Human Reproduction vol.15 no.9 pp.1881–1883, 2000

DEBATE continued

Embryo implantation and GnRH antagonists

GnRH antagonists in ART: lower embryo implantation?

Shahar Kol

Department of Obstetrics and Gynecology, Rambam Medical Center, Haifa, Israel

To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, Rambam Medical Center, Haifa, Israel. E-mail: skol@rambam.health.gov.il

This debate was previously published on Webtrack, June 12, 2000

Recently, concerns have been raised regarding possible adverse effects of gonadotrophin-releasing hormone (GnRH) antagonists on extra-pituitary reproductive cells and organs, i.e. ovarian cells, oocyte, embryo, endometrium. These concerns are based on numerous in-vitro studies suggesting decreased biosysnthesis of growth factors caused by local action of GnRH antagonists. Clinically, it has been shown that the use of high doses (≤1 mg daily) of GnRH antagonists is associated with low implantation rates in IVF. Although such direct adverse effect of GnRH antagonists cannot be ruled out at this time, so far clinical experience points to profound LH suppression as the major caveat associated with the use of high doses of GnRH antagonists. Very low LH concentrations are associated with aberrant concentrations of oestradiol during ovarian stimulation, which may in turn adversely effect implantation potential. The clinical data available thus far on the use of GnRH antagonists originate from protocols designed for clinical studies. It is predicted that as more clinical experience is gained, and with protocol modifications to suit individual patient response, GnRH antagonists will be comparable with the agonists in terms of cycle outcome.

Key words: ART/GnRH antagonists/implantation rates

A recent debate article (Hernandez, 2000) raises intriguing thoughts on potential adverse effect of gonadotrophin-releasing hormone (GnRH) antagonists in extra-pituitary tissues. Specifically, by decreasing the biosynthesis of growth factors, GnRH antagonists may compromise key events in the reproductive process. This in turn may result in low implantation rate during assisted reproductive technologies (ART). The above reasoning is based on a large body of evidence that documents the ubiquitous existence of GnRH receptors in cells and tissues associated with human reproduction.

We may all agree that continued research efforts aiming at exploring the physiology of GnRH receptors in the reproductive axis are warranted. Special emphasis should be put on crossing the Rubicon, as Dr Hernandez phrases, of ruling out any adverse clinical effect attributable to GnRH analogues (antagonists or agonists). Although a large number of publications cited by Dr Hernandez may indeed suggest such a possibility, it is premature to substantiate any clinical significance at this stage. One should exercise caution in drawing conclusions from in-vitro studies to clinical situations. For example, in one of the papers cited (Raga *et al*., 1999), murine embryos were cultured in the presence of 5–10 μmol/l concentration of GnRH antagonist. This concentration is ~100 times higher than the reported peak blood concentrations of ganirelix 1.1 h after a s.c. injection of the recommended (0.25 mg) dose (Oberyé *et al*., 1999). In addition, rodents and humans may differ in terms of the distribution of GnRH receptors in reproductive cells. In fact, it was claimed that human granulosa cells do not have GnRH receptors (Verbost *et al*., 1999). Lastly, in contrast to the data mentioned by Dr Hernandez, GnRH antagonists may not affect steroid production by rat granulosa cells, while the agonist (buserelin) strongly reduces FSH-stimulated steroid production in these cells (Verbost *et al*., 1999).

The potential effect of GnRH antagonists on the developing embryo merits a closer look. While Dr Hernandez cites a ~30 h half life for cetrorelix, data on ganirelix suggest half life of only 13 h after s.c. administration (Oberyé *et al*., 1999). At any rate, the projected concentrations of the antagonists on embryo transfer day seems to be too low to suggest any effect.

We cannot ignore the fact that the available clinical experience thus far with the antagonists shows a trend toward a lower pregnancy rate in ART, although the difference is not statistically significant (Albano *et al*., 2000). The reasons may have to do with a direct effect on the reproductive tissues as Dr Hernandez speculates, but may also be related to the following aspects.

Firstly, the learning curve: it is expected that the performance of any ART clinic with the antagonists will improve as more clinical experience is gained. The dictated treatment protocols in clinical studies thus far have not allowed the flexibility to modify treatment to meet individual patients' response.

