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The Effect of Some Progestins on Pituitary Gonadotrophin Excretion Patterns in Women

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Our knowledge of the influence of progestational agents on human pituitary gonadotrophins is rather scarce. This fact is due to methodological problems and to the existence of a number of variables in our experimental designs. During the normal menstrual cycle, for instance, the time of application, the duration of treatment, the dosage and the nature of the particular agent are relevant points which may be varied in a nearly unlimited manner. Hence it is not surprising that definite statements on the action of progestational steroids are extremely difficult. We have made several attempts during past years to contribute some more data by longitudinal studies of gonadotrophin excretion patterns in normal and pathological conditions before, during and after treatment with progestins. A few of these results will be briefly summarized.

1. Influence of progestational agents on the LH excretion during the normal menstrual cycle

Three progestational compounds, 17α-ethinyl-19-nortestosterone, progesterone and 6-chloro-9β,10α-pregna-1,4,6-triene-3,20-dione (Ro 4-8347), dehydrochlorretroprogesterone, were studied by daily immunochemical estimation of urinary LH levels during the normal menstrual cycle. Fig. 1 represents typical results when 20 mg ethinylnortestosterone, 50 mg progesterone or 8 mg dehydrochlorretroprogesterone were applied daily from the 6th to 8th or 8th to 10th day of the menstrual cycle.

The effect of this treatment was not homogeneous. The first two compounds showed a rather modest influence which may be characterized as a slight increase in the urinary LH activity immediately after the initiation of therapy. The LH peak which is generally observed during the midcyclic time was not affected. The treatment with dehydrochlorretroprogesterone did not provoke the same effect. The following midcyclic LH peak, however, was much smaller or even missing. The length of the cycle was not altered significantly. Ovulation was probably not suppressed as judged by the basal body temperature and the pregnanediol excretion.

