recombinant gonadotrophins for induction of final follicular maturation. Additional factors should be considered when choosing gonadotrophin type, including safety, cost and drug availability.
Introduction

Luteinizing hormone (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 human chorionic gonadotrophin (hCG) has been used for several years to mimic the endogenous LH surge as there are considerable structural similarities between hCG and human LH, and hence both hormones stimulate the same receptor (1). 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 (2). 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 (3) which is a potentially lethal condition when severe (4-5).

Recombinant hCG (rhCG) and recombinant LH (r-LH) preparations are derived from genetically engineered Chinese hamster ovary cell through recombinant DNA technology. The production process begins after growth and expression of the cells from a well-characterized cell bank. The hCG is secreted into the culture medium and harvested over 30 days. The product is purified by repeated chromatographic steps to yield a product with a high specific activity. The high purity of this product facilitates characterization and quantitation by physicochemical means, reducing the need for animal bioassays, and makes the drug suitable for subcutaneous injection and hence self-administration (6). We wish to assess the safety and efficacy of recombinant hCG and recombinant LH compared to urinary hCG (used for more than 25 years) for induction of final follicular maturation and luteinization in women undergoing assisted conception.
Objectives

To investigate the efficacy and safety of recombinant human chorionic gonadotrophin (rhCG) or recombinant LH preparation relative to urinary human chorionic gonadotrophin (uhCG) for inducing final follicular maturation and early luteinization in patients undergoing assisted conception.

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials comparing recombinant human chorionic gonadotrophin or recombinant LH preparation to urinary human chorionic gonadotrophin for inducing final follicular maturation and early luteinization in patients undergoing assisted conception were included. The method of randomisation and allocation concealment were considered.

Types of participants

Subfertile couples undergoing triggering ovulation as part of an assisted reproductive cycle using either recombinant human chorionic gonadotrophin or recombinant LH preparation vs urinary human chorionic gonadotrophin in the protocol of ovulation induction.

Types of interventions

Recombinant human chorionic gonadotrophin (rhCG) or recombinant LH preparation versus urinary human chorionic gonadotrophin (uhCG) for triggering of ovulation. Dose, route and schedule of rhCG and uhCG injected were considered.

Types of outcome measures

Primary outcomes:

- Ongoing pregnancy rate / Live birth rate (per woman or per couple). If live birth rates are not reported then ongoing pregnancy rate per woman or per couple will be used.
- Pregnancy rate per woman or per couple. Pregnancy is defined by:- fetal heart activity on ultrasound assessment - trophoblastic tissue on pathologic exam at time of miscarriage or surgery for ectopic pregnancy.
- Incidence of ovarian hyperstimulation syndrome (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 as haematocrit, haemoglobin, renal functions and imaging techniques as ovarian and abdominal ultrasound and chest X-ray)

**Secondary outcomes**: Miscarriage rate per woman randomised, Number of oocytes retrieved, Tolerance and Cost-effectiveness

**Search strategy for identification of studies**

All reports which described randomised controlled trials in which triggering of ovulation was performed with recombinant human chorionic gonadotrophin or recombinant luteinizing hormone versus urinary human chorionic gonadotrophin were obtained using the following search strategy:- (1) We searched the Cochrane Menstrual Disorders and Subfertility Review Group specialised register of controlled trials (27 August 2003). See the Review Group for more details on the make-up of the register. (2) We searched the Cochrane Central Register of Controlled Trials (Issue 4, 2003) on The Cochrane Library. (3) We searched MEDLINE (1966 to Feb 2004) and EMBASE (1980 to Feb 2004) databases using following key-words and/or MeSH: recombinant human luteinizing hormone, Recombinant hCG, choriogonadotropin alfa, Ovidrel, Luveris, LHadi, Profasi, Pregnyl, OHSS, randomised controlled trial, pt., controlled clinical trial, pt., Randomised Controlled Trials/, Random allocation/, Double-blind method/, Single-Blind Method/

(4) Hand searching the reference lists of included studies, review and relevant textbooks. The search was not be restricted to language. (5) Abstracts of The American Society for Reproductive Medicine and European Society for Human Reproduction and Endocrinology meetings. (6) 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 (Al-Inany H & Mansour R) with disagreements resolved by a third reviewer (Aboulghar M). The authors were contacted where papers contain insufficient information to make a decision about eligibility.
The quality of all studies eligible for the review were assessed independently by the two reviewers (Al-Inany H & Mansour R), with discrepancies resolved by discussion with third reviewer (Aboulghar M).

