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The Effect of Various Dosages of Lynestrenol on the FSH, LH and Total Gonadotrophin Activity during the Menstrual Cycle

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The present communication deals with the effect of various dosages of lynestrenol (17α-ethinyl-estrenol) on the FSH, LH and total gonadotrophin activity in women with a normal menstrual cycle. The agent was given in a dosage of 0.5 mg from the 1st to the 28th day and in dosages of 0.5 and 15.0 mg from the 5th to the 25th day of the cycle. Each dose was investigated in six women. Urine collection and basal body temperature recordings were performed throughout all of the cycles.

For this investigation we adopted the following technique:

1. After extraction of the 24-hour urines by the kaolin acetone method described by Albert et al. (1958),
2. the 48-hour urinary extracts of the corresponding days of cycles of six women taking the same dosage of lynestrenol were pooled. Thereafter we performed
3. the estimation of the gonadotrophic activity of the pooled extracts by means of
   a) the augmentation test in rats to determine FSH activity,
   b) the pregnosticon test to determine the immunological LH activity, and
   c) the mouse uterus test, a non-specific indicator for the so-called "total gonadotrophin activity".
4. The results were expressed in terms of IU HMG/24 h using the Second IRP for HMG as the reference preparation.

All experiments were performed according to the specifications of Borth, Diczfalusy and Heinrichs (1957). In the great majority of tests, a 6-point assay design was employed using 6–10 animals or pregnosticon reactions per group.

Before presenting the results I would like to mention briefly what I think is the normal pattern of gonadotrophin excretion in untreated healthy, sexually mature women, especially since I am aware that our findings are not in agreement with those of several other investigators. (Fig. 1).

These excretion curves were obtained after the urinary gonadotrophin extracts of 20 complete ovulatory cycles had been pooled vertically and the gonadotrophic activity had been estimated by the same bio- and immunoassays as described above. The three curves are characterised by fairly similar excretion rates of FSH, LH and total gonadotrophic activity in the follicular and the luteal phases, and by a distinct peak not only of LH and total gonadotrophic but also of FSH activity. The existence of a FSH midcycle peak was confirmed when individual cycles were studied (Fig. 2).

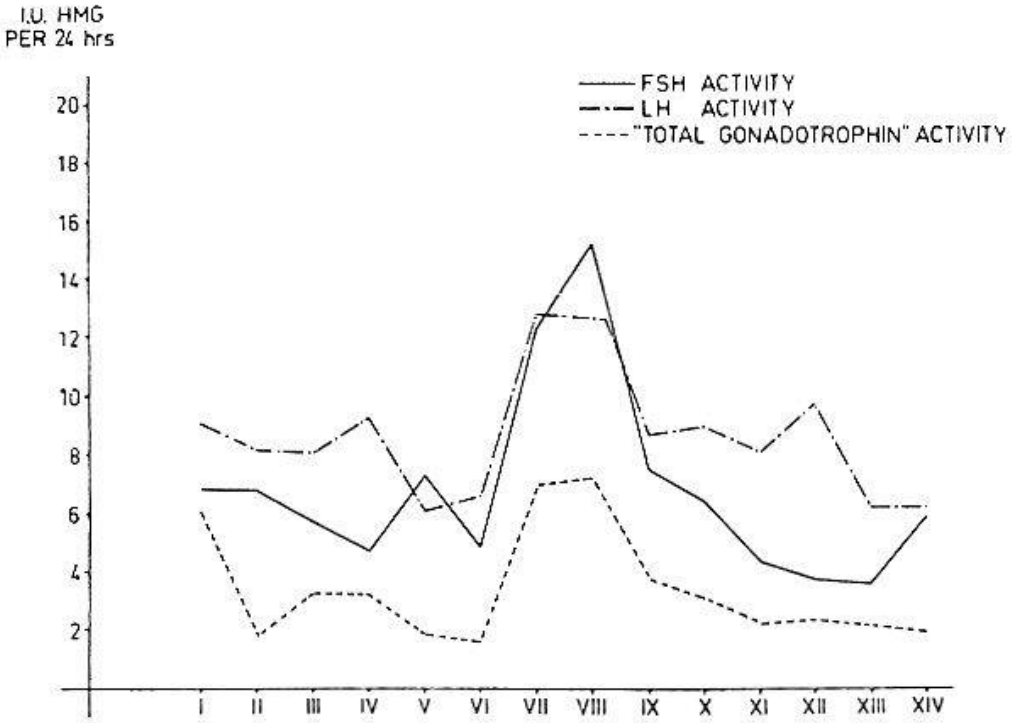

Fig. 1. Gonadotrophin excretion during the normal menstrual cycle.