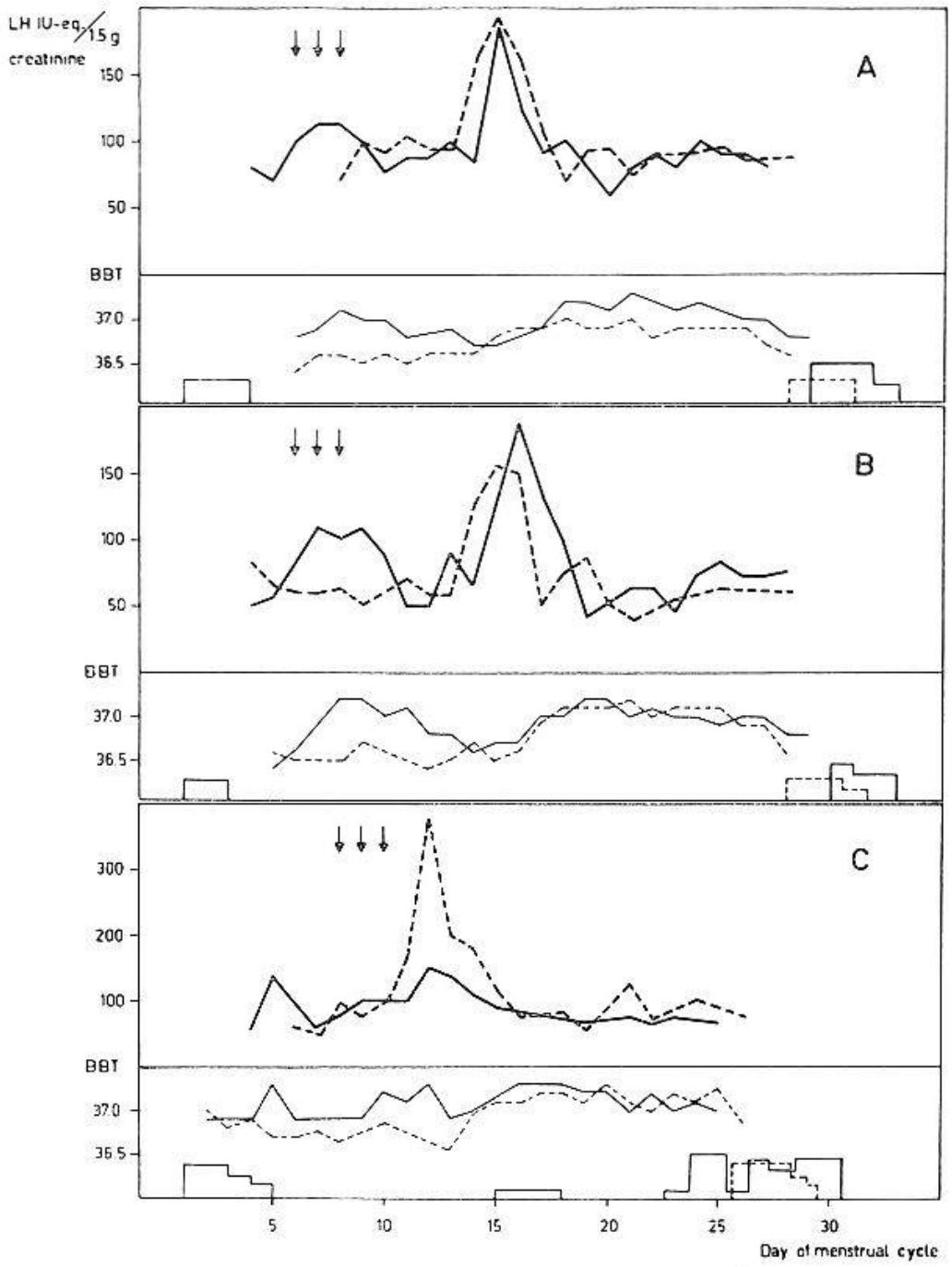

Fig. 1. Effect of progestational agents administered during the proliferative phase of the menstrual cycle upon urinary LH excretion. – A: ethinylnortestosterone 20 mg/day orally; B: progesterone 50 mg/day intramuscularly; C: dehydrochlorretroprogesterone 8 mg/day orally. ------ control cycle, —— treatment cycle.

After administration of ethinylnortestosterone and progesterone during the secretory phase from the 21st to the 24th day of the menstrual cycle (Fig. 2), again no relevant effects could be found with respect to the LH excretion and the length of the cycle. After the administration of 8 mg of dehydrochlorretroprogesterone during three days in the same period, an exceptional rise in the urinary LH activity was observed. This finding, however, requires further confirmation before any conclusions may be drawn.

