Meta-analysis of GnRH antagonist protocols: do they reduce the risk of OHSS in PCOS?

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CRD summary
The authors concluded that GnRH antagonist protocols were associated with shorter duration of gonadotrophin stimulation, lower total dose of gonadotrophins and lower levels of moderate and severe ovarian hyperstimulation syndrome (OHSS) combined. Methodological weakness, presence of confounding factors in some studies and differences between studies make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To compare the impact of gonadotrophin-releasing hormone (GnRH) antagonist protocol with GnRH long agonist protocol on ovarian hyperstimulation syndrome in women with polycystic ovarian syndrome (PCOS) who are undergoing in-vitro fertilisation (IVF) treatment.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to August 2010 for articles in any language. MeSH headings and search terms were reported. Conference Proceedings Citation Index, Current Controlled Trials and mRCT were searched. References of retrieved articles and relevant reviews were handsearched. Researchers in the field were contacted for unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared GnRH long agonist protocols with GnRH antagonist protocols in women with PCOS undergoing IVF were eligible for inclusion. Studies had to use human chorionic gonadotrophin as the ovulation trigger. Studies were included whether IVF was with or without intracytoplasmic sperm injection. Studies were excluded if GnRH agonist was used in the antagonist arm as the ovulation trigger in cases of high risk for ovarian hyperstimulation syndrome. The primary outcome was rate of ovarian hyperstimulation syndrome. Secondary outcomes were total duration and dosage of gonadotrophin used for ovarian stimulation, oestradiol concentration on the day of triggering ovulation, number of oocytes retrieved and cycle cancellation, clinical pregnancy rate, ongoing pregnancy rate miscarriage rate and live birth rate.

Included studies compared GnRH agonists (triptorelin, buserelin and leuprolide acetate) with GnRH antagonists (cetrorelix or ganirelix). Multidose, fixed dose or flexible dose protocols were followed for antagonist administration. Gonadotrophins used were either recombinant follicle stimulating hormone (FSH), urinary derived FSH or a combination of both. In most studies oral contraceptive pills were used prior to ovarian stimulation in both antagonist and agonist groups. Where stated the human chorionic gonadotrophin used was pregnyl or noveral. Definitions of PCOS varied between studies.

Two reviewers independently selected the studies for review. Disagreements were resolved through consultation with a third reviewer.

Assessment of study quality
The quality of included studies was evaluated according to Centre for Reviews and Dissemination (CRD) criteria for method of randomisation, allocation concealment, blinding, use of intention-to-treat analyses and follow-up rates.

Two reviewers conducted the quality assessment.

Data extraction
For dichotomous outcomes, the number of events in each group was extracted and used to calculate risk ratios (RRs) with 95% confidence intervals (CI). For continuous data, the mean and standard deviation for each group were extracted and used to calculate standardised mean differences with 95% CI. Authors were contacted for further information.

Two reviewers extracted the data.
Methods of synthesis

Pooled risk ratios with 95% CIs were calculated for dichotomous outcomes. Continuous outcomes were pooled using weighted mean differences (WMD) with 95% CIs. Statistical heterogeneity was assessed using the $I^2$ statistic and through visual inspection of forest plots. Where statistical heterogeneity was greater than 50%, a random-effects model (DerSimonian and Laird) was used for the meta-analysis. Where statistical heterogeneity was less than 50%, a fixed-effects model (Mantel-Haenszel) was used. Statistical heterogeneity was investigated according to population, exposure and study quality.

Results of the review

Nine studies were included for review (966 participants, range 41 to 220). Three studies were published in abstract form only. An appropriate method of randomisation was described in six studies. Allocation concealment was reported in two studies. Laboratory staff were blinded in one study. Intention-to-treat analyses were used in four studies. The follow up rate was 100% in eight studies and not reported in one study.

Rate of ovarian hyperstimulation syndrome (OHSS): When all cases of OHSS were considered, use of GnRH antagonist significantly reduced the rate of OHSS compared with GnRH agonist (RR 0.60, 95% CI 0.48 to 0.76; seven studies; 714 participants). When only moderate and severe cases of OHSS were considered GnRH antagonist was associated with a significantly lower rate of OHSS compared with GnRH agonist (RR 0.59, 95% CI 0.45 to 0.76; three studies, 410 participants). There were low levels of statistical heterogeneity for OHSS combined ($I^2$=0%) and moderate to severe OHSS (14%). There were no significant differences between GnRH agonist and GnRH antagonist groups for severe OHSS only, moderate OHSS only and mild OHSS only. There were high levels of statistical heterogeneity for the outcome of mild OHSS (73%) but not for moderate or severe OHSS (0%).

Secondary outcomes: Antagonist protocol was associated with significantly shorter gonadotrophin stimulation (WMD -0.74, 95% CI -1.12 to -0.36; seven studies, 714 participants) and significantly lower total dose of gonadotrophin (WMD -0.28 95% CI -0.43 to -0.13; seven studies, 714 participants) compared to agonist protocol. There were high levels of statistical heterogeneity for total duration of gonadotrophin stimulation (82%) but not for total dose of gonadotrophin (24%). There were no significant differences between GnRH agonist and GnRH antagonist protocols for the outcomes of oestradiol concentration on day of ovulation trigger, number of oocytes retrieved, cycle cancellation rate, clinical pregnancy rate and miscarriage rate. There was evidence of significant statistical heterogeneity for oestradiol concentration and number of oocytes retrieved ($I^2$=58%) but not for other outcomes.

Authors' conclusions

GnRH antagonist protocols were associated with shorter duration of gonadotrophin stimulation, lower total dose of gonadotrophins and lower levels of moderate and severe OHSS combined. Data on severe OHSS was inconclusive. Clinical and ongoing pregnancy rates were similar between groups.

CRD commentary

The review addressed a clear question with well-defined inclusion criteria. Several relevant databases were searched. Steps were taken to identify unpublished studies and the search was not language restricted, which minimised risks of publication and language biases. Study selection, data extraction and quality assessment were conducted in duplicate but it was unclear whether this was independent for data extraction and quality assessment so reviewer error and bias could not be ruled out definitively. The quality of included studies was assessed and there were methodological weaknesses in some studies (such as lack of intention-to-treat analyses and laboratory staff blinding) that may have affected the reliability of the results.

Suitable methods were used to combine the studies. Variations in definitions of OHSS and differing stimulation protocols between studies may have undermined the reliability of the results. Statistical heterogeneity was assessed and was found for some outcomes. The results may have been confounded by use of additional processes to reduce OHSS in some studies.

Methodological weakness, presence of confounding factors in some studies and differences between studies make the reliability of the authors' conclusions unclear.

Implications of the review for practice and research
Practice: The authors stated that the antagonist protocol may be associated with reduced costs but this had not been confirmed by formal economic analyses.

Research: The authors stated a need for further large randomised controlled trials with adequate sample size, standardised definition, classification and diagnosis of OHSS with live birth rate as an outcome. Economic evaluations were needed.

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