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Influence on Gonadotrophins of Progestational Agents

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1. Influence of the retrosteroid Ro 4-8347 on the gonadotrophin excretion (GTH excretion) of postmenopausal women

The so-called total gonadotrophin excretion in the 24-h-urine was measured by means of the mouse uterus weight method (2nd International standard preparation) (Fig. 1).

Controls: 4 females in the age of 47, 54, 58, and 59 years
Doses: 2 mg/day during 30 days
4 mg/day during 14 days
6 mg/day during 14 days

During the period preceding treatment gonadotrophic activity was determined at least three times with the following results:

a) Dosage 2 mg/day. – Under 2 mg the GTH excretion was variable. 3 women showed a preliminary drop of the GTH value. This effect, however, was only evident within the first 6 days of medication. In one case an increase of the GTH value could be observed.

b) Dosage 4 mg/day. – All 4 cases showed an increased GTH value. A peak value was produced on the 5th day of medication. This rise is of significant statistical importance. After 5 days the level of GTH-excretion fell to the value preceding medication.

c) Dosage 6 mg/day. – In general, GTH values showed no deviation from the test with a dosage of 4 mg/day.

2. Influence of Ro 4-8347 on the gonadotrophin excretion and the menstrual cycle in 14 women with oligomenorrhoea or amenorrhoea

In most cases a treatment of 4 mg/day was given over a period of 10–14 days, in some cases and/or 6–8 mg/day during 3–5 days (Table I).

Gonadotrophin excretion. 4 women showed an increased GTH excretion which, however, could be statistically proved only once. Five times, values remained constant. Three times the GTH values were lower during treatment. In two cases it was impossible to compare the GTH value received.

Bleedings. 13 women reported bleeding similar to that during menstruation mostly after several treatments. In one case of psychogenic amenorrhoea no menstrual bleeding was reported.

