

## WILL THE GnRH-ANTAGONIST REPLACE THE GnRH-AGONIST?

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Two GnRH antagonists, cetrorelix (Cetrotidew; Serono International S.A., Geneve, Switzerland) and ganirelix (Orgalutranw; Antagonw; Organon, Oss, The Netherlands), are currently commercially available for use in ovarian stimulation. In 1999, when the first GnRH antagonist attained market approval, it was expected that these new compounds would rapidly replace GnRH agonists in clinical practice due to several advantages: GnRH antagonists can be administered in the spontaneous cycle, side-effects resulting from hypoestrogenism caused by down-regulation with GnRH agonists are absent, and treatment time is drastically reduced. However, the place of GnRH antagonists in ovarian stimulation has long remained controversial. A Cochrane Meta-analysis (2002) on the phase III studies comparing GnRH agonist and GnRH antagonist treatment regimens suggested a comparatively lower clinical pregnancy likelihood in GnRH antagonist cycles. This generated a lot of concern and led to a low acceptance of GnRH antagonists. However, it has not been made clear in 2002, that the difference in clinical pregnancy rate between agonist and antagonist was not accompanied by a statistically significant difference in live birth rate - which is the truly relevant outcome parameter in IVF.

By 2005, 22 randomized controlled trials (3176 subjects) comparing agonist and antagonist for ovarian stimulation in IVF have been published in peer review journals. In a recent meta-analysis, these trials have been evaluated and summarized. It was found that the probability of live birth after ovarian stimulation and IVF does not depend on the use of either agonist or antagonist for pituitary suppression. Furthermore, this result remained stable in subgroup analyses that ordered the studies by type of population studied (poor response, PCOS etc.), gonadotropin type used for stimulation (urinary, recombinant), type of agonist protocol used (long, short), type of agonist used, type of antagonist protocol used (fixed, flexible), type of antagonist used (cetrorelix, ganirelix), presence of allocation concealment or the presence of co-intervention (such a oral contraceptive pill pre-treatment). Total treatment duration, duration of ovarian stimulation with gonadotropins, and the incidence of severe OHSS requiring hospitalisation are significantly reduced after GnRH antagonist stimulation.

Infertility treatment has overall become a mature science with ovarian stimulation still being a central element of assisted reproduction, especially in the perception of the patient. Whereas not too long ago pregnancy, with little consideration of side-effects of the treatment, appeared an acceptable outcome, the field of infertility treatment increasingly faces demands for safety, simplicity, high efficacy and ease of access. This also impacts on ovarian stimulation, and future progress should stress that these demands must be met. The current available evidence from the literature suggests that the outcome difference with respect to live birth likelihood between the two GnRH analogues has long been over-estimated. This insight paves the way for patient friendly, safe and short-time ovarian stimulation using GnRH antagonists as a first choice GnRH analogue in IVF.