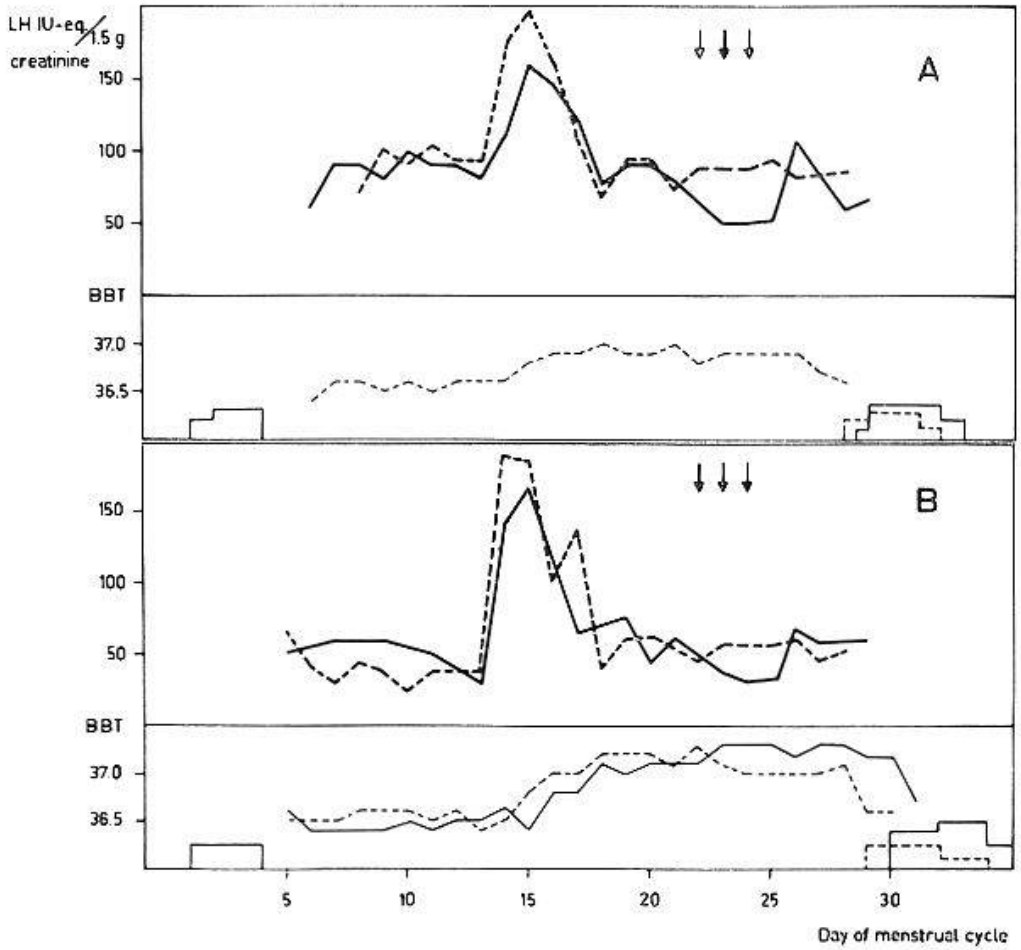

Fig. 2. Effect of progestational agents administered during the secretory phase of the menstrual cycle upon urinary LH excretion. – A: ethinylnortestosterone 20 mg/day orally; B: progesterone 50 mg/day intramuscularly. ------ control cycle, —— treatment cycle.

The application of 10 mg ethinylnortestosterone per day from the 6th to 24th and of 4 mg of dehydrochlorretroprogesterone from the 10th to the 23rd day of the menstrual cycle provoked a more or less complete suppression of the midcyclic LH peak, when compared with the preceding control cycle (Fig. 3). The mean excretion level, however, was not significantly altered.

2. Influence of progestational agents on the FSH and LH excretion in postmenopausal women

Progesterone was administered intramuscularly in an oily solution over six days in dosages of 5 and 50 mg per day. Ethinylnortestosterone was given in a daily dose of 20 mg over the same period. The FSH excretion was determined by the augmentation reaction in immature rats. The LH excretion was measured with the ovarian ascorbic acid depletion assay. The results are shown in Fig. 4. Progesterone did not reveal effects which were considered to be significant. The low dose, however, was stimulating rather than inhibiting the urinary FSH and LH activity. There was no change in