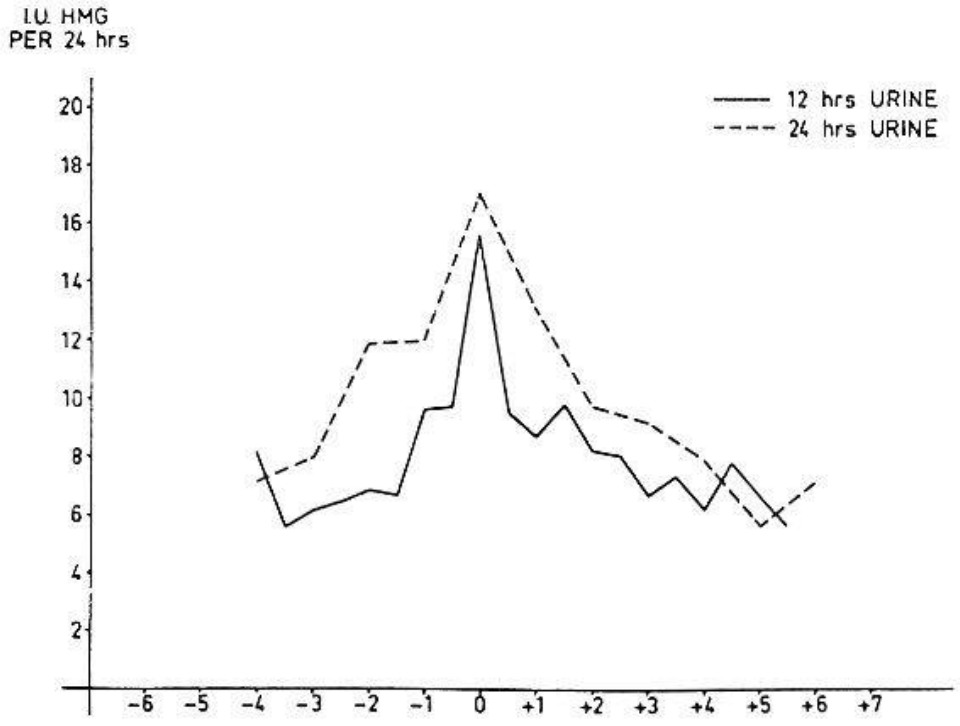

Fig. 2. FSH excretion during the midcycle.

The continuous line represents the mean FSH excretion midcycle when 12-hour urine portions from 7 cycles were investigated, the dotted line the figures obtained when 24-hour urine samples from 5 cycles were studied.

Here now are the results obtained when lynestrenol was given from the 1st to the 28th day in a dosage of 0.5 mg daily (Fig. 3).

