Letter to the Editor

Clinical evidence for an LH ceiling?

Dear Sir,

We read with interest the letter by M. Filicori (Filicori et al., 2003) commenting on our pilot studies published earlier in Human Reproduction (Loumaye et al., 2003).

Filicori et al. remind us that they have repeatedly reported a reduction in ‘small’ follicles (<10 mm) by administering LH activity during the follicular phase. This supports a ‘ceiling’ for LH on antral follicles with a diameter <10 mm; however, they challenge such effect of LH on larger follicles (>10 mm). This is based on four pilot studies published by the same group (Filicori et al., 1999, 2001, 2002a, b).

There are some significant methodological differences between their work and ours. (i) Their studies were conducted in normal, ovulatory women down-regulated with a GnRH agonist and undergoing controlled ovarian stimulation, whereas we studied anovulatory women undergoing ovulation induction aiming at monofollicular development. (ii) Their studies were single-centre, open-label studies and no information on the randomization method is provided (Filicori, 2001; Filicori et al., 2002a, b), whereas ours were multi-centre, double-blind, placebo-controlled studies using a centralized, computer-assisted randomization process with stratification by centre. (iii) Either HMG (which contains variable amounts of LH and HCG) or u-HCG were used by Filicori et al., whilst we used rhLH. (iv) In two of their studies, the LH activity was administered from the beginning of the stimulation (Filicori et al., 1999, 2001), while in two studies LH activity was started at day 8 of the stimulation whatever the individual follicular development (Filicori et al., 2002a, b). In contrast, we administered LH on an individual basis when a pre-defined follicular development was reached (i.e. when follicle sizes were between 10 and 14 mm).

However, despite these differences in methodology, a reduction in the number of large follicles is reported in two of Filicori et al.’s studies in the group of patients receiving some LH activity compared with the FSH only group. In one study, the number of follicles >14 mm was reduced by 25% ($P = 0.05$), and the number of follicles 10–14 mm by 14% (not significant) (Filicori et al., 1999). In the second study, a clear trend toward a dose-dependent reduction in the number of follicles >14 mm and follicles 10–14 mm is reported, but pairwise comparisons were reported to be not significant (Filicori et al., 2002a). No trend test was performed, and considering the small sample size, it is difficult to conclude whether the lack of statistical difference is due to absence of true difference or to insufficient power.

Filicori’s suggests that in our study designated A, the reduction of follicles in the LH alone group was due only to the withdrawal of FSH. We indeed mention in our discussion that complete withdrawal of exogenous FSH administration appears to be too detrimental, especially in WHO group I patients. However, our data also show clearly that LH did not sustain follicle growth despite follicles size between 10 and 13 mm. Granulosa cell LH receptor acquisition is documented to occur in follicles of <8 mm, in both healthy women and patients with polycystic ovary (Jakimiuk et al., 2001). Additional evidence that LH plays some role in restricting the number of follicles available for ovulation was found in the FSH + LH group, where there were very few follicles 14–18 mm compared with FSH alone (see our Figure 1). Finally, the apparent difference at baseline in the estradiol mean value is not supported by the median values, and the analysis of the mean number of follicles at the end of the treatment was adjusted for the number of follicle at baseline. This excludes a bias due to difference at baseline.

The discussion on the dose of LH is relevant. Sullivan et al. (1999) reported maintenance of estrogen secretion during the late follicular phase with a daily dose of up to 750 IU rhLH/day, but no data are provided on the number and individual size of follicles. Filicori et al. reported no effect on the number of follicles with a dose of 200 IU HCG, which corresponds to >1000 IU LH activity in the bioassay (Filicori et al., 2002b). Contrasting with this observation, we recently completed a larger study testing several doses of rLH + 37.5 IU rhFSH versus 37.5 IU rhFSH + placebo in WHO group II anovulatory women overresponding to FSH (three or more follicles 11–15 mm). The proportion of patients who had only one follicle >16 mm was rLH dose dependent, and with a dose of 30 µg/day rLH (~750 IU) it was found to be 3-fold higher than with FSH alone ($P < 0.05$) (Serono Study 21441, data on file). Altogether, this suggests that beyond the dose, the type of LH activity, the patient’s pathology and the follicular development status when LH administration is initiated may all have a significant impact on the ceiling for LH.

In conclusion, both our data and some data published by Filicori et al. strongly suggest a ceiling for LH during the late follicular phase, for both small and large antral follicles, as originally proposed (Hillier, 1994). Considering the immense need for reducing the incidence of multiple pregnancy and birth when inducing ovulation in anovulatory women, we recommend pursuing further investigation of the ceiling for LH and its putative therapeutic application in minimizing the number of pre-ovulatory follicles.

Note: the estadiol median value at baseline of the 225 IU rLH group in study B in our Table IV (Loumaye et al., 2003) should indeed read 851.2 pmol/l instead of 8512 pmol/l.

References

Filicori, M., Cognigni, G.E., Taraborelli, S., Spettoli, D., Ciampaglia, W., Tabrelli De Fatis, C. and Pocognoli, P. (1999) Luteinizing hormone activity supplementation enhances follicle-stimulating hormone efficacy and


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