The checklist used to assess quality of studies included

Section I: Internal Validity (1) Was the assigned treatment adequately concealed prior to allocation? (2) Were the outcomes of patients who withdrew or were excluded after allocation described and included in an "intention to treat" analysis? (3) Were the outcome assessors blind to assignment status? (4) Were the treatment and control group comparable at entry (descriptive information)? (5) Were the subjects blind to assignment status following allocation? (6) Were the treatment providers blind to assignment status? (7) Were the care programmes, other than the trial options, identical? (8) Were the withdrawals <10% of the study population

Section II: External Validity

(1) Were the inclusion and exclusion criteria for entry clearly defined? (2) Were the outcome measures used clearly defined? (3) Were the accuracy, precision, and observer variation of the outcome measures adequate? Meaning that was Confidence interval mentioned or can be calculated (4) 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 standardised, 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.) (1) Method of randomisation. (2) Presence or absence of blinding to treatment allocation. (3) Number of participants randomised, excluded, or lost to follow-up. (4)
Whether an "intention to treat" analysis was done. (5) The presence of a power calculation. (6) Duration, timing and location of the study. (7) Study design: parallel or crossover (extract first phase data and treat as a parallel design) (8) Sources of any funding

**Characteristics of the study participants** (1) Definition and duration of pre-existing subfertility in both male and female (2) Previous administered treatment(s) (3) Age of participants, both male and female

**Interventions used** (1) Type of treatment used. (2) Methodology of technique used. (3) Number of interventions (4) Number of cycles (5) Methods of fertilisation (intrauterine insemination (IUI), in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI)

**Outcomes**
(1) Definition of clinical pregnancy used (2) Methods used to assess all outcomes (3) The number of started and completed cycles for each treatment modality. (4) The number of clinical pregnancies (total and ongoing). (5) The number of women with OHSS or women who experienced cancelled cycles as a result of high perceived risk of OHSS (6) 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 confidence intervals and more formally by checking the results of the chi-squared test. Where possible results of trials were pooled.

For dichotomous data, two by two tables were be generated for each trial and expressed as an odds ratio (OR) with 95% confidence intervals (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, recombinant hCG is considered the experimental treatment. An increase in the odds of outcome with recombinant hCG 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 are more than ten trials included in the review to examine the stability of the results in relation to differences in methodological quality (inclusion of all trials compared to trials of high quality only), however, our review did not meet this criteria

**Description of studies**

Fifteen studies, that used recombinant hCG or recombinant LH for triggering ovulation, were identified and critically appraised.

**Excluded studies**

Eight studies were excluded from the analysis as they did not meet our inclusion criteria (7-14). The reasons for excluding these studies are described in table of "Characteristics of Excluded Studies".

**Included studies**

The seven remaining randomised trials met the inclusion criteria. Publication dates ranged from 2000 to 2003. Six trials were published as peer-reviewed papers (6, 15-19). One study was unpublished (20). The six peer-reviewed papers represent a total of 1027 women seeking assisted reproduction. Details of each study are provided in the table "Characteristics of Included Studies".
Recombinant hCG was used in four trials (6; 15; 16; 18) and recombinant LH was used in three trials (17; 19; 20). Most studies were pharmaceutically supported by the same company (Serono) except (19) 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 at least 18 but not older than 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 OHSS before. All trials involved IVF/ICSI cycles except (18) that used IUI or timed intercourse.

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

Most trials were multicenter, with the exception of (19). Six trials used long protocol of gonadotrophin releasing hormone agonist for pituitary down regulation. GnRH agonist was started in the mid-luteal phase (cycle day 21 to 24) by either daily intranasal or subcutaneous administration. Ovarian stimulation was started after two weeks if pituitary downregulation was established (serum estradiol level <50pg/ml). In both treatment groups, ovarian stimulation was started with a daily dose of 75 -450 IU recFSH (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. Recombinant FSH (Gonal F) was used in all trials. Pituitary down regulation using long protocol of GnRH agonist was done in all except one trial (18).

