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Cytological and Endometrial Effects of Retroprogesterone Ro 4-8347

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In this decade of progestagens any new progestational agent is a welcome subject for clinical research. We are today able to select the most suitable progestational agent to produce the effect most desired out of the wide range of activity of endogenous progesterone. From this point of view the new progestational agent 6-chloro-9β,10α-pregna-1,4,6-triene-3,20-dione (Ro 4-8347), was found to be of interest.

The present report is based on a study of 79 cases which received treatment with Ro 4-8347. These cases involved various ovarian dysfunctions and included 22 cases of amenorrhea, 14 cases of oligomenorrhea, 26 cases of cyclic menstruation with anovulation, 4 cases of meno-metrorrhagia and 2 cases of luteal phase deficiency (Table I).

Material and methods

The cases studied may be divided by two criteria. The hormonal status of the patient at the start of treatment and the dose and duration of medication. Since ovarian activity is usually a dynamic process, the hormonal state criterion adopted by us is only a useful arbitrary criterion.

The cases were divided into 3 cytologic groups. The first included 23 cases in which vaginal smears showed a superficial cell count of less than 10%. The second included cases with superficial cell count between 11–40%, and there were 47 such cases. The third group was of 9 cases having more than 40% superficial cells in the vaginal smear.

The dose schedule and duration of treatment were divided into two groups. The "short course" of treatment consisted of a daily dose of 4–10 mg, usually 10 mg, and lasted from 2–6 days. The rational of the "short course" comes from the clinical observation that a short course of progesterone, in doses of 50–100 mg, given during high follicular activity, will often induce ovulation in anovulatory or oligomenorrheic cases [1, 2]. The "long course" of treatment consisted of a daily dose of 2–6 mg for periods of 10–20 days. This "long course" was adopted also in view of the reports of Stamm and co-workers [3] on a high rate of ovulation induction in anovulatory cases following this dose schedule.

Vaginal smears were taken 2–3 times weekly at which time cervical mucus arborisation was also studied. In each case the maturation index was determined. However, in this report the superficial cell counts only will be reported. Basal body temperature

Table I

Cases treated with Ro 4-8347

Amenorrhea	22
Oligomenorrhea ...	14
Anovulation	26
Metrorrhagia	4
Luteal deficiency .	2
Others	11
Total	79

Table II

Summary of effects of Ro 4-8347 on vaginal cytology

Superficial cells in vaginal smear	Total number of cases	Estrogenic effect	Progestational effect	No effect	Withdrawal bleeding
I. Less than 10%	*23*				
a) short course treatment	10	3	1	6	3
b) long course treatment	13	4	3	6	8
II. Between 11 and 40% ...	*47*				
a) short course treatment	19	4	10	5	11
b) long course treatment	28	4	20	4	25
III. More than 40%	*9*				
a) short course treatment	5	3	2	–	3
b) long course treatment	4	1	3	–	4

was taken in most cases. Endometrial biopsies were performed at the onset of bleeding or shortly after the termination of Ro 4-8347 administration.

Results

The results of Ro 4-8347 administration depended in a great measure on the functional state of the ovary and the dose schedule employed.

1. Vaginal cytology following Ro 4-8347 (Table II)

a) Cases with *superficial cells count less than 10%*. – In only 4 out of 23 cases did we observe a progestational effect in the vaginal smear. However, in 7 cases there was evident estrogenic activity expressed by increased cornification and disappearance of parabasal cells or agglutination phenomena. There was a shift to the right of the maturation index. This estrogenic effect was produced by "short course" (3 of 10 cases) as well as "long course" (4 of 13 cases) Ro 4-8347 administration.

In 12 of the 23 cases (50%) no modification was observed in the vaginal smear (this group of cases includes also 4 women in menopause).

Withdrawal bleeding was produced in 11 cases including 5 patients in whom no change was observed in the vaginal smear. In other words withdrawal bleeding was not related to the change in the vaginal smear and may take place also in cases with an estrone deficiency smear. This indicates that the effect of Ro 4-8347 is more pronounced on the endometrium than on the vaginal smear.

b) Cases with *superficial cell count between 11–40%*. – In this group of cases, a luteal effect was observed in 30 out of 47 cases (63%). This occurred equally with the short as well as the long courses of treatment. This is not unexpected in view of the progestational nature of Ro 4-8347.

However, in 12 of these cases the luteal effect in the vaginal smear set in during or at the termination of Ro 4-8347 medication. In other words the luteal effect of the drug is not only a direct one, but may be mediated via ovarian luteinization. We have confirmation of this mode of activity in other 2 observations. In 8 cases of moderate estrogenic activity an increased estrogenic effect followed upon Ro 4-8347 administration. In 2 women with cyclic ovulatory menstruation the follicular phase became longer with increased estrogenic activity and ovulation took place 3–6 days later than the expected day of ovulation with a shorter luteal phase which followed.

c) *Cases with superficial cell count higher than 40%*. – In 5 of 9 such cases a luteal effect was found in the vaginal smears. This followed the "long course" of treatment. The "short course" of treatment was often followed by withdrawal bleeding with no concomitant luteal effect on the vaginal mucosa. Seven of the 9 cases had withdrawal bleeding.

