Letters to the Editor

What clinical evidence for an LH ceiling?

Dear Sir,

Loumeye et al. (2003) have studied the administration of recombinant (r)LH in the last stages of follicular stimulation in WHO type I and type II anovulatory patients (World Health Organization, 1973). Although we participated in these studies as Clinical Investigators we were not consulted when this manuscript was drafted and we dissent with the conclusion that LH activity negatively affects late folliculogenesis. Larger antral follicles express granulosa cell LH receptors; LH stimulation allows these follicles to develop despite the declining FSH concentrations encountered in the late follicular phase of the menstrual cycle (Zeleznik et al., 1984; Campbell et al., 1999). When combined with FSH, rLH increased the number of preovulatory follicles >10 mm in a dose-dependent manner (The European Recombinant Human LH Study Group, 1998), and low-dose hCG accelerated the growth of >14 mm diameter follicles (Filicori et al., 1999a,b). Although we repeatedly observed that LH activity administration can decrease the number of small (<10 mm diameter) preovulatory follicles, larger antral follicles were never reduced by this manoeuvre (Filicori et al., 2001; 2002a,b). We also demonstrated that ovarian follicles >14 mm continue to grow (Filicori et al. 2002b) and yield reproductively competent oocytes (Filicori et al., 2002c) when FSH administration is partly or completely replaced by low-dose hCG. Furthermore, rLH alone can maintain estrogen secretion when rFSH is discontinued (Sullivan et al., 1999), and it was recently shown that late follicular phase hMG administration after rFSH priming is beneficial for assisted reproduction outcome in women with low endogenous LH (Commenges-Ducos et al., 2002).

Conversely, Loumeye et al. showed that, in stimulated cycles of WHO type I anovulatory patients (World Health Organization, 1973), the late follicular phase administration of rLH 225 IU/day alone was associated with a marked decrement in the number of preovulatory antral follicles >11 mm; from these results they concluded that LH administration can trigger the growth arrest of these follicles. However, we feel that an alternative and more likely explanation for the findings of this study can be proposed. We believe that follicle regression in the hypogonadotrophic patients of Study A, treated with rLH only, was caused by the discontinuation of FSH treatment when ovarian follicles were not yet mature enough to be supported by LH alone; this may have depended on a lack or an insufficient expression of granulosa cell LH receptors. In animal models, a sudden withdrawal of FSH has been shown to be associated with antral follicle demise, while LH administration supported folliculogenesis when FSH discontinuation was more gradual (Campbell et al., 1999). The finding that preovulatory follicles >11 mm were not reduced when Loumeye et al. administered the same rLH dose in combination with rFSH (in this group there was actually a non-significant trend towards more >11 mm follicles) clearly indicates that FSH deprivation rather than any detrimental actions of LH caused this effect.

Furthermore, no information is provided on the follicle pattern in the different treatment groups on the first day of the blinded phase (T1). However, on that day serum estradiol (E2) levels seemed to be higher in at least some of the patients treated with rFSH/rLH (although unfortunately Table III does not provide a statistical assessment of these results); this feature suggests that a greater number and/or more mature follicles could have been present on day T1 in that group. If that was the case, the randomization process may have been flawed. In addition, estrogens synergize with FSH to induce LH receptor expression in granulosa cells (Rani et al., 1981); reduced estrogen may have further contributed to doom follicle development through inadequate granulosa cell LH receptor levels.

The regression of antral follicles in the rLH-only group could also be related to the rLH dose and administration regimen adopted. To maintain follicle estrogen secretion and repro-
ductive competence in the absence of FSH administration in the last days of ovarian stimulation, Sullivan et al. (1999) gave 150 or 375 IU of rLH at 12 h intervals (i.e. 300–750 IU/day) instead of 225 IU every 24 h as in this study; the short half-life of rLH suggests that such an administration scheme could be more suitable. In our studies, support of folliculogenesis without FSH administration was ensured by 200 IU/day of hCG that correspond to at least 1200 IU/day of LH (Filicori et al., 2002b; c); in addition to the higher potency of this drug regimen, the longer half-life of hCG also guaranteed a more stable occupation of LH receptors than the use of rLH.

Limited conclusions on the action of rLH in anovulatory WHO type II patients can be drawn from Study B as no significant between-group differences in the number of ≥11 or ≥14 mm follicles occurred by the end of rLH/placebo administration. However, also in this study the finding that apparently higher E2 levels were present in the placebo-treated patients on the day of the rLH/placebo start (again no statistics provided) raises doubts regarding the comparability of folliculogenesis in the various groups at the time of FSH discontinuation and on the randomization process in general (parenthetically the E2 median on the day of rLH/placebo start in the rLH 225 IU/day group that is reported in table IV as 8512 pmol/l is probably incorrect as the range of the E2 values on the same day was 384–3880 pmol/l).

In summary, we feel that the results of the study by Loumaye et al. provide inadequate information to assess the effects of late follicular phase rLH administration during ovulation induction and no clear evidence that LH exerts detrimental effects on the development of larger antral follicles.

References


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