Controlled ovarian hyperstimulation interventions in infertile women aged 40 years or older undergoing in vitro fertilization

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CRD summary
This review assessed the effectiveness and safety of different controlled ovarian hyperstimulation interventions for the treatment of infertile women, aged 40 years and over, undergoing in vitro fertilisation. There was insufficient data to support any conclusions. This was a generally well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the effectiveness and safety of different controlled ovarian hyperstimulation interventions for the treatment of infertile women, aged 40 year or over, undergoing in vitro fertilisation.

Searching
MEDLINE, the Cochrane Library and the Chinese Biomedical database were searched. Search terms were reported, but search dates were not. Bibliographies of retrieved articles were handsearched for additional material. Non-English articles were considered if an English abstract was available.

Study selection
Randomised controlled trials (RCTs) that compared at least two interventions for controlled ovarian hyperstimulation in infertile women (40 years or older) undergoing in vitro fertilisation were eligible for inclusion. Studies were excluded if more than one controlled ovarian hyperstimulation intervention was aimed at altering ovarian response.

The review outcomes were: live birth rate, pregnancy rate, number of embryos, number of retrieved oocytes, dosage of human menopausal gonadotrophin, and adverse events.

Interventions were different for each included trial, as follows: various combinations of menotropins and gonadotropin-releasing hormone-analogue; long protocols with triptorelin or gonadotropin and comparisons of daily growth hormone injections with placebo; long protocols of ovulation induction compared with short protocols; recombinant follicle-stimulating hormone-analogue alone compared with recombinant follicle-stimulating hormone plus recombinant luteinising hormone. All the included women were infertile, but different trials excluded patients with ovarian cysts, azoospermia, polycystic ovary syndrome or low levels of follicle-stimulating hormone.

Two reviewers assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed trial quality using the methods of Wu and Liu which assessed the following criteria: randomisation; allocation and concealment; blinding; selective reporting; and measures of treatment effects.

Data extraction
Two reviewers independently extracted data.

Methods of synthesis
The trials were combined in a narrative synthesis, supported by accompanying data tables.

Results of the review
Four RCTs were included in the review (n=611 women). One trial had three parallel arms and three trials had two parallel arms. All trials were judged to have some risk of bias. Three trials had moderate risk of selection bias because there was no allocation concealment or description of randomisation methods. Three trials had a high risk of performance and detection bias because blinding was not used.
Menotropins alone versus menotropins plus mini-dose or standard dose gonadotropin-releasing hormone-analogue (one RCT; n=219 women): There were no differences in take-home baby rate, clinical pregnancy rate or cycle cancellation rate between the treatment groups. Significantly more oocytes were obtained with gonadotropin-releasing hormone plus menotropin compared with menotropin alone (p=0.03). Significantly more embryos were suitable for transfer in those women receiving menotropin plus standard dose gonadotropin-releasing hormone compared with the other two treatment groups (p=0.04). However, there was an increased risk of miscarriage in the menotropin plus standard dose gonadotropin-releasing hormone group (62.5%) compared with the other two treatment groups (36.4%).

Daily injections of growth hormone versus solvent placebo (one RCT; n=100 women): There were no differences in number of oocytes retrieved, embryos obtained, duration/dose of exogenous gonadotrophins to achieve controlled ovarian hyperstimulation and cancellation rates between the treatment groups. There were significantly higher delivery rates (22% versus 4%) and live birth rates (5.2% versus 1.1%) in the growth hormone protocol than in the placebo (p<0.01). No adverse effects were noted.

Short protocol versus long protocol of buserelin plus recombinant follicle-stimulating hormone (one RCT; n=220 women): There were no differences in the duration/dose of exogenous gonadotrophins required to achieve controlled ovarian hyperstimulation or in cancellation rates between treatment groups. Significantly higher pregnancy rates were achieved in the long protocol group compared with the short protocol group (p<0.01). Significantly more oocytes (p<0.001) and embryos (p<0.001) were obtained with the long protocol compared to the short protocol technique. No adverse effects were noted.

Recombinant follicle stimulating hormone alone versus recombinant follicle stimulating hormone plus recombinant luteinising hormone (one RCT; n=72 women): The hormones were administered using a flare-up protocol. There were no differences in number of oocytes retrieved, duration/dose of exogenous gonadotrophins to achieve controlled ovarian hyperstimulation, pregnancy rates or cancellation rates between treatment groups. No adverse effects were noted.

Authors' conclusions
There was insufficient data to support any particular controlled ovarian hyperstimulation intervention for infertility management during in vitro fertilisation in women aged 40 year or over.

CRD commentary
The review addressed clear research questions with clear inclusion and exclusion criteria. Relevant sources were searched to locate the included studies. Limiting the search to published studies meant that important studies may have been missed, introducing the potential for publication bias. Sufficient attempts were made to minimise biases and errors in the review process.

Relevant criteria were used to examine the trial quality, although the results were not presented clearly. A narrative synthesis was appropriate given the level of clinical heterogeneity between included trials.

The authors' conclusions reflected the evidence presented. This review was generally well conducted 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 more good quality RCTs are required that are multi-centre, well designed, double blinded and contain relevant outcomes. It would also be advantageous to study cost effectiveness for the different interventions.

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