Patients were given either 250 mcg rHCG or rec LH SC & IM placebo or 5000 IU uHCG IM & SC placebo in five trials to ensure blinding (15-18; 20). The urinary hCG used was Profasi, Serono. Thirty to thirty-six hours after triggering, oocyte pick-up was performed in all trials except (18) (which was focused on ovulation induction). IVF or ICSI in all trials except (18) and no more than three embryos were to be replaced 2 to 5 days thereafter. Luteal-phase support was given per the clinic's routine practice and was started no later than the day of embryo transfer. Pregnancy test was done 18 to 21 days after HCG if no menstruation then ultrasound was done 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 (6; 15-19). Limited data from the last trial were obtained by contacting the pharmaceutical company (20).

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 multi-centre trials. All trials provided intention-to-treat analyses. Each couple contributed data from only the first cycle of treatment.

Randomisation, allocation concealment, and blinding

Six trials used a computer generated randomisation list to allocate participants. Randomisation was done in blocks of four in one trial (17). In one trial the method of randomisation was not stated (18).

Allocation concealment refers to whether the randomisation sequence was adequately concealed until interventions were assigned. In the multicentre trials which used a central computer to generate randomisation allocation concealment appeared to be adequate (6; 15-17; 20). 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 (15-18; 20), 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 require 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 "Description of Studies"). Heterogeneity between the
trials could be introduced by differences between the studies in ICSI use, means of GnRHa administration (nasal or by injections), reason of 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 (6; 15-18; 20).

Recombinant hCG versus urinary hCG: Four trials were included enrolling 747 participants (6; 15-16; 18).

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 recombinant hCG group and 22.8% in the urinary hCG group; OR 0.98, 95% CI 0.69 to 1.39).

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 to 1.36).

Severe ovarian hyperstimulation syndrome: 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 vs 1.9 in the urinary group; OR 1.89, 95% CI 0.74 to 4.82). Use of the dose of 500 µg rhCG resulted in more cases of severe OHSS; 3.4% of women compared to 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, Fishers exact test) (6).

Miscarriage rate per clinical pregnancy: There was no statistically significant difference between both drugs regarding the miscarriage rate (16% in the recombinant group vs 17.4% in the urinary group; OR 1.89, 95% CI 0.74 to 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, randomised, placebo-controlled, double-blind and double-dummy studies, J_5; 16; 18 found a reduction in the incidence of local site reactions in favour of rhCG (OR 0.47, 95% CI 0.32 to 0.70). One trial recorded 12/44 mild or moderate adverse events (such as pain in the injection site) in the rhCG group compared to 17/40 in the uhCG group (15). In another trial 22/97 women receiving rhCG reported adverse events compared to 42/93 in the uhCG group (16). 26/85 women receiving rhCG in the 18 trial reported at least one adverse event compared to 39/92 in the uhCG group. (6), 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 250µg rhCG, 500µg rhCG and 200µg uhCG groups.

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

Recombinant hLH versus urinary hCG
Three trials enrolling 472 women were identified (17; 19; 20). One trial did not report any data that could be pooled with the other trials (20).

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 recombinant hLH group and 19.7% in the urinary hCG group. The odds ratio was 0.94 (95% CI 0.50 to 1.76).
One of the studies comparing rhLH and uhCG (20) 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 were sent by the pharmaceutical company who was conducting the trial after contacting them for additional data.

Clinical pregnancy rate per woman

94
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 recombinant hLH group and 26.3% in the urinary group; OR 0.93, 95% CI 0.53 to 1.63).

Severe ovarian hyperstimulation syndrome 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 vs 12.4% in the urinary group; OR 0.82, 95% CI 0.39 to 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 vs 23.7% in the urinary group; OR 0.82, 95% CI 0.39 to 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 (17).

**Tolerability**
Only one trial reported tolerability (17). The most frequent non-serious adverse events were abdominal enlargement (29 cases), abdominal pain (19 cases), injection site pain (14 cases), diarrhoea (10 cases) and nausea (7 cases). Over the trial 158 events occurred in 71 women treated with rhLH (55%) and 171 events in 77 women treated with uhCG (63.6%) (OR 0.70, 95% CI 0.42 to 1.16). Three serious adverse events requiring hospitalisation (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 hospitalisation; retention of fetal placenta, abdominal pain, suspected ovarian torsion, diarrhoea (2 women), and pre-eclampsia.

