To agonize or antagonize in gonadotrophin stimulation cycles?

Ricardo Enrique Felberbaum was born in 1961 in Frankfurt am Main. He studied human medicine at the University of Cologne and became MD in 1986. After clinical specialization as a gynaecologist and obstetrician, he joined the group of Klaus Diedrich at the Medical University of Lübeck in 1993. Since then he has done extensive investigations in the use of GnRH antagonists for ovarian stimulation in assisted reproduction treatment, as well as in the treatment of uterine fibroids and endometriosis. Since 1996 he has been the chairman of the German national IVF registry.

Dr Ricardo Enrique Felberbaum

Ricardo Felberbaum[1,3], Georg Griesinger[2], Dominique Finas[1], Anja Dawson[1], Klaus Diedrich[2]
[1]Department of Obstetrics and Gynecology, Clinic of Kempten, Academic Teaching Hospital, University of Ulm; [2]Department of Obstetrics and Gynecology at the Medical University of Lübeck, Germany
[3]Correspondence: Department of Obstetrics and Gynecology, Klinikum Kempten-Oberallgäu, Robert Weixler Straße 50, 87439 Kempten, Germany. Tel: +49 831 5303393; Fax: +49 831 5303457; e-mail: Ricardo.Felberbaum@Klinikum-Kempten.de

Abstract

High hopes accompanied the release of gonadotrophin-releasing hormone (GnRH) antagonists onto the market at the end of the last millennium. Today, it must be admitted that not all of these hopes have been realized. According to large meta-analyses, treatment time for ovarian stimulation could be significantly shortened, and the incidence of severe ovarian hyperstimulation syndrome (OHSS) could also be reduced. However, the achieved clinical pregnancy rates seem not to be equivalent to those obtained after ovarian stimulation using GnRH agonists in the so-called long protocol. Very recent studies have demonstrated that oversuppression of LH after initiating GnRH antagonist administration seems not to be responsible for that observation. Moreover, supplementation with recombinant LH does not increase success rates. However, an analysis based on the data of the German IVF registry (DIR), scrutinizing more than 1800 cycles in so-called ideal patients (age <35 years, first treatment cycle, pure tubal infertility, only classical IVF), did not demonstrate any differences in pregnancy rates between GnRH antagonists and GnRH agonists. These data seem to indicate that GnRH antagonists should be used as 'first choice treatment' in ovarian stimulation.

Keywords: *GnRH antagonists, healthy user effect, ovarian stimulation, pregnancy rates*

Introduction

While GnRH antagonists were released to the market at the end of the last millennium, many people believed that they would have a significant impact on attitudes towards ovarian stimulation for assisted reproduction. It was claimed that they would reduce treatment time as well as amount of gonadotrophins, costs and risks, making life easier and treatment more pleasant. The necessity or non-necessity of luteal phase support was an open question at that time, but the most important hypothesis was that clinical results would be equivalent to those obtained by using GnRH agonists, or even better (Felberbaum *et al*., 1998).

Phase III studies and meta-analyses

However, things developed in a different way and not all of these prophecies were fulfilled. While in several phase III trials there was a slight tendency towards better results using GnRH agonists compared with antagonists, no statistically significant differences could be shown (Ludwig *et al*., 2001). Moreover, there was a clear and almost statistically significant reduction in the incidence of severe ovarian hyperstimulation syndrome (OHSS III), which normally makes hospitalization of the patient necessary (Albano *et al*., 2000; Ludwig *et al*., 2001). This remains one of the most important achievements following the development of GnRH antagonists.

It came as a dramatic blow when Al-Inany and Aboulghar published their Cochrane Database Analysis in 2001, claiming that GnRH antagonists definitely shortened treatment time significantly, and also prevented the patient from experiencing the typical oestradiol withdrawal symptoms and cyst formation. On the other hand, there were significantly fewer pregnancies after ovarian stimulation with GnRH antagonists (Al-Inany and Aboulghar, 2002).

Fewer pregnancies after GnRH antagonists: why?

This meta-analysis signified the starting point of a vigorous debate about the possible causes of this observation. It also raised debate as to whether the primary data might be biased by many factors such as learning curve, treatment of second choice and healthy user effect.

One of the striking arguments was that GnRH antagonists might lead to oversuppression of LH after their use when ovarian stimulation was performed with recombinant FSH (r-FSH) alone, which is devoid of any LH activity. Indeed, the first studies using the antagonist cetrorelix, even in high dosages, were performed using urinary human menopausal gonadotrophins (HMG) possessing both FSH and LH activity (Felberbaum *et al*., 1996). In particular, the Ganirelix Dose Finding Study had given important hints that LH oversuppression could occur, and could have deleterious effects on outcomes (Ganirelix Dose Finding Study Group, 1998).

