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human reproduction update **IN A NUTSHELL**

# GnRH antagonists are safer than agonists: an update of a Cochrane review

## Background

GnRH agonists or antagonists can be used to prevent LH surges during ovarian stimulation for assisted reproduction. GnRH agonists down-regulate GnRH pituitary receptors. GnRH antagonists directly and rapidly inhibit gonadotrophin release. In a 2006 systematic review involving 29 trials, the average clinical pregnancy rate was 4.7% lower with GnRH antagonist treatment and the incidence of ovarian hyperstimulation syndrome (OHSS) was 2% lower compared with GnRH agonist treatment (Al-Inany *et al.*, 2006). The current update includes 45 trials which addressed live birth or ongoing pregnancy rate (OPR) in GnRH antagonist and GnRH agonist protocols among women undergoing assisted reproduction treatment (Youssef *et al.*, 2011).

## Methods

The authors searched electronic databases including MEDLINE, EMBASE and the Cochrane Library, proceedings of major reproductive medicine conferences and reference lists of retrieved articles, until April 2010. Eligible reports were randomized trials comparing GnRH agonist and GnRH antagonist protocols in women undergoing IVF or ICSI cycles. The primary outcome was live birth. Secondary outcomes included OPR and OHSS rates. The meta-analysis calculated summary average rates, rate differences and rate ratios in the individual trials using the inverse variance procedure, or in case of heterogeneity, random effects models (Deeks *et al.*, 2001).

## Results

**Trial quality.** Forty-five randomized controlled trials (RCTs) including 7511 participants were eligible for the meta-analyses. Thirty-four trials used computer generated randomization and sealed envelopes, while only six trials involved blinding.

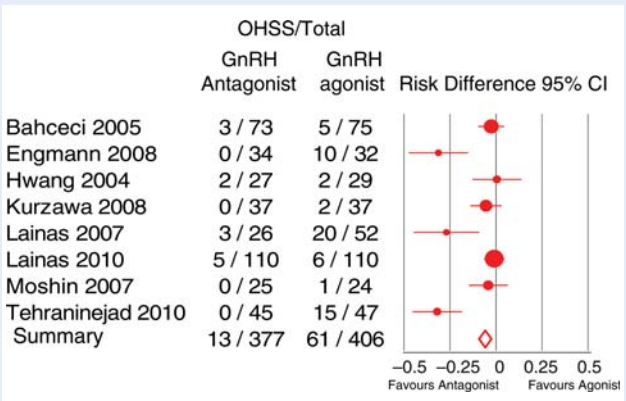


**Figure 1** Women with polycystic ovarian syndrome. Overall Mantel–Haenszel risk difference: −0.10 (95% CI −0.07, −0.14, *P*-value of <0.001). Heterogeneity $\chi^2 = 39.0$, degrees of freedom = 7, $P < 0.001$, $I^2 = 82\%$.

**Live birth or on-going pregnancy rates.** In nine trials involving 1515 women, the average live birth rate with GnRH agonist treatment was 31.5% (95% CI 24.3, 39.7). The live birth rate with GnRH antagonist treatment averaged 1.5% lower (95% CI −2.9, 5.9). In 28 RCTs involving 5014 women, the average OPR with GnRH agonist treatment was 29.8% (95% CI 25.4, 34.6). The OPR with GnRH antagonist treatment averaged 2.0% lower (95% CI −0.4, 4.5). The 95% CIs for the risk difference for both live birth rates and OPRs included zero and neither was significant. The summary rate ratios (relative risks) were as follows: live birth 0.89 (95% CI 0.76, 1.04, $P = 0.14$); OPR 0.91 (95% CI 0.83, 0.99, $P = 0.03$).

**Adverse events.** In 29 RCTs involving 5417 women, the average OHSS rate in the GnRH agonist group was 6.4% (95% CI 4.3, 9.2), ranging from 0.8 to 38.5%. The OHSS rate in the GnRH antagonist group averaged 2.7% lower (95% CI 0.9, 4.5, $P = 0.003$). The relative likelihood of OHSS with GnRH antagonist treatment was 50% of that with GnRH agonist treatment (95% CI 37–66). In eight trials involving 783 women with PCOS, the OHSS rate was 10% lower (95% CI 7, 14) with GnRH antagonist (Fig. 1). In addition, with GnRH antagonist treatment the chance of cancellation or coasting due to high risk to develop OHSS was only 53% of that with GnRH agonist treatment (95% CI 36, 78).

## Conclusions

In this update of a Cochrane review, OHSS rate in women receiving antagonist is significantly lower compared with the agonist protocols. It may be time to consider the GnRH antagonist protocol for patients at high risk of developing OHSS.

## References

Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. *Cochrane Database Syst Rev* 2006;**3**:CD001750.

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG (eds). *Systematic Reviews in Health Care: Meta-analysis in Context*, 2nd edn. London: BMJ Publishing Group, 2001, 285–312.

Youssef MAFM, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, Khattab SM, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008046. DOI:10.1002/14651858.CD008046.pub3.

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