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

**Discussion**
In infertile women undergoing ovulation induction, the use of human chorionic gonadotropins to achieve final follicular maturation and triggering follicular rupture is well established. Urinary hCG has been used for several years but recombinant technology
allowed for the production of recombinant hCG with high purity and its batch-to-batch consistency.

The present systematic review included seven randomised controlled trials of high quality with almost similar inclusion and exclusion criteria, similar design and methodology. We included one trial that did not use down-regulation (18) 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, and 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 livebirth / ongoing pregnancy rate and OHSS incidence between recombinant and urinary drugs except (20). 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 one third).

Results of the two published trials and the unpublished trial comparing rhLH and uhCG showed no statistically significant difference in clinical outcomes. Due to the results of the unpublished trial (20), Serono (the pharmaceutical company producing rhLH) has decided not to register high dose recombinant LH for clinical use. 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 which resulted in a decrease of pregnancy rate. (personal contact with company)

Results of one trial showed that increasing the dose of recombinant hCG (single 500 μg dose of rhCG) may led to a higher rate of ovarian hyperstimulation syndrome compared with a 250 ug 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 ug 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
recombinant hCG in obese patients. It may not be solved by a recombinant product as with uhCG.

**Conclusions**

There is no evidence of a difference 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 ug 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 urinar and recombinant hCG. The role of recombinant hCG 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.
### Characteristics of included studies

