Letters to the Editor

What is the LH ceiling level for follicular growth arrest in late follicular phase?

Dear Sir,

We read the article by Loumaye et al. (2003) with interest. They drew a conclusion that recombinant (r)LH alone can trigger follicular growth arrest in suggesting the existence of an ‘LH ceiling’ during late follicular maturation. The authors showed that almost one third of patients had follicular growth arrest in the rLH-administered groups; conversely, the follicles persisted in growing in the control groups. While the authors administered 225 IU/day or 450 IU/day of rLH in World Health Organization (WHO) type I and type II patients, they did not come to a conclusion what is the LH ceiling level for ovarian stimulation.

Recently, we achieved a successful twin pregnancy after very high-dose hMG and GnRH antagonist as the regimen for ovarian stimulation. A 30 year old Chinese female with a history of secondary infertility for 3 years, due to tubal factor, had three previous controlled ovarian stimulations (COS) for IVF trials. The previous IVF cycles were cancelled because of failure in COS using pituitary down-regulation. The dosage of gonadotrophin used was 225 IU of FSH (Metrodin; Serono, Switzerland) and 225 IU of hMG (Pergonal; Serono) per day in the third trial which was cancelled again due to lack of follicular growth after 8 days of ovarian stimulation. The estradiol (E2) level was 220 pg/ml on the ninth stimulation day. The fourth IVF cycle was started with a dose of 300 IU of hMG twice daily, beginning on the second day of the cycle and lasting 5 days. The treatment was monitored by daily transvaginal ultrasound (Figure 1). A follicle that had reached 14 mm was detected by transvaginal ultrasound on cycle day 7; therefore, s.c. cetorelix (Cetrotide; Serono) 0.25 mg was given daily for 4 days. The hMG regimen was continuously administered for 3 days at the same dosage. On day 10, hCG 10 000 IU was administered when the E2 and LH levels were 2409 pg/ml and 2.38 IU/l respectively. The oocyte retrieval was performed 36 h later; six oocytes were retrieved, four having been fertilized normally. On cycle day 14, three embryos at the 4–5-cell stage were transferred. Twin pregnancy was demonstrated 4 weeks later by transvaginal ultrasound. Two healthy babies, weighing 3300 and 3100 g, were delivered at 37 weeks gestation by Caesarean section on January 18, 2003.

FSH and LH are both essential in the process of folliculogenesis and steroidogenesis for the natural menstrual cycle. In COS for IVF, the FSH is an indispensable element for folliculogenesis. However, the LH appeared to play a debatable role regarding ‘threshold’ and ‘ceiling’ levels. Although low-dose LH administration during COS would optimize the folliculogenesis through the LH receptor expressed on granulosa cells in larger antral follicles, the addition of high-dose LH seemed to be detrimental to follicular growth (Hillier, 1994). Loumaye et al. seemed to demonstrate 225 IU/day of LH as the so-called ceiling level because follicular regression happened to six out of 10 patients administered with 225 IU/week.

Figure 1. The change of ovarian follicles and hormonal assay were recorded and hCG was administered on cycle day 10 when two follicles reached 18 mm. The follicular size showed progressing enlargement even under a very high hMG dose. OPU = oocyte pick-up; ET = embryo transfer.

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day of rLH-alone in late follicular phase. However, follicular regression was encountered only in one out of eight patients administered with 225 IU/day of rFSH/rLH and in three out of eight patients administered with 450 IU/day of rLH-alone. Meanwhile, enumerating the hormone profile during treatments with rLH, the authors showed that patients with 225 IU/day of rLH had different LH serum levels. In WHO type I, it was 1.3 IU/l before stimulation and 1.9 IU/l after stimulation; in WHO type II, it was 5.3 IU/l before stimulation and 6.8 IU/l after stimulation. It is inconsequent that the follicular regression occurred four out of six in WHO type I and two out of four in WHO type II. However, Loumaye et al. did not discuss why lower serum LH activity in WHO type II produced more follicular regression than did higher serum LH activity in WHO type II.

The hypothesis for the LH ceiling poses that LH, beyond a certain high level, suppresses granulosa proliferation, and initiates non-dominant follicle atresia (Hillier, 1994). Re-examining the data provided by Loumaye et al., we would like to point out that the data were misinterpreted and that declining FSH activity should be responsible for atresia of follicles (Campbell et al., 1999). In our case, even though the LH dosage was escalated to as high as 600 IU/day, continuously administered from the beginning to the end of COS, no untoward effect was encountered when the FSH administration was maintained. Higher LH activity was reported with 200 IU/day of hCG-alone to stimulate follicles in the late follicular phase; nonetheless, the equivalent LH bioactivity mentioned by the authors was based on speculation (Filicori et al., 2002).

In several prospective, randomized studies, hMG was proven to be as effective as rFSH in COS for assisted reproductive treatment (Gordon et al., 2001; Ng et al., 2001; Westergaard et al., 2001; European and Israeli Study Group, 2002; Kilani et al., 2003). These studies used hMG or rFSH from the beginning of ovarian stimulation with LH dosage ranging from 150 to 450 IU/day in hMG groups. Calculating the pregnancy rate in rFSH and hMG groups, a recent meta-analysis found a borderline significant outcome in favour of hMG (Al-Inany et al., 2003; Van Wely and Van der Veen, 2003). The detrimental effect advocated by the LH ceiling hypothesis seems to lack clinical evidence so far. However, if the LH ceiling really exists, it should be >600 IU/day of LH.

References


Ng EH, Lau EY, Yeung WS and Ho PC (2001) HMG is as good as recombinant human FSH in terms of oocyte and embryo quality: a prospective randomized trial. Hum Reprod 16, 319–325.


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