Analysis of pulsatility patterns showed dramatic declines in LH concentrations in serum after the onset of GnRH antagonist administration, in cases where ovarian stimulation was performed using r-FSH only. Within 3 h, LH concentrations of <0.3 mIU/ml were measured, far below what had previously been believed to be the lower ceiling concentration to sustain normal folliculogenesis and oestradiol biosynthesis (A. Dawson *et al*., personal communication). This sharp suppression was reflected by a fall in oestradiol concentrations with a certain delay, but nevertheless clearly detectable (**Figures 1** and **2**).

From a pathophysiological point of view, this made much sense, as a reduction in LH concentrations also meant a reduction in the synthesis of androgen precursor theca cells which were aromatized in granulosa cells.

If these variations in serum concentrations of LH and oestradiol can influence implantation and endometrial receptivity, then LH supplementation using recombinant LH (r-LH) should lead to better results. Unfortunately the first prospective randomized trial using r-LH and r-FSH in a combination of 1:2 in the so-called multiple dose protocol revealed depressing results. With the exception of higher oestradiol concentrations on the day of HCG administration, no differences in number and quality of cumulus–oocyte complexes retrieved, or in the quality of cultured embryos, could be observed. Yet implantation and clinical pregnancy rates were clearly poorer when r-FSH was used in combination with r-LH; r-FSH alone did better! What a surprise! Obviously r-LH remains a compound in search of its own indication, something very strange and rare in the history of pharmaceuticals (Griesinger *et al*., 2005).

Destiny of GnRH antagonists will be decided in daily clinical practice

As no clear explanation was at hand, it seemed as if time would identify the place of GnRH antagonists in ovarian stimulation. However, results obtained in a huge national registry were not very encouraging. In the year 2002, 5332 reported cycles of IVF using GnRH antagonists gave mean clinical pregnancy rates of 22.62, 26 and 24.87% when combined with u-FSH, r-FSH and HMG respectively. For comparison, mean clinical pregnancy rates after ovarian stimulation using GnRH agonists according to the long protocol were 29.56, 28.94 and 29.19% for u-FSH, r-FSH and HMG respectively. With ICSI, clinical pregnancy rates showed the same discrepancies (Deutsches IVF Register Yearbook, 2002).

GnRH antagonists in 'ideal patients'

In 2000, the first year after GnRH antagonists became available, 37,230 GnRH agonist long protocol and 7821 GnRH antagonist ovarian stimulation cycles were initiated. By 2003, numbers of cycles using GnRH antagonist utilization had increased 2.89-fold to a total number of 22,614. In contrast, 53,151 GnRH agonist cycles utilizing GnRH agonists were recorded in 2003, which translates into a 1.42-fold increase in long protocols using GnRH agonists from 2000 to 2003. Whereas in the year 2000, around one in seven ovarian stimulation cycles had utilized GnRH antagonists, by 2003 a total of one in four cycles were using GnRH antagonists.

These crude and raw data compilations seemed to imply that it made sense to extract the data of those treatment cycles in so-called 'ideal' patients. This meant patients aged <35 years, in their first treatment cycle, only those with tubal infertility and the application of only classical IVF. This analysis was performed for German data between the years 2000 and 2003.

With the short protocol using GnRH agonists, 901 cycles in ideal patients could be identified. In long protocols using GnRH agonists, 7712 cycles could be identified. Lastly, 1852 cycles used GnRH antagonists. Embryo transfer rates with the short protocol were 88.8 and 89.1% for the long protocol and 88% for the GnRH antagonist protocol.

Most important were results regarding mean rates of clinical pregnancies. The short protocol yielded 31%, the long protocol 37.8% and the GnRH antagonist protocol gave 36.1%. No statistical difference between GnRH agonists used according to the long protocol and the use of GnRH antagonists could be detected (**Table 1**)

Conclusions

GnRH antagonists are certainly used at the moment primarily as compounds of second choice. This is what 'healthy user effect' means. Clinically difficult patients, such as poor responders, older women and poor implanters, are usually chosen for this new treatment option. However, neither GnRH agonists nor GnRH antagonists are able to change the clinical profiles of the patients. Results published by Kolibianakis and co-workers showed how early and standardized onsets of the administration of GnRH antagonists and early administration of HCG could induce final follicular maturation and enhance clinical results after ovarian stimulation using GnRH antagonists (Kolibianakis *et al*., 2004). These data seem to indicate that GnRH antagonists should be used as 'first choice treatment' in ovarian stimulation. Time will tell if GnRH antagonists can replace GnRH agonists for stimulation.