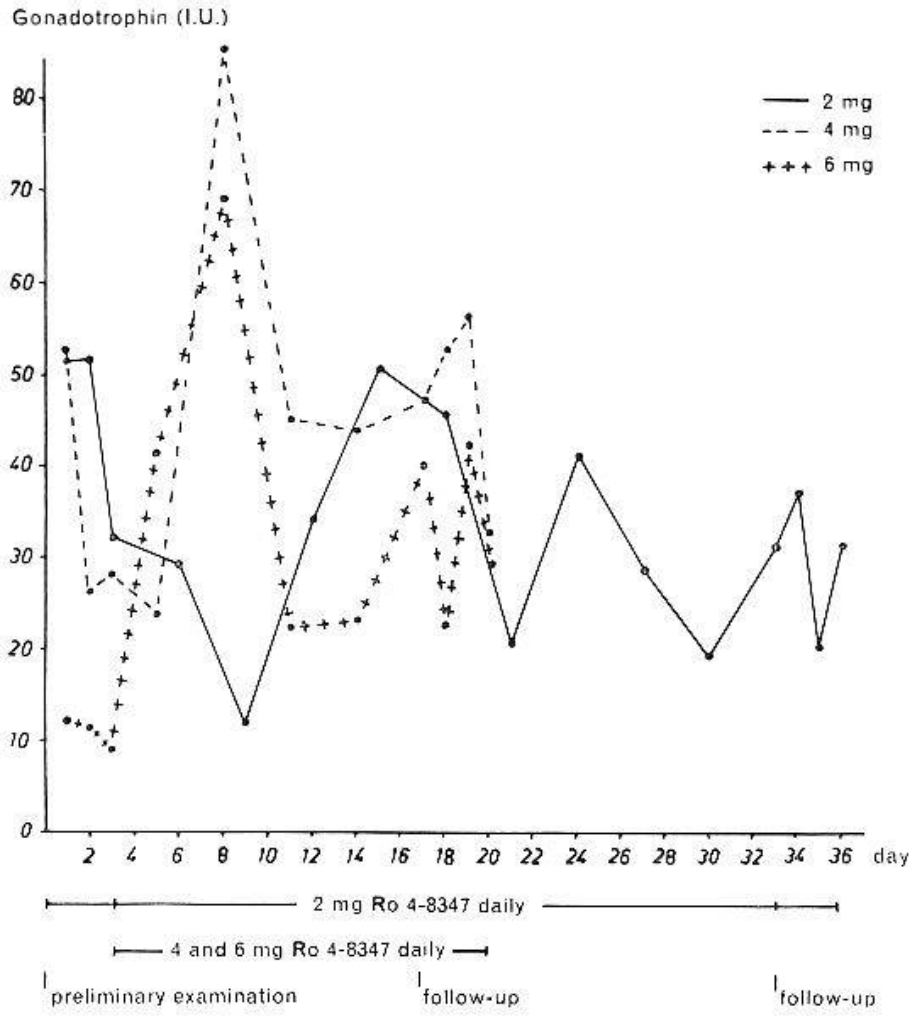

Fig. 1. Gonadotrophin-excretion in 24-h-urine, measured by mouse uterus weight method.

Basal body temperature. During therapy at least 10 women showed a biphasal course of temperature.

Pregnancies. 2 women with oligomenorrhoea became pregnant after treatment with Ro 4-8347. Stabilized cycles were achieved in 4 cases (aside from the gravidities).

3. Experimental attempt with animals to release gonadotrophin by means of Ro 4-8347

Ovariectomized estrogen-progesterone-blocked mature rats were intravenously injected with Ro 4-8347 and then the plasma concentration of FSH and LH was measured (FSH test: Steelman-Pohley; LH test: decrease of ovarian ascorbic acid according to Parlow). No direct FSH or LH effect could be revealed.

FSH release: Starting from a dosage of 5 μg/150 g body weight a definite release of FSH could be proved (Fig. 2). This effect was even improved by the application of 10 μg estrogen sulfate (i.v.). This dosage, on the other hand, did not affect the plasma FSH level.

Table I

Results of treatment with Ro 4-8347 of 14 patients with cyclic disorders

Name	Diagnosis	Withdrawal bleeding	At least 1 biphasic BT curve after Ro	Pregnancy	Cyclic stabilization
A. W.	Secondary amenorrhea	+	—	—	—
A. I.	Psychogenic cyclic disorder ...	—	—	—	—
B. I.	Hypogonadal menstrual disorder	+	+	—	(+)
B. L.	Oligomenorrhea	+	+	—	(+)
B. K.	Oligomenorrhea	—	—	—	—
F. U.	Oligomenorrhea	+	+	—	?
F. H.	Secondary amenorrhea	+	—	—	—
H. M.	Oligomenorrhea	+	+	—	—
He. M.	Secondary psychogenic amenorrhea	—	+	—	—
K. I.[1]	Primary oligomenorrhea ...	+	+	—	(+)
K. R.	Secondary amenorrhea	+	+	+	+
L. H.	Primary sterility	—	+	—	+[2]
S. I.	Secondary amenorrhea	+	—	—	—
Z. H.	Stein-Leventhal[3]	+	+	—	0

+ = certainly positive, (+) = probable, ? = doubtful, — = certainly negative, 0 = impossible.

[1] Curettage performed on this patient because of bleeding cervical polyp served as a control of Ro 4-8347 therapy at the same time.

[2] Regular periods; monophasic basal temperature curve.

[3] Diagnosis confirmed by wedge resection.

LH release: Using experimental methods to withdraw blood from animals 30 min after the injection of Ro 4-8347 we could detect the release of LH only rarely and to different extents (Fig. 3). Chronological investigations (Blobel et al., in preparation) have revealed, however, that the release of LH in comparison to the release of FSH takes place at different times (experiments with highly purified preparations of human gonadotrophin-releasing factors) (Fig. 4 and 5). Further investigations are concerned with the question as to whether or not the same is true for the release of LH by Ro 4-8347. At present this question, however, cannot yet be definitely answered.

Conclusions

Experimental studies with animals have revealed that the stimulating effect on the ovarian function by means of Ro 4-8347 seems to be based

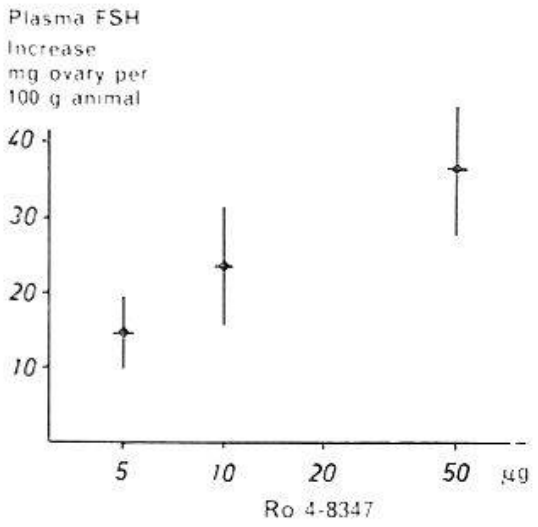

Fig. 2.

