Commentary

To add or not to add LH: consideration of LH concentration changes in individual patients

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Abstract

The availability of recombinant FSH and LH opens an opportunity to individualize ovarian stimulation. While the need for FSH is universal, a question remains whether exogenous LH is beneficial. Previous research on adding LH to an unselected group of patients failed to demonstrate any advantage. Indeed, it may seem presumptuous to expect that all patients will respond in the same manner. Recent studies hint that LH supplementation should be individualized. These studies indirectly suggest that the changes in LH concentration may be more important than the concentration per se. The growing follicle, and particularly oestradiol biosynthesis, may be sensitive to decreases in LH concentrations. The challenge is to identify the patient whose LH will drop during stimulation. This individualized approach will assure that supplemented LH will only be given to those who need it.

Keywords: individualized approach, LH dynamics, ovarian stimulation

Introduction

Ovarian stimulation paradigms have witnessed a significant shift in the medications used during the last 30 years. Until the mid-1990s, human menopausal gonadotrophin (HMG), comprising equal FSH and LH activity, was the only product used. The availability of recombinant FSH preparations led to stimulation protocols based on FSH only. The question whether gonadotrophins containing LH activity are needed in gonadotrophin-releasing hormone (GnRH) agonist-based cycles remains open (Balasch et al., 2003; Filicori and Cognigni, 2003). Following the introduction of GnRH antagonists, practitioners further raised the question whether LH activity is required during stimulation. Industry support to research in that direction came when recombinant human LH (hLH) became available. Most of this research sought to demonstrate that LH is needed by all patients. Current knowledge proves that adding LH to all patients is not justified. The decision to add LH should probably be individualized. In addition, agonist and antagonist-based cycles need to be considered separately. It is not the intention of this short communication to review in full the vast literature on the subject, but to offer a new perspective on the question at hand.

GnRH agonist-based protocols

Endogenous LH and clinical outcome

Sills et al. (1999) concluded that appropriate endogenous LH concentrations exist despite GnRH agonist pituitary suppression, thereby obviating the need for adding LH. Peñarrubia et al. (2003) showed that LH concentrations during stimulation cannot predict outcome. They assessed mean LH concentrations for each group of patients with similar outcome every other day during stimulation. Individual LH variability was not assessed.

Supplemented LH

Marrs et al. (2004) randomly assigned patients to receive hLH from day 6 of stimulation. The control group continued with FSH only. Both groups performed equally well, with a trend towards better results with hLH in patients >35 years of age. Humaidan et al. (2004) followed a similar protocol to find similar outcome. Balasch et al. (2001b) also concluded that there is no need for additional exogenous LH in down-regulated women. In fact, the addition of hLH may even have a negative impact on oocyte maturation and fertilization (Balasch et al., 2001a). In contrast, Lisi et al. (2005) found that there was an increase in pregnancy and delivery rates in patients stimulated with hFSH supplemented with hLH. Interestingly, the same group (Lisi et al., 2002), reporting a similar trial, concluded that the addition of hLH to an unselected group of patients appears to offer little benefit; however, there might be a selected group with profound LH suppression in whom the rate of implantation might be improved. Indeed, this was a significant step forward in departing from the paradigm of ‘one protocol fits all’ and trying to identify a subgroup of patients who may benefit from supplemented LH.

GnRH antagonist-based protocols

As soon as GnRH antagonists became clinically available, large industry-supported research promoted an LH-free, FSH-only GnRH antagonist-based protocol. However, often practitioners tend to add or switch to HMG once the antagonist is introduced...
to the stimulation protocol (personal communication). Recent industry-supported research acknowledges this trend: Wilcox et al. (2005) reported on a randomized trial comparing cetrorelix and ganirelix. Both treatment groups were given a daily dose of 75 IU of HMG (Pergonal), starting on the day of antagonist administration. Indiscriminate LH supplementation is probably redundant; however, further thought must be given to the source of the clinical trend to add HMG once GnRH antagonist treatment is initiated.