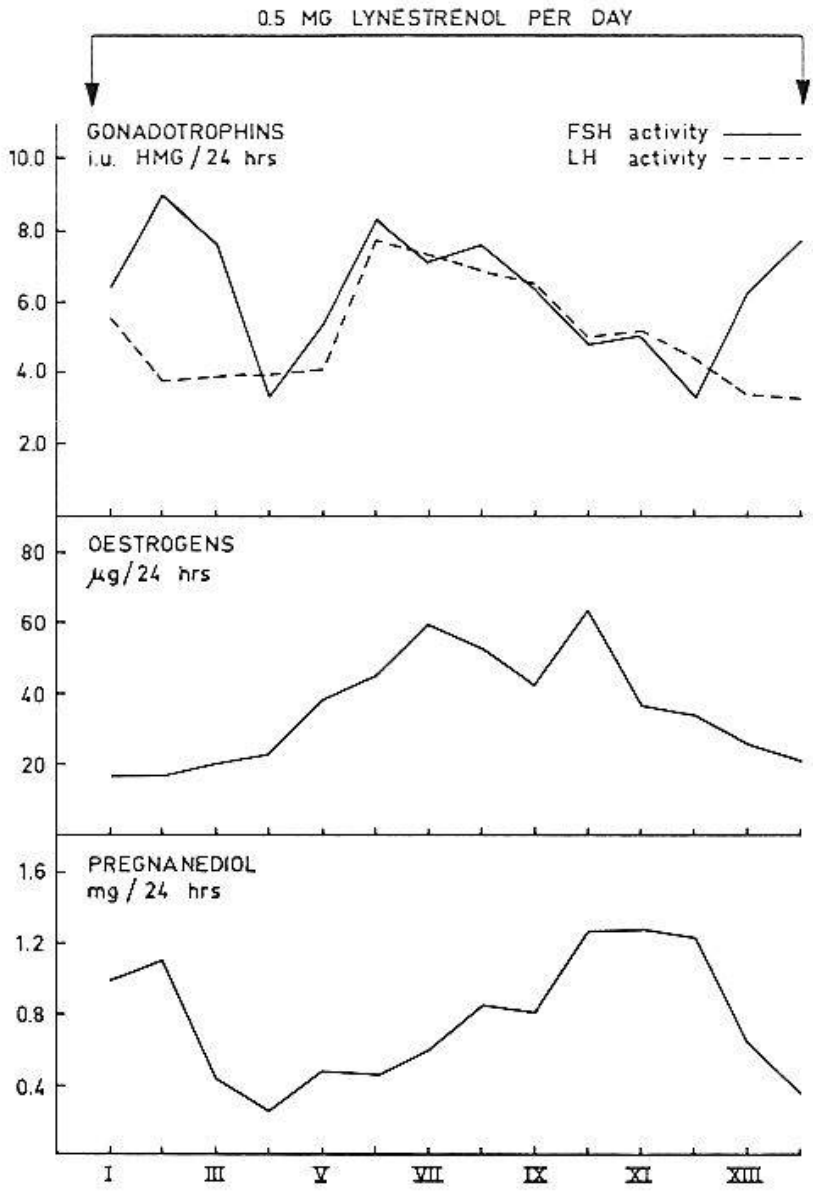

Fig. 3. Lynestrenol.

The curves indicate that very little change occurs in gonadotrophin excretion. Both the FSH and LH peaks at midcycle are still present. The fact that the peaks appear to be a little flatter than in the normal cycle which was shown above, might be due to the method of pooling the urinary extracts. Further investigations, especially those of individual estrogen and pregnanediol excretion, revealed that ovulation took place in all of the six women under treatment.

At this point I would like to mention that 0.5 mg lynestrenol per day has been found by Danezis to be a reliable contraceptive due to alterations in the cervical mucus. Our investigations have demonstrated that contraception is achieved in this case without inhibition of ovulation.

Fig. 4 indicates that even 5.0 mg of lynestrenol, given from the 5th to the 25th day of cycle, does not affect the FSH excretion; the midcycle peak is not suppressed. But the corresponding peaks of LH and total gonado-