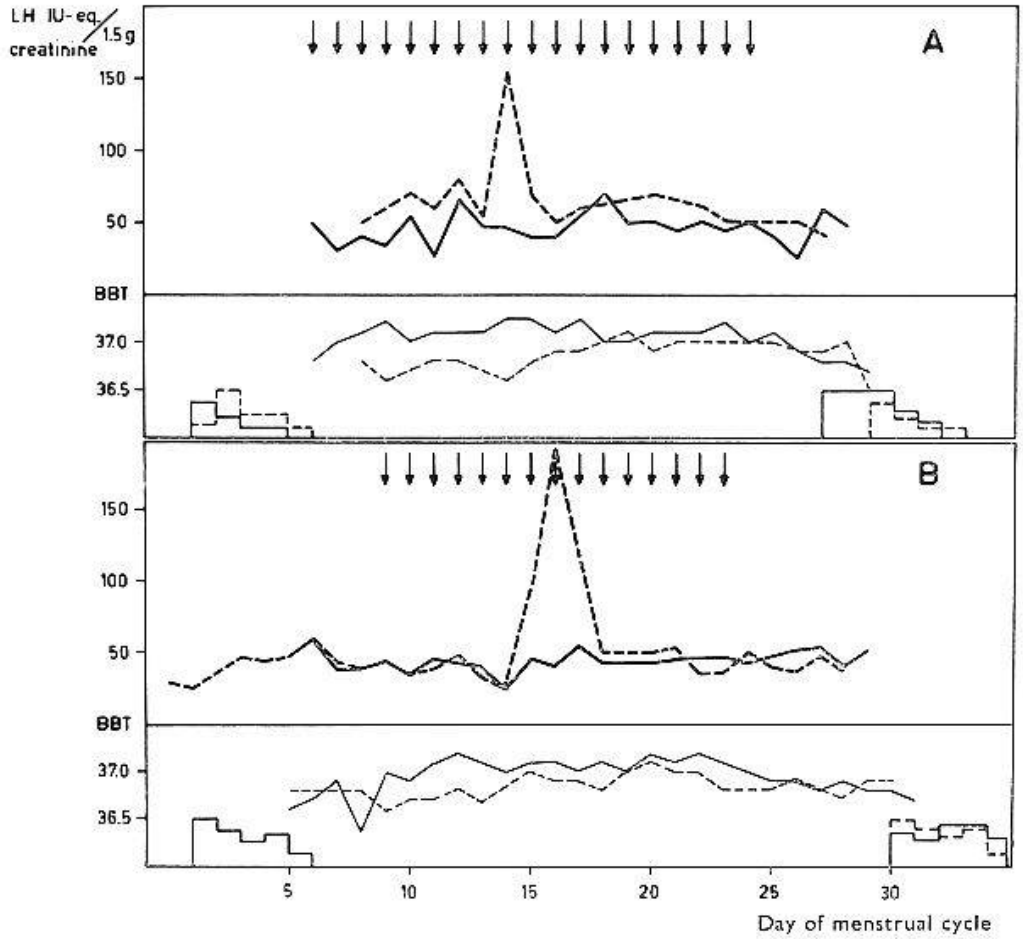

Fig. 3. Effect of continued administration of progestational agents during the menstrual cycle upon urinary LH excretion. – A: ethinylnortestosterone 10 mg/day orally; B: dehydrochlorretroprogesterone 4 mg/day orally. ------ control cycle, —— treatment cycle.

the excretion levels of these hormones after cessation of therapy. The application of ethinylnortestosterone provoked a depression of the FSH and LH values in urine when given as indicated above. After withdrawal of the medication a marked rise of both hormonal activities was observed.

3. Influence of progestational agents on the LH excretion in amenorrhoic women

These studies were conducted in women suffering from secondary amenorrhea. Some of the results are plotted in Fig. 5. Dosages of 4–12 mg dehydrochlorretroprogesterone were administered daily during 3–10 days. Consecutive immunochemical LH estimations were performed over a total of 20 treatment and control periods. Although a slight increase in the urinary LH activity was found in some of the treatment phases (Fig. 5), generally no significant alterations in the LH-excretion patterns could be detected.

The present results tend to elucidate the tedious problems which we are facing in studies concerning the effect of natural or synthetic steroid com-