<table>
<thead>
<tr>
<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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<tr>
<td>6</td>
<td>-Multicenter -RCT -Open -Randomisation, stratified for each center, was performed according to a computer generated list.</td>
<td>-297 infertile women between 18-38 yrs. -both ovaries present -Regular cycles of 25-35 days -Either &gt;2-yrs infertility or had tubal disease. -BMI ≥30 kg/m² -have undergone no more than one previous ART attempt.</td>
<td>-Pituitary downregulation with leuprolide acetate (Lupron) starting 7-8 days postovulation at a dose of 1.0 mg daily. -Once evidence of downregulation 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 SC). -When one follicle had reached a diameter of ≥18 mm, and 7 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 mg or 500 mg of rhCG SC or 10,000 IU USP IM of urinary hCG. -Patients (Only those who fulfilled the criteria for hCG administration) were randomized in groups of six. -Oocytes were retrieved 34-38 hours 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. -Progestosterone in Oil, 50 mg IM 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, &amp; day 6-7 post-hCG -Pregnancy rate -Pregnancy outcome -Incidence &amp; 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>
<td>A</td>
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<td>15</td>
<td>-Part of a large multi-trial -RCT -Double blind -Double dummy -Phase III -Allocation by a computer generated</td>
<td>-84 women who had undergone pituitary down regulation &amp; ovulation induction for ICSI or IVF. -No systemic diseases. -BMI &lt; 30 kg/m² -No PCOS -No Prev H/O severe OHSS -No medical condition that might interfere with the absorption, distribution, metabolism, or the</td>
<td>-400 mcg intra-nasal nafarelin x2/day from midluteal down regulation (till E2&lt;180pmol/L, Pg&lt;4 nmol/L, LH&lt;31IU/L. -If failed after 10 days, pnt is withdrawn from study. -Dose is reduced to 200 mcg nafarelin x2/day with start of OI (rFSH, Gonad F standard ART protocol). -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 ≥550 nmol/follicle; cumulative Gonal-F® dose &lt;7500 IU)</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</td>
<td>Sponsored by Ares - Serono</td>
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<td>randomisation list.</td>
<td>excretion of the drug</td>
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<td>- No prior or poor response to gonadotrophin therapy.</td>
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<td>- No H/O intolerance to FSH, GnRH-agonist, or HCG.</td>
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<td>- Non-smoking or consuming &lt; 20 cigarettes/day.</td>
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<td>- Not more than 3 previous AR attempts.</td>
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<td>- No infertility treatment in the last 2 menstrual cycles.</td>
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<td>- Males have no leukospemira or bacterial infection in seminal analysis within the last 3 months.</td>
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<td>- 190 Premenopausal women</td>
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<td>- Age: 20-38</td>
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<td>- Infertility due to: tubal factor, AFS stage I or II endometriosis, severe male factor (ICSI patients), or unexplained infertility.</td>
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<td>- Male with acceptable semen analysis (within last 6 months) or severe male factor (ICSI patients).</td>
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<td>- 3 previous ART attempts last at least 2 full menstrual cycles.</td>
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<td>- Regular, spontaneous menstrual cycles of 25-35 days.</td>
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<tr>
<td>- Acceptable follicular phase serum FSH, LH, PRL, and testosterone.</td>
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<tr>
<td>- BMI 1 30 kg/m²</td>
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<tr>
<td>- Presence of both ovaries &amp; normal uterine cavity.</td>
<td></td>
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<tr>
<td>- No CC or gonadotrophins in the 2 months.</td>
<td></td>
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<tr>
<td>- No extrauterine pregnancy in the last 3 months.</td>
<td></td>
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<tr>
<td>- No Prev IVF or GIFT failure due to poor response or failure of fertilization.</td>
<td></td>
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<tr>
<td>- No PCO.</td>
<td></td>
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<tr>
<td>- No H/O severe OHSS.</td>
<td></td>
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<tr>
<td>- No abnormal bleeding of unknown origin.</td>
<td></td>
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<tr>
<td>- Patient were given either 250 mcg rhCG SC &amp; IM placebo or 5000 IU uHCG IM &amp; SC placebo.</td>
<td></td>
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<tr>
<td>- Ovum pickup &amp; 2-3 ET 2-3 days later.</td>
<td></td>
<td></td>
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<tr>
<td>- Luteal support with 200 mg Pg vaginal pessaries from pickup day for 2 wks or till menses.</td>
<td></td>
<td></td>
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<tr>
<td>- 18-21 days after HCG if no menses then US day 42.</td>
<td></td>
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<tr>
<td>- No of normally fertilized oocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- No of cleaved embryos</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>- Endocrine profile</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>- US endometrial thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Obstetric outcome</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- Adverse events</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>- Local tolerance to injection</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- OHSS &amp; severity</td>
<td></td>
<td></td>
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<tr>
<td>- 400 mcg intra-nasal nafarelin x2/day for 10-25 days for down regulation (US: no evidence of ovarian activity, endometrial thickness &lt;10 mm, E2&lt;50pg/ml).</td>
<td></td>
<td></td>
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<tr>
<td>- When down regulation is ok, rFSH (Gonal F) SC daily 2-6x75 IU ampoules, 150-450 IU/day according to center practice with max dose 450IU/day or total of 7500 IU. Dose adjusted by US &amp; PL E2.</td>
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<tr>
<td>- 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) (ptnt were given either SC 250 µg rhCG (vial) plus uHCG placebo (ampoule) or 5000 IU uHCG (ampoule) plus rhCG placebo (vial).</td>
<td></td>
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<tr>