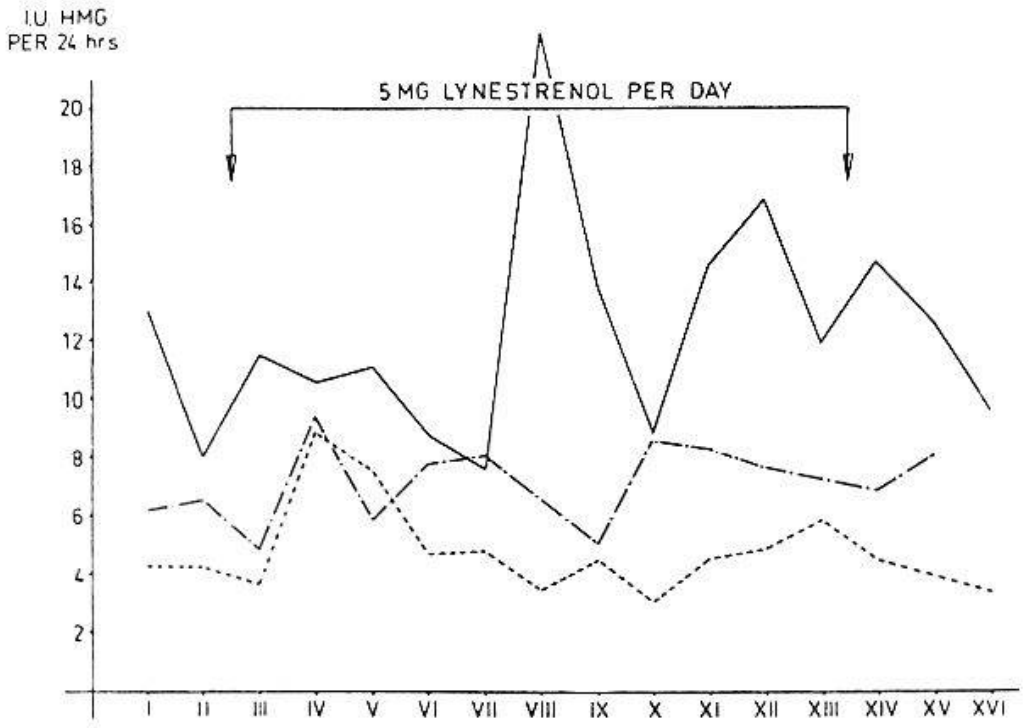

Fig. 4. Lynestrenol. —— FSH activity. -·-· LH activity. – – – "total gonadotrophin" activity.

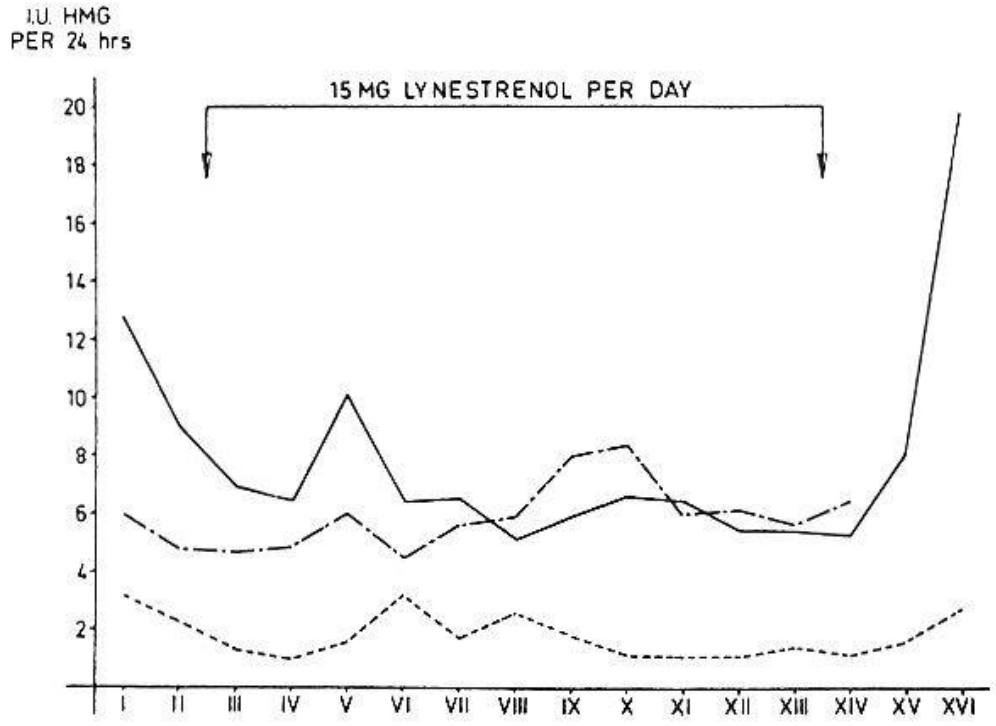

Fig. 5. Lynestrenol. —— FSH activity. -·-· LH activity. – – – "total gonadotrophin" activity.