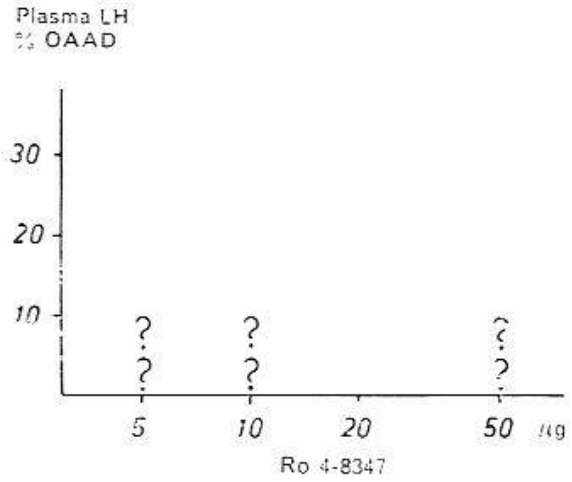

Fig. 3.

Fig. 2. FSH-release starting from a dosage of 5 μg/150 g body weight.

Fig. 3. LH-release in plasma 30 min after injection of Ro 4-8347.

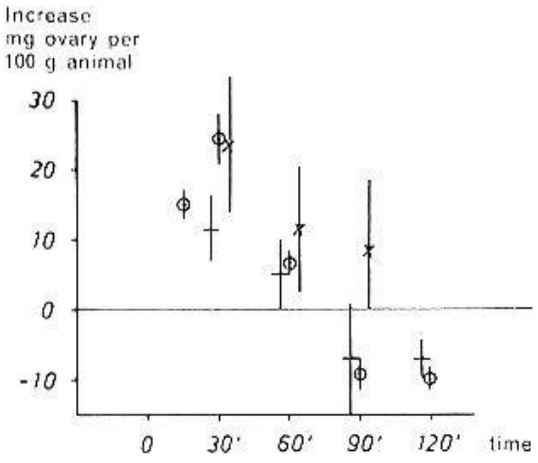

Fig. 4.

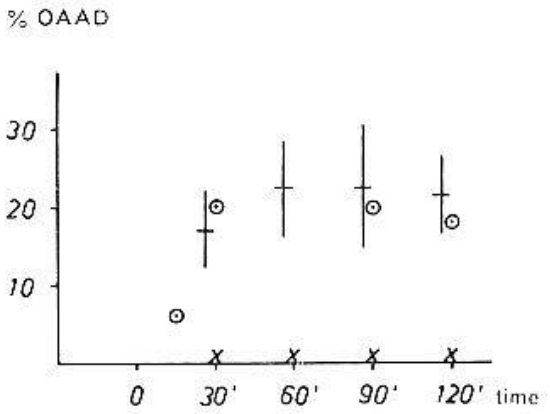

Fig. 5.

Fig. 4. Plasma concentration of FSH in estrogen-progesterone-blocked ovariectomized rats (– after 0.1 μg hypothalamus preparation, ⊙ after 37.5 μg estrone sulfate, × after 5 μg Ro 4-8347).

Fig. 5. Plasma concentration of LH in estrogen-progesterone-blocked ovariectomized rats (– after 0.1 μg hypothalamus preparation, ⊙ after 37.5 μg estrone sulfate, × after 5 μg Ro 4-8347).

primarily on its antiestrogenic effect. Similar results have been reached with clomifen citrate.

Investigations in collaboration with S. Heller, E. Schmidt, H. D. Schlumberger, and F. Schumm.

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Discussion

W. Hohlweg: Ich freue mich sehr, dass Sie ähnliche Resultate bekommen haben. Wir haben jetzt Versuche im Gange, wie eine Kombination der beiden Präparate wirkt. Es könnte nämlich sehr interessant sein, wenn man jetzt Ro 4-8347 als FSH-Stimulator und das Clomiphen als LH-Stimulator verwendet; dann müsste man eigentlich meiner Meinung nach ganz besonders gute Resultate bekommen, die vielleicht später auch klinisch von Wert sein könnten.