Endogenous LH and clinical outcome

Merviel et al. (2004) looked retrospectively on the effect of LH concentration on the day of human chorionic gonadotrophin (HCG). Clinical outcome of patients with LH ≤0.5 was comparable to that of patients with LH ≥0.5. Table 2 in that paper suggests that both groups had a similar magnitude of LH decrease from day 8 (cetrorelix 3 mg administration) to the following day, day 9. However, from that day to the day of HCG administration, the LH concentrations remained constant in both groups. Similarly, Kolibianakis et al. (2004) assessed cycle day 8 LH concentration as outcome predictor. They found that profound LH suppression on day 8 was associated with excellent clinical results. Although not specifically assessed for, their data suggest that the group with lowest LH concentrations on day 8 (and best clinical outcome) had a steady LH concentration during the late follicular phase (from day 8 until day of HCG administration).

Supplemented LH

Cédrin-Durnerin et al. (2004) studied the effect of additional hLH following a single dose of cetrorelix 3 mg. Their results showed that in this unselected group of patients there is no benefit to add hLH. Griesinger et al. (2005) used a daily antagonist protocol (cetrorelix 0.25 mg) and reached similar results. Acevedo et al. (2004), using an elegant donor–recipient model (to ‘filter out’ the endometrial factor) found that LH supplementation improved pregnancy rate in recipients whose embryos originated from GnRH antagonist (daily cetrorelix 0.25 mg) treated donors.

Hints for individualized approach

Clearly, the above cited research gave conflicting results, leaving the practitioner bewildered as to how to optimize ovarian stimulation. Recent studies took novel approach that may shed some light on the question. De Placido et al. (2005) found that in 12–14% of down-regulated patients the initial response to FSH is suboptimal (in terms of follicular growth and oestradiol rise). They suggested that these patients are the candidates for hLH supplementation. Their results support this hypothesis. Data in Table II in their paper demonstrate that the normal responders increased their mean LH concentrations from 1.5 to 4.3 after 8 days of stimulation, while the mean LH concentration in the suboptimal responders decreased from 1.2 to 0.7 during this same period of time. Although the study did not focus on these changes, they suggest that the follicular unit is sensitive not necessarily to the current concentration of LH, but rather to the dynamics of the change in these concentrations.

Data from GnRH antagonist-based cycles hint at the same direction. Huirne et al. (2005) conducted a GnRH antagonist dose-finding study. They showed that the area under the curve (AUC) adjusted (rather than absolute AUC) for baseline LH on day 6 (start day of antagonist, see Figures 1 and 6 of the paper) was predictive of clinical pregnancy. If this value was less than –2.2, no pregnancy was recorded. A negative value for adjusted AUC means that the LH concentration dropped during the antagonist co-treatment (day 6 to day of HCG), with no relevance to the actual concentrations. The only significant covariant to clinical pregnancy in univariate analyses was changes in LH concentrations. In other words, this paper suggests that the direction and rate of change in LH concentrations are the important factors governing the follicular unit development, not the LH concentration itself.

Conclusions

Personal daily clinical observation and the last two cited papers introduce a novel concept to the study of follicular growth in relation to LH concentration. The most important factor seems to be the dynamics of changes in LH concentration, not the actual concentration at a given point. Oestradiol biosynthesis reflects LH changes, not the serum concentration per se. Is it possible that a significant drop in LH (regardless of the actual concentration) interferes with normal follicular oestradiol rise, reflecting abnormal follicular function? Further research is needed to confirm or refute this notion. If found relevant, ways to predict individual patient response in that aspect should be sought, so that an individualized approach to treatment can be planned. The author’s personal experience is that LH should be routinely measured during stimulation. This may shed light on individual response to GnRH analogues. Knowing individual response helps to ‘fine tune’ future treatment cycles if needed. In a ‘first timer’ on antagonist-based cycles, it is preferable to add recombinant LH or partly switch to HMG on the day of antagonist administration.

References


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Received 18 July 2005; refereed 17 August 2005; accepted 13 September 2005.