<td>- Ovum pickup 34-38 h after HCG administration.</td>
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<tr>
<td>- Cumulus oophorus maturity was assessed, cumulus removed, oocyte nuclear maturity assessed, IVF done &amp; the numbers of one pronuclear (1PN), 2PN &amp; multi-pronucleate eggs on day 1 after retrieval were recorded. On days 2-3, the number of blastomeres, embryo grading &amp; the outcome of each embryo were recorded &amp; up 3 embryos were replaced.</td>
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<tr>
<td>- Luteal support with 600 mg Pg pessaries from pickup day for 3 wks after diag of pregnancy or till menses.</td>
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<tr>
<td>- Primary:</td>
<td></td>
<td></td>
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<tr>
<td>- No of oocytes retrieved per patient</td>
<td></td>
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<tr>
<td>- Secondary:</td>
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<tr>
<td>- No of patients with at least 1 oocyte retrieved</td>
<td></td>
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<tr>
<td>- No of oocytes retrieved / No of follicles ≥10 mm diameter on the day of HCG</td>
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<tr>
<td>- No of mature oocytes</td>
<td></td>
<td></td>
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<tr>
<td>- No of 2PN fertilized oocytes -- No of 2PN cleaved embryos</td>
<td></td>
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<tr>
<td>- S. Pg &amp; HCG conc. on day 1 post-HCG, on the day of oocyte retrieval, on the day of embryo transfer and on day 6-7 post-HCG.</td>
<td></td>
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<tr>
<td>- Implantation rate per embryo transferred.</td>
<td></td>
<td></td>
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<tr>
<td>- Luteal phase endometrial thickness</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- No of biochemical &amp; clinical pregnancies</td>
<td></td>
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<td></td>
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<tr>
<td>- No of multiple pregnancies</td>
<td></td>
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<tr>
<td>- Abortion rate</td>
<td></td>
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<tr>
<td>- No of live births</td>
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<tr>
<td>- Supported by Ares-Serono.</td>
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<tr>
<td>- Patient withdrawal - poor response to stimulation - not meeting the criteria for pituitary suppression after 25 days of nafarelin administration at risk of OHSS - serious adverse event - protocol violation - non-compliance - administrative reason - discovery of ineligibility - pregnancy</td>
<td></td>
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</tbody>
</table>
| 17 | -RCT  
-Double-blind  
-Randomisation by a computer in balanced blocks of four. | -259 Premenopausal women between 18 & 39 yr.  
-BMI ?  
-have a menstrual cycle lasting between 21 & 35 days.  
-have serum hormone levels of FSH 12 IU/L or less, PRL 1040 mU/L or less, & TSH within the normal range of 0.3-4.1 mU/L. & show normal results in pretreatment hematology, 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 yr of infertility, & a postcoital test showing at least one forward progressive sperm /HPF), male factor (only if an oocyte fertilization rate of > 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  
| 200 mg/day SC self administered GnRH-a (Suprefact, Buserelin) for down-regulation starting in the mid-luteal phase (for a minimum of 10 days & a max of 25 days) & continuing until 24 h before rhLH or u-hCG.  
-Down regulation was confirmed by US (no evidence of ovarian activity) & plasma E2 levels (~150 pmol/L or, 40 pg/mL). If after 25 days no desensitization, the woman is removed from study.  
-After down regulation, SC rhFSH is started & dose is adjusted by US monitoring & 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 & 25 of pituitary suppression, on the day of rhLH or u-hCG administration (day 0), & at least once between days 6 & 9.  
-LH, P4, E2, hCG, inhibin, testosterone, & androstenedione were determined once between days 10 & 25 of pituitary suppression (except for hCG), on the day of rhLH or u-hCG administration (day 0), & on days 1-3, day 6 or 7, & day 8 or 9.  
-In addition, E2 was also determined on all days the patient came in for US.  
-Anti-FSH & anti-LH antibodies were determined on the first day of rhFSH treatment, & total renin was determined on the day of rhLH or u-hCG  
| -patient's or physician's own request  
-Primary:  
-The No. of oocytes retrieved in the different study arms.  
=Secondary:  
-Follicular & oocyte development.  
-No. of embryos.  
-Implantation rate.  
-Pregnancy rates.  
-No. of cryopreserved embryos & their fate.  
-The course of different hormone levels.  
-Supported by Serono International B
| 18 | - Multicenter RCT  
- Double blind  
- Double dummy  
- Phase III  
- Method of randomisation not stated.  
- 198 women  
- Anovulatory or oligo-ovulatory (average cycle length > 40 days or amenorrhoea)  
- Aged 20 to 38  
- 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 gonadotrophins or CC, the last cycle of which > 2 months before the study  
- Acceptable hormones within 3 months of study: FSH < 3 IU/L & > 12 IU/L. PG < 10 nmol/L, PRL < 800 mIU/L, rhFSH (Gonal-F) was used to induce follicular maturation in a chronic low dose protocol. rhFSH was initiated on days 3 to 5 of a spontaneous or progesterone/oral contraceptive-induced menstrual bleed, at a starting dose of 75 IU, once daily SC. 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 & serum E2. If ovarian response was inadequate after 14 treatment days, the rhFSH dose was increased by 37.5 IU (& at 7-day intervals if required). rhCG or u-hCG was administered to the patient < 32 hours after the last dose of rhFSH, when the administration. Serum hCG was also determined on day 15 & days 18 or 19. - rhLH or u-hCG was given in the evening, within 24 h of the last rhFSH & GnRH-a administration (the largest follicle > 18 mm, at least one other follicle had a mean diameter of 16 mm, & serum E2 levels were within an acceptable range for the number of follicles present. - Patients in treatment arms 1, 2, & 3 received an im injection of u-hCG (5,000 IU or placebo) in the buttck & a sc injection of rhL (either 5,000 IU, 15,000 IU, 30,000 IU, or placebo) in the abdomen. - Patients in arm 4 received a single im injection of u-hCG (5,000 IU or placebo) & two sc injections of rhLH. The first rhLH injection (15,000 IU or placebo) was given on the same day as hCG, & 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 u-hCG 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 & continued up to menstruation or for at least the first 3 weeks of pregnancy if the patient became pregnant. |

