GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis

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CRD summary
This review concluded that gonadotrophin-releasing hormone (GnRH) antagonists offer a number of potential advantages over GnRH agonists for poor responders undergoing ovarian stimulation for in vitro fertilisation. However, given the limited number of small heterogeneous studies on which the analysis was based, the authors’ conclusion might not be reliable.

Authors' objectives
To review the literature on the utilisation of gonadotrophin-releasing hormone (GnRH) antagonists for ovarian stimulation for in vitro fertilisation (IVF) in special patient groups.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched to February 2006. The references of retrieved articles and the proceedings of the American Society of Reproductive Medicine and the European Society of Human Reproduction and Embryology (1999 to 2004) were also checked; details of the review methods are available in an earlier paper (see Other Publications of Related Interest no.1).

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion; in relation to women at risk of OHSS, uncontrolled observational studies were also included.

Specific interventions included in the review
Studies comparing GnRH agonists and GnRH antagonists for ovarian stimulation were eligible for inclusion. For patients at risk of ovarian hyperstimulation syndrome (OHSS), studies of GnRH-agonist triggering of final oocyte maturation in GnRH antagonist protocols, without a comparator, were eligible. The included studies used short or long agonist protocols and fixed or flexible protocols. All of the included randomised controlled trials (RCTs) used multiple-dose GnRH antagonist regimens. The observational studies used multiple-dose regimens, or multiple- and single-dose regimens. With the exception of 1 study, patients in the polycystic syndrome (PCOS) studies received pre-treatment with the oral contraceptive pill.

Participants included in the review
Women undergoing ovarian stimulation for IVF who had a poor ovarian response to exogenous gonadotrophins (poor responders), or had PCOS, or were at risk for OHSS, were eligible for inclusion. The definition of the term 'poor responders' varied amongst the included studies, though the majority defined it as an inappropriate ovarian response to stimulation in a previous cycle.

Outcomes assessed in the review
The outcomes of interest were clinical or ongoing pregnancy per woman, duration of stimulation (days), gonadotrophin consumption (ampoules), number of cumulus-oocyte complexes retrieved and OHSS incidence.

How were decisions on the relevance of primary studies made?
Two investigators independently screened studies for inclusion.
Assessment of study quality
Two investigators independently assessed RCTs in relation to whether the participant allocation was truly random and concealed.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were extracted for dichotomous outcomes, and Hedges standardised mean differences and 95% CIs were extracted for continuous data. The authors did not state how many investigators performed the data extraction.

Methods of synthesis
How were the studies combined?
In the absence of statistically significant heterogeneity (p>0.05) effect sizes were combined using a fixed-effect meta-analysis; a random-effects analysis was used where significant heterogeneity was detected. The observational studies were discussed in a narrative synthesis.

How were differences between studies investigated?
Studies of poor responders, PCOS patients and patients at risk of OHSS were pooled separately and studies were stratified according to whether a long or short agonist protocol had been used. Statistical heterogeneity was assessed using Cochran's Q statistic.

Results of the review
Eight RCTs (n=575) of poor responder patients were included. The studies included 4 RCTs (n=305) of PCOS patients, and 2 RCTs (n=27) and 13 observational studies (n=439) of patients at risk of OHSS.

Poor responders: 7 of the 8 studies reported a truly random method of allocation and 5 studies reported allocation concealment. There were no statistically significant differences between GnRH antagonist and GnRH agonist protocols in duration of stimulation, gonadotrophin consumption and clinical pregnancy rate for the overall analysis (short and long agonist protocols combined) or the stratified analysis (short and long agonist protocols pooled separately). The number of oocytes was higher for GnRH antagonist compared with long GnRH agonist protocols (OR 0.41, 95%CI: 0.0, 0.83, p=0.05; 2 studies), but there was no statistically significant difference between GnRH antagonist and short GnRH agonist protocols. There was evidence of statistical heterogeneity in the analysis of duration of stimulation and gonadotrophin consumption.

Patients with PCOS: 2 of the 4 studies reported a truly random method of allocation and 1 study reported allocation concealment. There were no statistically significant differences between GnRH antagonist and long GnRH agonist protocols in gonadotrophin consumption, clinical pregnancy rate, incidence of OHSS or the number of oocytes. The duration of stimulation was reduced for GnRH antagonist compared with long GnRH agonist protocols (OR -0.86, 95% CI: -1.14, -0.59, p<0.01; 3 studies). There was evidence of statistical heterogeneity in the analysis of cumulus-oocyte complexes.

Patients at risk of OHSS: 8 of the 13 observational studies were retrospective. The findings of the 2 RCTs were contradictory as to whether agonist triggering in GnRH antagonist protocols was effective compared with human chorionic gonadotrophin, based on pregnancy rate and live birth rate. Clinical pregnancy rates in the RCTs and observational studies ranged from 0 to 75%. Many of the observational studies reported no cases of OHSS but, given the small sample sizes and unclear definitions and assessment methods used, it is not appropriate to draw firm conclusions from this.

Authors' conclusions
It appears that GnRH-agonist triggering is associated with a lower incidence of mild and moderate OHSS. However, there is limited evidence for the prevention of severe OHSS. Overall, GnRH antagonist ovarian stimulation protocols offer a number of potential advantages compared with long GnRH agonist protocols, including the option of triggering

**CRD commentary**
There was a clearly stated review question and several relevant sources were searched for studies. However, only limited attempts were made to locate unpublished studies through conference abstracts, thus there may be a risk of publication bias. Appropriate methods were used to reduce error and bias in the study selection and quality assessment processes, though it is unclear whether similar methods were used in the data extraction. The quality of the RCTs was assessed; although the observational studies were not formally assessed it is clear from the details provided that they were generally of a poor quality. Relevant study details were provided and the analysis seemed appropriate. Overall, the authors’ broad conclusion, that GnRH antagonist ovarian stimulation protocols offer a number of potential advantages compared with the long GnRH agonist protocol, might not be reliable given the limited number of small heterogeneous studies on which the analysis was based.

**Implications of the review for practice and research**
Practice: The authors stated that the use of GnRH-agonist triggering in patients at risk of OHSS should be considered an experimental procedure.

Research: The authors stated that more studies are required to substantiate the findings of benefit with GnRH antagonist. Further investigation is required into the reason for the lower likelihood of pregnancy after GnRH-agonist triggering and luteal phase support with vaginal progesterone and oral oestradiol, and an optimal protocol needs to be established. Large observational studies are required to establish the potential of GnRH-agonist triggering to prevent severe OHSS in at-risk groups.

**Bibliographic details**

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**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Drug Administration Schedule; Female; Fertility Agents, Female /pharmacology; Fertilization in Vitro /drug effects /methods; Gonadotropin-Releasing Hormone /analogs & derivatives /antagonists & inhibitors /pharmacology; Humans; Infertility, Female /drug therapy; Odds Ratio; Ovarian Hyperstimulation Syndrome /chemically induced; Ovulation Induction /methods; Polycystic Ovary Syndrome /drug therapy; Randomized Controlled Trials as Topic; Retrospective Studies; Treatment Outcome

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Record Status
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.