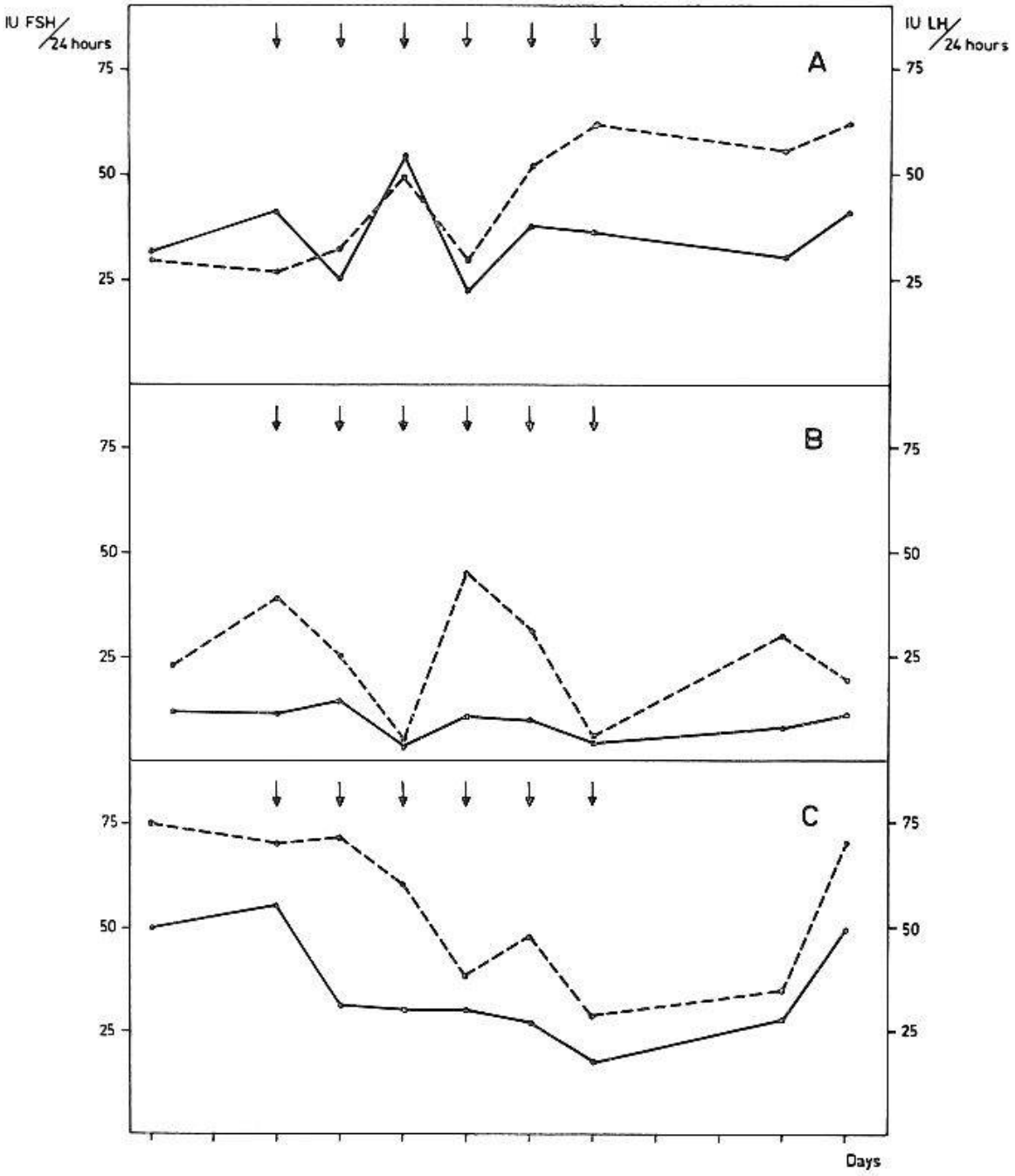

Fig. 4. Effect of progestational agents upon FSH and LH excretion in postmenopausal women. – A: progesterone 5 mg/day intramuscularly; B: progesterone 50 mg/day intramuscularly; C: ethinylnortestosterone 20 mg/day orally. ------ FSH, —— LH.

