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

Acevedo B, Sanchez M, Gomez JL *et al*. 2004 Luteinizing hormone supplementation increases pregnancy rates in gonadotropin-releasing hormone antagonist donor cycles. *Fertility and Sterility* **82**, 343–347.

Balasch J, Peñarrubia J, Fábregues F *et al*. 2003 Ovarian responses to recombinant FSH or HMG in normogonadotropic women following pituitary desensitization by a depot GnRH-agonist for assisted reproduction. *Reproductive BioMedicine Online* **7**, 35–42.

Balasch J, Creus M, Fabregues F *et al*. 2001a The effect of exogenous luteinizing hormone (LH) on oocyte viability: evidence from a comparative study using recombinant human follicle-stimulating hormone (FSH) alone or in combination with recombinant LH for ovarian stimulation in pituitary-suppressed women undergoing assisted reproduction. *Journal of Assisted Reproduction and Genetics* **18**, 250–256.

Balasch J, Vidal E, Peñarrubia J *et al*. 2001b Suppression of LH during ovarian stimulation: analysing threshold values and effects on ovarian response and the outcome of assisted reproduction in down-regulated women stimulated with recombinant FSH. *Human Reproduction* **16**, 1636–1643.

Cédrin-Durnerin I, Grange-Dujardin D, Laffy A *et al*. 2004 Recombinant human LH supplementation during GnRH antagonist administration in IVF/ICSI cycles: a prospective randomized study. *Human Reproduction* **19**, 1979–1984.

De Placido G, Alviggi C, Perino A *et al*. 2005 Recombinant human

LH supplementation versus recombinant human FSH (rFSH) step-up protocol during controlled ovarian stimulation in normogonadotrophic women with initial inadequate ovarian response to rFSH. A multicentre, prospective, randomized controlled trial. *Human Reproduction* **20**, 390–396.

Filicori M, Cognigni G 2003 Efficiency and efficacy of exogenous gonadotrophins containing LH activity. *Reproductive BioMedicine Online* **7**, 254–255.

Griesinger G, Schultze-Mosgau A, Dafopoulos K *et al*. 2005 Recombinant luteinizing hormone supplementation to recombinant follicle-stimulating hormone induced ovarian hyperstimulation in the GnRH-antagonist multiple-dose protocol. *Human Reproduction* **20**, 1200–1206.

Huirne JA, van Loenen AC, Schats R *et al*. 2005 Dose-finding study of daily GnRH antagonist for the prevention of premature LH surges in IVF/ICSI patients: optimal changes in LH and progesterone for clinical pregnancy. *Human Reproduction* **20**, 359–367.

Humaidan P, Bungum M, Bungum L *et al*. 2004 Effects of recombinant LH supplementation in women undergoing assisted reproduction with GnRH agonist down-regulation and stimulation with recombinant FSH: an opening study. *Reproductive BioMedicine Online* **8**, 635–643.

Kolibianakis EM, Zikopoulos K, Schiettecatte J *et al*. 2004 Profound LH suppression after GnRH antagonist administration is associated with a significantly higher ongoing pregnancy rate in IVF. *Human Reproduction* **19**, 2490–2496.

Lisi F, Rinaldi L, Fishel S *et al*. 2005 Evaluation of two doses of recombinant luteinizing hormone supplementation in an unselected group of women undergoing follicular stimulation for in vitro fertilization. *Fertility and Sterility* **83**, 309–315.

Lisi F, Rinaldi L, Fishel S *et al*. 2002 Use of recombinant LH in a group of unselected IVF patients. *Reproductive BioMedicine Online* **5**, 104–108.

Marrs R, Meldrum D, Muasher S *et al*. 2004 Randomized trial to compare the effect of recombinant human FSH (follitropin alfa) with or without recombinant human LH in women undergoing assisted reproduction treatment. *Reproductive BioMedicine Online* **8**, 175–182.

Merviel P, Antoine JM, Mathieu E *et al*. 2004 Luteinizing hormone concentrations after gonadotropin-releasing hormone antagonist administration do not influence pregnancy rates in in vitro fertilization–embryo transfer. *Fertility and Sterility* **82**, 119–125.

Peñarrubia J, Fábregues F, Creus M *et al*. 2003 LH serum levels during ovarian stimulation as predictors of ovarian response and assisted reproduction outcome in down-regulated women stimulated with recombinant FSH. *Human Reproduction* **18**, 2689–2697.

Sills ES, Levy DP, Moomjy M *et al*. 1999 A prospective, randomized comparison of ovulation induction using highly purified follicle-stimulating hormone alone and with recombinant human luteinizing hormone in in-vitro fertilization. *Human Reproduction* **14**, 2230–2235.

Wilcox J, Potter D, Moore M *et al*. 2005 Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertility and Sterility* **84**, 108–117.

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