- Primary:  
- Ovulation evidenced by midluteal S. Pg > 30 nmol/L (9.4 ng/mL), or a clinical pregnancy regardless of the midluteal phase Pg level.  
- Secondary:  
- Mean luteal phase level of S. Pg (average of 2 measures on days 5 to 10 after hCG). - S. hCG was measured on the day of hCG administration, on Monitored by B Serono CRA Department |
testosterone <6.0 nmol/L, DHEAS <20.0
μmol/L, 17-OH Pg <14.4 nmol/L, &
TSH 0.3-4.1 mlU/L or 0.4-4.0 mlU/L or
a free normal serum thyroxin level (11-24
pmol/L)
-twent patent tubes & a normal uterine
cavity
-BMI ?18 kg/m² & ?35 kg/m²
-Male partner with semen analysis
within the past 6 months showing
acceptable values for semen ( >10
million spermatozoa/ml, >25% with
linear progression & normal morphology
according to the local laboratory, & no
significant infection within the last 6
months;
-No clinically significant condition
-Negative HIV serology
-Negative hepatitis B surface antigen
serology, unless vaccinated
-No abnormal gynecological bleeding of
unknown origin
-No previous history of severe OHSS
-No active substance abuse

following criteria were met (one follicle with mean
diameter >18 mm; no more than three follicles with
mean diameters >16 mm; no more than four follicles
with mean diameters 11 to 15 mm; & E2 levels
within an acceptable range for the number of follicles
present, but no >5,500 pmol/L i.e. 1,500 pg/mL)
- Each patient received two SC injections: either
rhCG 250 g (vial), & a "uhCG" placebo (ampule); or
uhCG 5,000 IU (ampule), & an "rhCG" placebo
(vial).
-No uterine support
IU1 or timed intercourse as appropriate.

days 1 & 2 after, & on the same
days of Pg assessment.
-Other hormones (e.g.,
androstene-dione & E2) were
also analyzed.
-US assessment (in centers that
used
it).
-Luteal phase endometrial
thickness.
-No. of biochemical & clinical
pregnancies
-No. of multiple pregnancies
-Abortion rate
-No. of live births
-The duration of the luteal phase
in nonpregnant patients.
-Incidence & severity of adverse
events.
-Incidence of OHSS

19
-RCT
-single center
-open
-Randomisation was
done according to a
computer-generated table.
-Allocation was
done using
sealed envelopes
-30 patients
-primary infertility
-aged 27 to 37 years
-basal follicle-stimulating hormone
(FSH) concentration of <12 IU/L
-No patient had polycystic ovary
disease or had undergone more than two
previous IVF/ICSI attempts
-Recombinant human FSH 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 greater than 18 mm
in diameter, hCG (5,000 IU i.m. in the buttock;
Profasi; Serono) or rhLH (5,000 IU [250 g] s.c. in the
abdomen) was administered.

20
-Multicenter
-International
-RCT
-Double blind
-Double
-Premenopausal women between 18 & 39
yr.
-have menstrual cycle lasting between
21 & 35 days
-have

GnRH-a for down-regulation starting in the midluteal
phase (for a minimum of 10 days & a max of 25
days) & continuing until 24 h before rhLH or u-hCG.
-Down regulation was confirmed by US (no evidence
of ovarian activity) & plasma E2 levels (<150 pmol/L

Primary:

-Pregnancy rate / woman

Supported by grants from the Fondo de
Investigacion Sanitaria

A

B

sponsored by
Serono
International
- Allocation by a computer generated randomisation list.

- Serum hormone levels of FSH 12 IU/L or less, PRL 1040 mIU/L or less, & TSH within the normal range of 0.3-4.1 mIU/L; & show normal results in pretreatment hematology, 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 yr of infertility), & a postcoital test showing at least one forward progressive sperm (HPF), male factor (only if an oocyte fertilization rate of > 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 gonadotrophins for at least 1 month before screening, & a normal uterine cavity confirmed by hysteroscopy, or hysterosalpingography or a US scan performed within the past 5 yr.

After down regulation, SC rFSH is started & dose is adjusted by US monitoring & 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 & 25 of pituitary suppression, on the day of rhLH or u-hCG administration (day 0), & at least once between days 6 & 9.