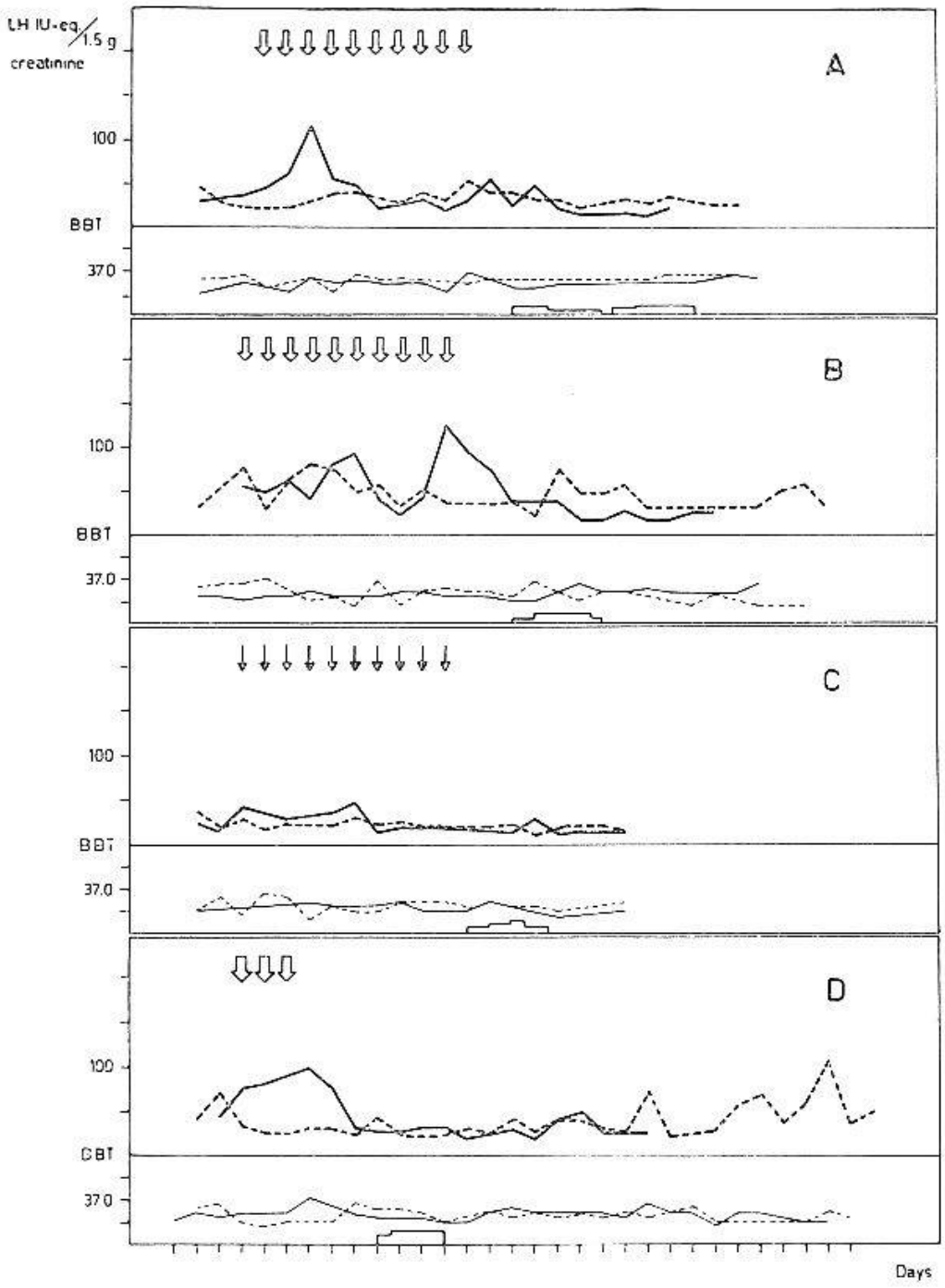

Fig. 5. Effect of progestational agents upon LH excretion in the urine of women suffering from secondary amenorrhea. Dehydrochlorretroprogesterone orally: A: 8 mg/day; B: 8 mg/day; C: 4 mg/day; D: 12 mg/day. ------ control, —— treatment.

pounds on pituitary gonadotrophins in women. Similarly to the findings following the administration of estrogens, we may conclude that depending on the dose, duration and time of application of progestins both stimulation and inhibition of gonadotrophins are possible. The yet unsolved problems will require systematic studies involving daily or even more frequent determinations of the relevant hormonal activities.

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Discussion

B. Lunenfeld: What method did you use for the LH determination and for the FSH determination?

P. Keller: The method for the LH determination was developed by Schuurs and is dependent on the hemagglutination technique but may be conducted on unconcentrated urine. There was quite recently a symposium on this immuno-chemical procedure which will be published in the near future in an Acta Endocrinologica Supplementum. The FSH values were estimated by means of the augmentation reaction described by Steelman and Pohley.

B. Lunenfeld: When using this immunological hemagglutination inhibition test, what did you use as the standard?

P. Keller: As a standard we have used 1. the International Reference Preparation (2nd IRP) and 2. for certain of these studies a house standard of human menopausal gonadotrophin which contained 440 IU of LH when tested biologically. Results were given in IU-equivalents LH per 24 h or per 1.5 g of creatinine.

L. Martini: Did you try the retro-compound in combination with estrogenes?

P. Keller: Not yet.