GnRH agonist versus GnRH antagonist in poor ovarian responders: a meta-analysis

CRD summary
This review concluded that poor ovarian responders treated with gonadotrophin-releasing hormone (GnRH) antagonist had a significantly higher number of retrieved oocytes than those treated with long protocols of GnRH agonist, while women treated with GnRH agonist flare-up protocols had a significantly higher number of retrieved oocytes than those treated with GnRH antagonist. Overall, the poor reporting of the review methods and the apparent differences between the studies suggest that the findings may not be reliable.

Authors' objectives
To determine the efficacy of gonadotrophin antagonist (GnRH-ant) compared with GnRH agonist (GnRHa) as coadjuvant therapy for ovarian stimulation in poor responders in in vitro fertilisation (IVF)/intracytoplasmic sperm injection cycles.

Searching
MEDLINE, EMBASE, Science Citation Index and the Cochrane Controlled Trials Register were searched from 1990 to 2006 with no language restrictions. Gateway, Trials Central and OMNI were searched for grey literature. The search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared GnRH-ant and GnRHa for ovarian stimulation in poor responders were eligible for inclusion. All of the included studies assessed a multiple low-dose (0.25 mg) antagonist regimen (cetrorelix or ganirelix). The included studies used, as a reference treatment, either a long protocol with a GnRHa (leuprolide or buserelin) beginning in the mid-luteal phase of the preceding cycle or a flare-up protocol with a GnRHa (triptorelin, leuprolide). Definitions of poor responders varied between the studies and included at least two failed IVF attempts, number of oocytes, poor ovarian response in previous IVF cycles, or used serum peak oestradiol concentrations and/or preovulatory follicle measurement during previous cycles. The participants were aged from 25 to 46 years. Studies assessing the number of retrieved and mature oocytes were eligible for inclusion. The secondary outcomes included cycle cancellation rate (CCR) due to poor responses, clinical pregnancy rate (CPR) per cycle, CPR per oocyte retrieval and CPR per transfer.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not fully state how the studies were assessed for validity, but it appears that the method of randomisation and blinding were evaluated. Two reviewers independently assessed each study for methodological rigour and potential for bias.

Data extraction
Authors were contacted for missing data where appropriate. The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a meta-analysis using a fixed-effect model. Summary estimates were reported as odds ratios (ORs) or weighted mean differences (WMDs), with corresponding 95% confidence intervals (CIs). Heterogeneity was assessed using the $\chi^2$, Cochran’s Q and Breslow-Day tests.

Results of the review
Six RCTs (approximately 274 participants) were included in the review.
The method of randomisation was reported in all 6 studies, while blinding was reported in one.

A significantly higher number of retrieved oocytes were found in the GnRH-ant group compared with the long protocol GnRHa group (WMD 1.12, 95% CI: 0.18, 2.05, p=0.018; 2 studies), but no statistically significant differences were found in the number of mature oocytes. Conversely, a significantly higher number of retrieved oocytes was found in the flare-up GnRHa group in comparison with the GnRH-ant group (WMD -0.51, 95% CI: -0.99, -0.04, p=0.032; 4 studies).

There were no statistically significant differences between GnRH-ant and GnRHa (long and flare-up protocols) in terms of the CCR, CPR per cycle initiated, CPR per oocyte retrieval and CPR per embryo transfer.

There was no evidence of statistical heterogeneity between the trials, except in the analysis of the number of mature oocytes with the GnRH-ant versus GnRHa flare-up protocols (p<0.001).

**Authors' conclusions**
The results showed that women undergoing treatment with GnRH-ant had a significantly higher number of retrieved oocytes compared with long protocols of GnRHa. However, the analysis also showed that women treated with GnRHa flare-up protocols had a significantly higher number of retrieved oocytes compared with treatment with GnRH-ant. There were no statistically significant differences between GnRH-ant and GnRHa (long and flare-up protocols) in terms of the CCR, CPR per cycle initiated, CPR per oocyte retrieval and CPR per embryo transfer. However, further research is needed because of the small sample sizes and between-study differences.

CRD commentary
The inclusion criteria were clearly defined. Some relevant sources were searched, and efforts were made to locate unpublished studies and to reduce language bias. Methods were used to minimise reviewer error and bias in the assessment of validity, but it is not clear whether similar steps were taken at the study selection and data extraction stages. The validity assessment was not fully described, although only RCTs were included and some details of adequacy of randomisation were reported. Details of the study characteristics highlighted considerable clinical variation and statistical heterogeneity was also found for some analyses. The authors appropriately described some limitations of the evidence, and stated that no conclusions about pregnancy rates could be drawn because of the limited available data and because the number of oocytes is only an intermediate outcome which does not necessarily predict pregnancy rates. Overall, the poor reporting of the review methods and the apparent differences between the studies suggest that the findings may not be reliable. However, the authors' conclusion that further studies are required given the small sample sizes and heterogeneity seems reasonable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further well-conducted RCTs comparing GnRH-ant multi-dose with GnRHa flare-up protocols are required. In addition, criteria for the definition of poor ovarian responders need international standardisation.

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