Secondly, in a dose-finding study it was clearly demonstrated that too high doses of GnRH antagonist (≥0.5 mg/day) impair implantation (Ganirelix Dose Finding Group, 1998), whereas spare embryos cryopreserved during cycles with too high doses of GnRH antagonist result in acceptable pregnancy rates after thawing (Kol *et al*., 1999). On the other hand, too low doses of GnRH antagonist (≤0.125 mg) resulted in an increased incidence of premature LH rises, so it may be concluded that the therapeutic window is rather small. To date, no explanation for the direct or indirect effect of too high doses of GnRH antagonist on implantation has been established. However,

under too profound LH suppression, oestradiol concentrations during the late follicular phase may plateau or even decrease, which is in sharp contrast to the natural cycle or stimulated cycles with GnRH agonists or low doses of GnRH antagonists. Therefore, it is tempting to speculate that aberrant concentrations of oestradiol (or its rate of change) influence endometrial development, rather than a direct effect of GnRH antagonists. Aberrant oestradiol rise is secondary to low concentrations of endogenous LH that cannot keep the machinery of oestradiol production running, by supplying sufficient concentrations of aromatase precursors (the 2-cell theory). Very low LH concentrations may result from pituitary down-regulation by GnRH agonists or competitive inhibition by GnRH antagonists, the outcome will probably be the same in terms of oestradiol dynamics and implantation potential.

Thirdly, clinical experience with GnRH antagonists has not yet delineated the full scope of individual response to the 0.25 mg dose in terms of LH suppression. Conceivably, some patients may 'hyper-respond' as evident by very low LH concentrations during stimulation cycles. These cycles may have much in common with high dose GnRH antagonist cycles mentioned above. Assuming that in these patients pituitary suppression is too profound, and that such condition is less favourable for implantation, these patients may benefit from lowering the dose of GnRH antagonist, which will increase the amount of endogenous LH. Protocol individualization and small dose adjustments will be required to optimize clinical outcome in the near future.

In short, with the necessary protocol modifications to suit individual patient response, GnRH antagonists will be comparable with the agonists in terms of cycle outcome. The antagonists should be welcome as a significant addition to the ART pharmacology arsenal. GnRH antagonists offer a number of potential advantages, the most important of which is the ability to trigger ovulation with GnRH agonists, eliminating any threat of ovarian hyperstimulation syndrome (OHSS) (Kol *et al*., 2000). With increasing clinical experience this strategy will gain popularity, leaving OHSS a disease of the past in ART.

To conclude, while continuing efforts at exploring potential effects of GnRH (native, antagonists and agonists) on extrapituitary tissues are encouraged, we can proceed with caution to make routine clinical use of this valuable therapeutic addition in ART.

References

Albano, C., Felberbaum, R.E., Smitz, J. *et al*. (2000) Ovarian stimulation with HMG: results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin. *Hum. Reprod*., **15**, 526–531.

Ganirelix Dose Finding Group (1998) A double-blind, randomized, dose finding study to assess the efficacy of the GnRH antagonist Ganirelix (Org 37462) to prevent premature luteinizing hormone surges in women undergoing ovarian stimulation with recombinant follicle stimulating hormone (Puregon). *Hum. Reprod*., **13**, 3023–3031.

Hernandez, E.R. (2000) Embryo implantation: the Rubicon for GnRH antagonists. *Hum. Reprod.*, **15**, 1211–1216.

Kol, S., Lightman, A., Hilljensjo, T. *et al*. (1999) High doses of GnRH antagonists in IVF cycles do not adversely affect the outcome of subsequent freeze–thaw cycles. *Hum. Reprod*., **14**, 2242–2244.

Kol, S., Mannaerts, M. and Itskovitz-Eldor, J. (2000) Triggering of preovulatory LH surge after treatment with the GnRH antagonist (Antagon) in IVF cycles and the prevention of ovarian hyperstimulation syndrome (OHSS). *J. Soc. Gyn. Invest*., **7**, 300A.

Oberyé, J.J., Mannaerts, B.M., Kleijn, H. J. and Timmer, C.J. (1999) Pharmacokinetic and pharmacodynamic characteristics of ganirelix (Antagon/Orgalutran). Part I. Absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. *Fertil. Steril*., **72**, 1001–1005.

Raga, F., Casan, E.M., Kruessel, J. *et al*. (1999) The role of gonadotropin-releasing hormone in murine preimplantation embryonic development. *Endocrinology*, **140**, 3705–3712.

Verbost, P.M., Smitz, J., Peddemars, C. *et al*. (1999) Effects of GnRH-agonist and antagonists on steroid production in rat and human granulosa cells. [Abstr. no. 101.] *Gynecol. Endocrinol.*, **13** (Suppl), 51.