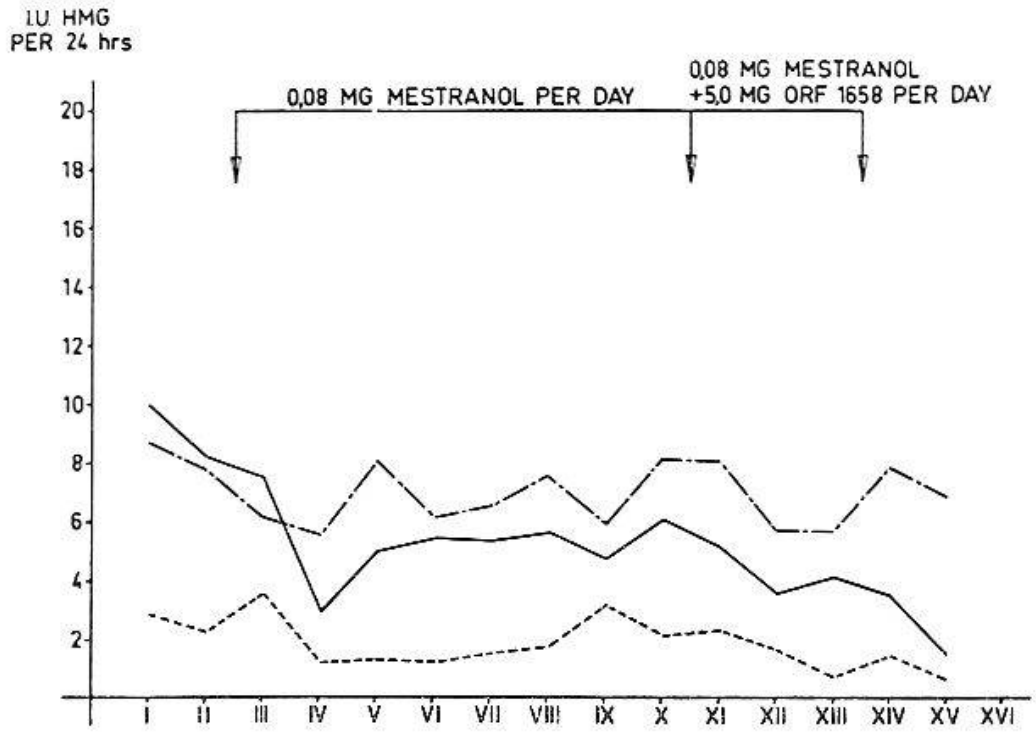

Fig. 6. ORF 1658. —— FSH activity. –·– LH activity. - - - "total gonadotrophin" activity.

trophin excretion are missing. Additional investigations demonstrated that all of the cycles during the treatment with 5.0 mg of lynestrenol were anovulatory.

The effect of 15.0 mg of lynestrenol is shown on Fig. 5. It is obvious that this higher dosage of the progestational agent suppressed the midcyclic peak of all three gonadotrophic activities under investigation. Even the basal excretion of FSH activity appears to be lower when a 15.0 mg dose is given.

There is still not very much agreement as to whether or not antiovulatory progestational compounds inhibit ovulation by suppression of the pituitary gonadotrophins. The results so far presented indicate that 0.5 mg of lynestrenol is insufficient to inhibit ovulation, the ovulation-inducing peaks of FSH and LH being unaffected. A dosage of 5.0 mg, however, was found to suppress the LH peak, and 15.0 mg was able to inhibit both the FSH and LH peak at midcycle. As additional investigations have shown, the latter dosages also prevented ovulation.

Fig. 6 demonstrates the effect of 80 γ mestranol on gonadotrophin excretion. The method is the same as that described above. With the onset of estrogen therapy, FSH excretion falls to a very low level. No midcyclic excretion peak of either FSH or LH can be observed. Even the basal FSH excretion is obviously reduced.

Summary

It can be said that progestational agents in sufficiently high dosage are well able to inhibit ovulation by suppression of FSH and LH peaks at midcycle. Orally active estrogens such as mestranol exert a similar effect even at a dosage 200 times lower than that of lynestrenol.

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Discussion

A. Darragh: Is it possible to tell me how much lynestrenol is converted to an estrogenic substance?

H. Schmidt-Elmendorff: We have not studied that.

P. Keller: I think we agree quite well on the results we obtained by this method. However, I do have a small criticism: the use of units. It is dangerous to use the well defined IU for total gonadotrophic and for immunochemically estimated LH activity.

H. Schmidt-Elmendorff: I agree with you here is not yet any standard unit for the mouse uterus test and one should use the second IRP for HMG only in terms of milligram equivalents for 24 hours.

B. Lunenfeld: Today, the IRP for gonadotrophins is stated in international units for FSH and for LH and stated in milligram equivalents for total gonadotrophins. So I think you were completely right in what you did except that you cannot compare these results with the results of any other laboratory. They are valid if they are compared with your own results from patient to patient and from urine to urine only.