Optimizing GnRH antagonist administration: meta-analysis of fixed versus flexible protocol
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CRD summary
This review compared flexible and fixed administration of gonadotrophin-releasing hormone antagonist. The authors concluded that there was no significant difference between regimens for pregnancy rate, but there was a statistically significant reduction in the amount of recombinant follicle-stimulating hormone used with the flexible protocol. Given the uncertainty surrounding the review methodology and primary study details, the authors' conclusions should be interpreted with caution.

Authors' objectives
To determine whether flexible administration of gonadotrophin-releasing hormone (GnRH) antagonist, according to follicular size, would be more beneficial than starting GnRH on a fixed day.

Searching
MEDLINE, EMBASE, and the specialised register of the Cochrane Menstrual Disorders and Subfertility Group were searched. In addition, the reference lists of included studies, reviews and relevant textbooks, and abstracts of major international meetings were handsearched. The search terms were not reported and the authors did not state whether any language restrictions were applied to the search.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies of ovulation induction using GnRH antagonist as part of an assisted reproductive cycle were included. All trials used recombinant follicle-stimulating hormone (FSH) for multiple follicular development, with a starting dose ranging from 150 to 300 IU. Two studies administered GnRH antagonist when the leading follicle was at least 14 mm, while the other two studies administered GnRH antagonist when the leading follicle was at least 15 mm.

Participants included in the review
Studies of subfertile couples undergoing ovulation induction were included in the review.

Outcomes assessed in the review
The primary outcomes were pregnancy rate (per woman or per couple) and incidence of luteinising hormone (LH) surge. The secondary outcomes were the number of oocytes retrieved, number of antagonist ampoules used and amount of gonadotrophins needed.

How were decisions on the relevance of primary studies made?
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 studies appeared to have been assessed for the adequacy of randomisation. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
The raw data were extracted from each study and summarised in a 2x2 table. An odds ratio (OR) and associated 95% confidence interval (CIs) were calculated for the dichotomous data for each study. For continuous data, it appears that the mean and standard deviation were calculated for each study.

Methods of synthesis
How were the studies combined?
Dichotomous data were combined in a meta-analysis using the Mantel-Haenszel method. Continuous data appear to have been combined, using a fixed-effect model, to calculate a weighted mean difference (WMD) and corresponding 95% CI.

How were differences between studies investigated?
Studies that used adequate methods of randomisation were examined in a subgroup analysis for the outcome pregnancy rate. Statistical heterogeneity appears to have been assessed using the chi-squared test.

Results of the review
Four RCTs (n=484) were included in the review.

One study did not use adequate methods for randomisation.

There was a trend towards a higher pregnancy rate per woman with the fixed protocol compared with the flexible protocol, but this difference was not statistically significant (OR 0.7, 95% CI: 0.47, 1.05). There was no statistically significant difference between treatment groups in the incidence of premature LH surge. There were statistically significant reductions in both the number of antagonist ampoules (WMD -1.2, 95% CI: -1.26, -1.15) and the amount of gonadotrophins used (WMD 95.5 IU, 95% CI: 74.8, 116.1) in the flexible protocol relative to the fixed protocol. However, the results for the amount of gonadotrophins used showed statistically significant heterogeneity (P=0.0051). There was a trend towards an increase in the number of oocytes retrieved with the flexible protocol (WMD 1.28, 95% CI: 0.9, 1.6).

The removal of one trial that did not use adequate randomisation from the analysis did not alter the results for pregnancy rate.

Authors' conclusions
Although the fixed protocol appeared to produce a higher pregnancy rate than the flexible protocol, there was no statistically significant difference between the two. There was a statistically significant reduction in the amount of recombinant FSH used with the flexible protocol.

CRD commentary
The study objective was defined clearly in terms of the intervention, participants, study design and outcomes of interest. Appropriate sources were searched, although it was unclear whether any language restrictions were applied to the search. The methods used to select studies and extract the data were not described, so it was not possible to properly assess the validity of these processes. If one reviewer carries out these tasks alone, the risk of introducing bias is increased. It was also not clear whether study quality was assessed on any criteria other than randomisation, or how many reviewers performed this assessment.

Few details of the included participants were provided, making it difficult to assess whether the statistical pooling of the studies was appropriate. In addition, statistical heterogeneity was detected in the analysis of amount of gonadotrophins used, which calls into question the validity of this result. Given the lack of information about both the review methodology and the included studies, it was difficult to fully assess the reliability of the review findings. As such, the authors' conclusions should be interpreted with caution.
Implications of the review for practice and research
Practice: The authors stated that in the flexible protocol, the administration of antagonist should not be delayed too long, so that the pregnancy rate is not affected, and the inhibition of LH surge is sufficient.

Research: The authors stated that the possible association between the flexible protocol and a reduction in the amount of GnRH antagonist consumed per cycle should be examined using a larger sample size, to determine whether the reduction would be cost-effective or whether it affects implantation rate.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.