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## [Intervention Review]

# Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles

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## ABSTRACT

### Background

For the last few decades urinary human chorionic gonadotrophin (uhCG) has been used to trigger final oocyte maturation in cycles of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Recombinant technology has allowed the production of two drugs, recombinant human chorionic gonadotrophin (rhCG) and recombinant luteinising hormone (rLH), that can be used for the same purpose, to mimic the endogenous luteinising hormone (LH) surge. This allows commercial manufacturers to adjust production according to market requirements and to remove all urinary contaminants, facilitating the safe subcutaneous administration of a compound with less batch-to-batch variation. However, prior to a change in practice, it is necessary to compare the effectiveness of the recombinant drugs to the currently used urinary human chorionic gonadotrophin (uhCG).

#### Objectives

To assess the effects of subcutaneous rhCG and high dose rLH versus uhCG for inducing final oocyte maturation in subfertile women undergoing IVF and ICSI cycles.

#### Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (April 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 3), MEDLINE (1946 to April 2015), EMBASE (1980 to April 2015) and PsycINFO (1806 to April 2015) as well as trial registers at ClinicalTrials.gov on 13 May 2015 and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal on 14 May 2015.

## **Selection criteria**

Two review authors independently scanned titles and abstracts and selected those that appeared relevant for collection of the full paper. We included randomised controlled trials comparing rhCG and rLH with urinary hCG for final oocyte maturation triggering in IVF and ICSI cycles for treatment of infertility in normogonadotropic women.

## Data collection and analysis

Two authors independently performed assessment for inclusion or exclusion, quality assessment and data extraction. We discussed any discrepancies in the presence of a third author to reach a consensus. The primary review outcomes were ongoing pregnancy/live birth and incidence of ovarian hyperstimulation syndrome (OHSS). Clinical pregnancy, miscarriage rate, number of oocytes retrieved and adverse



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events were secondary outcomes. We combined data to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs) and assessed statistical heterogeneity using the I<sup>2</sup> statistic. We evaluated the overall quality of the evidence for the main comparisons using GRADE methods.

## **Main results**

We included 18 RCTs involving 2952 participants; 15 compared rhCG with uhCG, and 3 compared rhLH with uhCG. The evidence for different comparisons ranged from very low to high quality: limitations were poor reporting of study methods and imprecision. Pharmaceutical companies funded 9 of the 18 studies, and 5 studies did not clearly report funding source.

### Ongoing pregnancy/live birth

There was no conclusive evidence of a difference between rhCG and uhCG (OR 1.15, 95% CI 0.89 to 1.49; 7 RCTs, N = 1136, I<sup>2</sup> = 0%, moderate quality evidence) or between rhLH and uhCG (OR 0.95, 95% CI 0.51 to 1.78, 2 RCTs, N = 289, I<sup>2</sup> = 0%, very low quality evidence) for ongoing pregnancy/live birth rates.

## OHSS

There was no evidence of a difference between rhCG and uhCG in the incidence of OHSS: moderate to severe OHSS (OR 1.76, 95% CI 0.37 to 8.45; 3 RCTs, N = 417, I<sup>2</sup> = 0%, low quality evidence), moderate OHSS (OR 0.78, 95% CI 0.27 to 2.27; 1 RCT, N = 243, I<sup>2</sup> = 0%, low quality evidence), mild to moderate OHSS (OR 1.00, 95% CI 0.42 to 2.38; 2 RCTs, N = 320, I<sup>2</sup> = 0%, low quality evidence) or undefined OHSS (OR 1.18, 95% CI 0.50 to 2.78; 3 RCTs, N = 495, I<sup>2</sup> = 0%, low quality evidence). Likewise, there was no evidence of a difference between rhLH and uhCG in OHSS rates for moderate OHSS (OR 0.82, 95% CI 0.39 to 1.69, 2 RCTs, N = 280, I<sup>2</sup> = 5%, very low quality evidence).

#### Other adverse events

There was no evidence of a difference in miscarriage rates between rhCG and uhCG (OR 0.72, 95% CI 0.41 to 1.25; 8 RCTs, N = 1196,  $I^2 = 0\%$ , low quality evidence) or between rhLH and uhCG (OR 0.95, 95% CI 0.38 to 2.40; 2 RCTs, N = 289,  $I^2 = 0\%$ , very low quality evidence). For other adverse effects (most commonly injection-site reactions) rhCG was associated with a lower number of adverse events than uhCG (OR 0.52, 95% CI 0.35 to 0.76; 5 RCTS, N = 561;  $I^2 = 67\%$ , moderate quality evidence). However, when we used a random-effects model due to substantial statistical heterogeneity, there was no evidence of a difference between the groups (OR 0.56, 95% CI 0.27 to 1.13). Only one study comparing rLH and uhCG reported other adverse events, and it was impossible to draw conclusions.

#### Authors' conclusions

We conclude that there is no evidence of a difference between rhCG or rhLH and uhCG for live birth or ongoing pregnancy rates or rates of OHSS.

## PLAIN LANGUAGE SUMMARY

#### Recombinant versus urinary human chorionic gonadotrophin for ovulation induction in assisted reproduction

#### **Review question**

Cochrane researchers reviewed the evidence on the effects of two drugs that artificially reproduce the hormones needed for foetal conception: recombinant human chorionic gonadotrophin (rhCG) and recombinant human luteinising hormone (rhLH), comparing them to urinary human chorionic gonadotrophin (uhCG) for subfertile couples undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles.

#### Background

For the last few decades, uhCG has been used to trigger final oocyte maturation in IVF and ICSI cycles. Recombinant technology has allowed the production of two drugs that can be used for the same purpose, to mimic the natural surge of luteinising hormone (LH). This allows commercial manufacturers to adjust production to market requirements and remove all urinary contaminants, facilitating patient safety during drug administration and standardisation of drug batches. However, prior to a change in practice, it is necessary to compare the effectiveness of the recombinant drugs to the currently used uhCG. The primary review outcomes were live birth or ongoing pregnancy, as well as incidence of ovarian hyperstimulation syndrome (OHSS).

#### Study characteristics

We found 18 studies in 2952 women undergoing IVF or ICSI. Fifteen trials in 2473 women compared rhCG with uhCG, and three trials in 479 women compared rLH with uhCG.

Women in the studies were 18 to 45 years old, with regular menstrual cycles and no history of OHSS. Types of subfertility included tubal disease, endometriosis, unexplained infertility and male factor infertility.

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Pharmaceutical companies funded 9 of the 18 studies; 4 studies were free of commercial funding, and the remaining 5 studies did not clearly report a funding source. The evidence is current to April 2015.

## **Key results**

There was no evidence of a difference between rhCG and uhCG or between RhLH and uhCG in rates of live birth/ongoing pregnancy or OHSS.

Studies did not report much evidence on adverse events other than OHSS, and the evidence they did report was inconclusive.

## Quality of the evidence

For the comparison 'rhCG versus uhCG', the evidence was of moderate quality for ongoing pregnancy/live birth rate and of low quality for incidence of OHSS. The main limitation of the evidence was lack of precision (i.e. study size was too small to rule out the role of chance). For the comparison 'rLH versus uhCG', the evidence was of very low quality for both ongoing pregnancy/live birth rate and incidence of OHSS. The main limitations of the evidence was of very low quality for both ongoing pregnancy/live birth rate and incidence of OHSS. The main limitations of the evidence were lack of precision and poor reporting of study methods.