Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis

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CRD summary
This well-conducted systematic review concluded that the addition of growth hormone could improve the probability of pregnancy and live birth in women with poor response to ovarian stimulation with gonadotrophin releasing hormone analogues and gonadotrophins for in-vitro fertilisation, but that further research is required owing to the small number of patients analysed. These conclusions are likely to be reliable.

Authors' objectives
To assess whether the addition of growth hormone can improve the probability of pregnancy in women who have poor response while undergoing ovarian stimulation with gonadotrophin releasing hormone analogues and gonadotrophins for in-vitro fertilisation (IVF).

Searching
MEDLINE, EMBASE, CENTRAL and registries of randomised controlled trials (RCTs) were searched up to May 2008; search terms were reported. Proceedings of meetings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, and the reference lists of relevant publications and review articles were also handsearched. No language restrictions were applied.

Study selection
RCTs that evaluated the addition of growth hormone to gonadotrophin releasing hormone analogues and gonadotrophins for ovarian stimulation for IVF in women who were characterised as poor responders were eligible for inclusion in the review (irrespective of the definition of poor ovarian response, the dose and protocol of growth hormone administered, or the type and protocol of gonadotrophin releasing hormone analogue or gonadotrophin used).

The included trials were published between 1991 and 2008. The dose and protocol of growth hormone administration varied between trials, as did the definition of poor ovarian response. Three of the included trials received financial support from a pharmaceutical company.

The primary outcome of interest was pregnancy per patient, both clinical pregnancy (detected at six to eight weeks gestation) and live birth. Several secondary outcomes were also reported.

Two reviewers independently selected studies for the review; disagreements were resolved by discussion.

Assessment of study quality
Two reviewers independently extracted data on the method of randomisation, allocation concealment, blinding, and whether a sample size calculation was performed; disagreements were resolved by discussion.

Data extraction
Odds ratios (ORs) and risk differences (RDs), with 95% confidence intervals (CIs), were calculated. For continuous outcomes, mean differences with 95% confidence intervals were calculated. When data were missing from trial reports, the authors were contacted to obtain the relevant data.

Two reviewers independently extracted data, disagreements were resolved by discussion.

Methods of synthesis
Odds ratios and risk differences were pooled using the Mantel Haenszel fixed-effect model in the absence of significant heterogeneity, or the DerSimonian and Laird random-effects model in the presence of significant heterogeneity.
(p<0.05). Heterogeneity was assessed using the $X^2$ test.

Subgroup analysis was performed based on the protocol of growth hormone used and explicitly stated embryo transfer policy.

The number needed to treat was also calculated.

Publication bias was assessed using the Harbord-Egger test.

**Results of the review**

Six RCTs (n=169 women) were included in the review. Three trials reported the method of randomisation. Two trials reported the method of allocation concealment. Four trials were double-blind. The number of participants in the included trials ranged from 14 to 61; none of the trials performed a sample size calculation.

The addition of growth hormone significantly increased the probability of clinical pregnancy (OR 2.82, 95% CI 1.24 to 6.38; six RCTs). The absolute increase in clinical pregnancy rate was 16% (95% CI 4 to 28; six RCTs). The number needed to treat was 6 (95% CI 4 to 25).

The addition of growth hormone significantly increased the probability of live birth (OR 3.15, 95% CI 1.26 to 7.85; five RCTs). The absolute increase of live birth rate was 17% (95% CI 5 to 30; five RCTs).

Subgroup analyses did not alter the results.

There was no evidence of significant publication bias.

**Authors' conclusions**

Growth hormone addition increased the probability of clinical pregnancy and live birth in women who had poor response while undergoing ovarian stimulation with gonadotrophin releasing hormone analogues and gonadotropins for IVF. However, the total number of patients analysed was small, so further research is required.

**CRD commentary**

The review addressed a clear question and was supported by well defined inclusion criteria. Several sources were searched in an attempt to identify all relevant studies, including sources of unpublished studies, reducing the potential for publication bias. No language restrictions were applied, reducing the potential for language bias. Study selection, data extraction and validity assessment procedures were undertaken in duplicate, reducing the potential for reviewer bias and error.

The validity of the included trials was assessed and the results were reported. Adequate details of the included trials were provided. Appropriate methods were used to pool the results and to investigate statistical heterogeneity.

This was a well conducted systematic review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further RCTs are warranted to assess whether growth hormone addition increases the probability of clinical pregnancy and live birth in women with poor response to ovarian stimulation with gonadotrophin releasing hormone analogues and gonadotropins for IVF, since the number of patients studied in previous RCTs is small.

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