RELEASE OF LH DURING TREATMENT WITH PURIFIED SHEEP FSH WITHOUT SIGNS OF ADEQUATE FOLLICULAR MATURATION IN WOMEN

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Four amenorrhoeic women were treated with a purified sheep FSH preparation. During treatment, plasma progesterone, oestradiol and LH concentrations were measured every 24 or 48 hr. In all the women, an LH peak was found during treatment, even though in three of these there was no evidence of adequate follicular maturation, as assessed by plasma oestradiol levels. These results indicate that a peak of plasma oestradiol need not necessarily be the unique stimulus for LH release and the possibility that FSH in humans can stimulate LH release directly through a short loop feedback mechanism should not be disregarded.

Recent studies on plasma oestradiol and LH levels have supported the growing view that a rise in the circulating oestrogen levels may provide the stimulus for pituitary LH release and subsequent ovulation (Catt, 1969; Corker, Naftolin & Exley, 1969). Further evidence that plasma oestradiol is the physiological trigger for the mid-cycle peak of LH has been provided by Vande Wiele, Bogumil, Dyrenfurth, Ferin, Jewelewicz, Warren, Rizkallah & Mikhail (1970) and by Dufau, Catt, Dulmanis, Fullerton, Hudson & Burger (1970). Very recently, however, Jewelewicz, Warren, Dyrenfurth & Vande Wiele (1971), using a purified human pituitary FSH in a woman with secondary amenorrhoea, observed a significant LH peak before any oestrogenic response was detected.

During the last year, we have had the opportunity of using purified sheep FSH for the induction of ovulation in amenorrhoeic women. The preparation used was obtained from Schering AG, Berlin. It was identified as SH 8.0820 batch No. 005. Each vial contained 15 NIH₁ FSH-Units, first standard preparation and 0.54 NIH₁ LH-Units, first standard preparation. For injection the material was dissolved in 2 ml of normal saline and administered intramuscularly.

Blood was taken daily, immediately before the administration of the next dose of the hormone and for several days after treatment ceased. The blood was collected into heparinized tubes, and after centrifuging, the plasma was

TEXT-FIG. 1. Hormone assay results from subject A.C. during and after treatment with SH 8.0820. BBT, basal body temperature.

stored at -15°C until assayed. Plasma progesterone was determined by the method of Johansson (1969), oestradiol by the method of Corker & Exley (1970), and LH by a double antibody radioimmunoassay system based on that of Midgley (1966), using an anti-hCG preparation. The antiserum was kindly donated by Dr C. A. Paulsen of Seattle, U.S.A. All assays were performed in duplicate.

Text-figure 1 shows the results on subject A.C., whose amenorrhoea had lasted for 2 years. A peak of plasma oestradiol was obtained after five injections of

TEXT-FIG. 2. Hormone assay results from subject M.G.M.Z. during and after treatment with SH 8.0820. BBT, basal body temperature.

SH 8.0820 (total dose of FSH: 75 NIH units). A peak of LH was observed 2 days later, probably resulting in ovulation as judged from plasma progesterone levels. Doses of HCG were not administered until Days 12, 13 and 14. The elevated LH levels on Days 13, 15 and 17 are due to a cross-reaction with the administered HCG.

Text-figures 2, 3 and 4 show the results from the other three subjects with secondary amenorrhoea (M.G.M.Z., A.H. and A.R., who had periods of amenorrhoea which had lasted for 7, $2\frac{1}{2}$ and 3 years, respectively).

As can be seen, an LH peak was observed during treatment with FSH (total doses 75, 135 and 150 NIH units, respectively). In these women, no significant increase of oestrogenic activity was detected before the LH peak as judged by Spinnbarkeit, cytology and ferning of the cervical mucus, although one of them (A.R.) did show slightly increased plasma oestradiol levels. In contrast to subject A.C., the LH peaks in these women were not followed by ovulation; probably no mature follicle was present at the time when the LH peak occurred.

TEXT-FIG. 3. Hormone assay results from subject A.H. during and after treatment with SH 8.0820. BBT, basal body temperature.

The patient in Text-fig. 4 responded to FSH administration with an oestradiol peak some days after the LH release but this oestradiol peak was not followed by a new LH release or ovulation.

At present no satisfactory explanation can be given for these findings or for those of Jewelewicz *et al.* (1971). The explanation given by these latter authors was that the plasma sample which yielded the high LH value had been contaminated, but, in view of the findings reported here, this explanation seems unlikely.

The FSH preparation used in this study was tested for cross-reaction in the LH assay system. The amount of cross-reaction found was extremely low and, in the dosage used, could not have accounted for the elevated plasma LH level reported in the present communication.

In addition, since a release of LH in the bull immediately following an injection of HCG has been recently reported (Katangole, Naftolin & Short, 1971),

TEXT-FIG. 4. Hormone assay results from subject A.R. during and after treatment with SH 8.0820. BBT, basal body temperature.

the possibility that exogenous gonadotrophin may provide a direct stimulus for the LH release in certain patients, perhaps through a short loop feedback system, merits further investigation.

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