- LH, P4, E2, hCG, testosterone, & androstenedione were determined once between days 10 & 25 of pituitary suppression (except for hCG), on the day of rhLH or u-hCG administration (day 0), & on days 1-3, day 6 or 7, & 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 & days 18 or 19.

- rhLH or u-hCG was given in the evening, within 24 h of the last rhFSH & GnRH-a administration (the largest follicle > 18 mm, at least one other follicle had a mean diameter of 16 mm.

- Patients in treatment arms received either (u-hCG or placebo) & the other arm received either (reLH or placebo) Oocyte retrieval was done 32-38 h after rhLH or u-hCG 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 & continued up to menstruation or for at least the first 3 weeks of pregnancy if the patient became pregnant.

Secondary:

- No. of oocytes.
- No. of embryos.
- No. of cryopreserved embryos & their fate.
### Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoine 1997</td>
<td>not RCT</td>
</tr>
<tr>
<td>Balasch 2003</td>
<td>case report (not RCT)</td>
</tr>
<tr>
<td>Emperaire 1994</td>
<td>not RCT</td>
</tr>
<tr>
<td>Hreinsson 2003</td>
<td>research for in vitro maturation of oocytes rather than for triggering ovulation</td>
</tr>
<tr>
<td>Littman 2003</td>
<td>used combination of urinary and recombinant hCG (not against each other)</td>
</tr>
<tr>
<td>Ludwig 2003</td>
<td>review article (not RCT)</td>
</tr>
<tr>
<td>Penarrubia 1999</td>
<td>not RCT</td>
</tr>
<tr>
<td>Zelinski-Wooten 1997</td>
<td>animal study</td>
</tr>
</tbody>
</table>
Review: Recombinant versus urinary human chorionic gonadotrophin for ovulation induction in assisted conception

Comparison: 01 rhCG versus uhCG for triggering ovulation

Outcome: 02 ongoing pregnancy / live birth rate per woman

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>rhCG</th>
<th>uhCG</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driscoll 2000</td>
<td>6/44</td>
<td>5/40</td>
<td>1.16</td>
<td>7.15</td>
<td>1.11 [0.31, 3.85]</td>
</tr>
<tr>
<td>ERHCG Group 2000</td>
<td>26/97</td>
<td>21/93</td>
<td>1.24</td>
<td>24.81</td>
<td>1.26 [0.65, 2.43]</td>
</tr>
<tr>
<td>Frank 2001</td>
<td>98/183</td>
<td>28/92</td>
<td>1.11</td>
<td>40.89</td>
<td>1.01 [0.58, 1.74]</td>
</tr>
<tr>
<td>IRHCG Group 2001</td>
<td>14/99</td>
<td>20/99</td>
<td>0.71</td>
<td>27.15</td>
<td>0.65 [0.31, 1.38]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>423</td>
<td>324</td>
<td></td>
<td>100.00</td>
<td>0.98 [0.69, 1.39]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Ch² = 1.73, df = 3 (P = 0.63), I² = 0%

Test for overall effect: I² = 0.12 (P = 0.91)

Figure 1: ongoing pregnancy / live birth rate per woman

Review: Recombinant versus urinary human chorionic gonadotrophin for ovulation induction in assisted conception

Comparison: 02 rhLH versus uhCG for triggering ovulation

Outcome: 01 ongoing pregnancy / live birth rate per woman

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>rhLH</th>
<th>uhCG</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERLH Group 2001</td>
<td>19/129</td>
<td>18/121</td>
<td>1.00</td>
<td>79.04</td>
<td>0.99 [0.49, 1.99]</td>
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<tr>
<td>Menau 2002</td>
<td>8/16</td>
<td>3/15</td>
<td>2.00</td>
<td>20.96</td>
<td>0.76 [0.18, 3.24]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>144</td>
<td>136</td>
<td></td>
<td>100.00</td>
<td>0.94 [0.50, 1.76]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Ch² = 0.10, df = 1 (P = 0.75), I² = 0%

Test for overall effect: Z = 0.19 (P = 0.85)

Figure 2: ongoing pregnancy rate / live birth rate per woman (rLH vs uhCG)
References


10. Hreinsson J, Rosenlund B, Friden B, Levkov L, Ek I, Suikkari AM et al. Recombinant LH is equally effective as recombinant hCG in promoting oocyte


20. [No authors listed]. 20: Luverisis (r-hLH) compared to u-hCG. Serono (unpublished data).