2. Endometrial changes following Ro 4-8347 administration

The endometrial response to Ro 4-8347 administration was studied in 22 cases (Table III). In all of the cases studied a secretory type endometrium was a constant finding. However, the degree of response varied with the duration and dose of treatment.

Group I: These were 11 patients who received Ro 4-8347 in the "short course" of treatment, namely a daily dose of 4–10 mg, mostly 10 mg in 4–7 days, mostly 5 days.

In 7 of these cases the endometrium was a secretory type endometrium with a predominantly glandular reaction and was dated from day 17 to 20 of the cycle. In other 3 cases the endometrial response was of a more advanced type. The secretory activity in the glands was consistant with days 24 to 26th of the cycle. and the stroma showed pseudodecidual changes. In only 1 case of metrorrhagia did the endometrium remain in the proliferative phase.

Group II: It consisted of 11 patients who received the "long course" of Ro 4-8347 in doses of 2–5 mg for 10–20 days. The endometrial response in most of these cases was of the late secretory type consistant with days 24 to 28th of the cycle. In 3 cases, however, areas of secretory glands with clear cytoplasma, and prominent nuclei, large and hyperchromatic, were found.

Table III

Effect of Ro 4-8347 on endometrium

Case, name	Diagnosis	Dose mg/day	Day start	Duration (days)	Type of endometrium
	a) Cases receiving a "short course" of treatment				
1. R. T.	Anovulation	4	7	5	secretory day 18th–20th glands secretory
2. L. M.	Anovulation	10	18	5	secretory day 20th, with cystic hyperplasia
3. Z. Y.	Anovulation	10	10	2	secretory day 19th
4. M. S.	Anovulation	8	10	5	secretory day 20th–22nd
5. F. R.	Anovulation	10	14	5	premenstrual day 24th
6. M. F.	Anovulation	10	14	7	secretory day 24th–25th premenstrual
7. C. R.	Anovulation	10	14	5	secretory day 25th–26th pseudodecidual
8. Z. Z.	Anovulation	10	12	5	secretory day 18th–20th
9. G. Z.	Anovulation	10	14	5	secretory day 18th–20th
10. S. E.	Metrorrhagia	10	28	4	proliferative
11. F. H.	Metrorrhagia	10	25	4	secretory day 18th
	b) Cases receiving a "long course" of treatment				
12. B. N.	Ovulatory cycle suppression	4	6	10	secretory day 20th
13. D. B.	Ovulatory cycle suppression	4	5	10	secretory day 18th
14. H. R.	Anovulation	2	5	20	secretory day 22nd
15. L. S.	Anovulation	5	12	14	secretory day 24th pseudodecidual
16. D. R.	Oligomenorrhea, anovulation	4	16	20	premenstrual
17. T. Y.	Anovulation	4	5	18	secretory glands; mostly small, secretory stroma; pseudodecidual reaction
18. S. M.	Oligomenorrhea, anovulation	4	6	15	secretory day 24th–26th
19. G. M.	Anovulation	5	14	10	secretory day 24th–26th
20. S. A.	Ovulatory cycle suppression	2	8	20	secretory day 18th–20th Arrias-Stella pattern
21. B. V.	Anovulation	5	14	14	secretory day 26th–28th premenstrual, Arrias-Stella pattern
22. C. D.	Ovulatory cycle suppression	4	5	20	cystic dilatation glands, few secretory glands, Arrias-Stella pattern

These areas recall the Arias-Stella pattern. Some cases had areas of a proliferative pattern of cystically dilated glands in a pseudodecidual stroma similar to those observed following prolonged progestagen medication.

Discussion

Two features of Ro 4-8347 activity were thus observed in the present study. This retrosteroid is a strong progestational agent with an elective effect on the endometrium. Its effect on the vaginal epithelium is not as prominent. In doses of 10 mg daily for 3–5 days it will produce withdrawal bleeding from a secretory type endometrium, provided this is estrogen primed, although a luteal reaction in the vaginal epithelium may not be present. Another indication of its strong endometrial effect is the finding of a profound decidual reaction on the part of the stroma with marked decrease of the glandular elements to a degree of "glandular exhaustion" after a 14–20 days course of treatment.

The second feature of Ro 4-8347 is its effect on gonadotrophin secretion. In normally menstruating women we have observed a prolongation of the follicular phase with increased estrogenic activity, delayed ovulation and shortening of the luteal phase. On the other hand, when given to anovulatory or oligomenorrhoic patients it will cause increased estrogenic activity with induction of ovulation. In these cases the luteal effect in the vaginal smear began during or at the termination of medication. The mechanism of its gonadotrophin stimulation is not clear. It is possible that because it is an anti-estrogenic agent, the reduction in estrogen effect triggers off a rapid rebound of gonadotrophin secretion. However, the response to Ro 4-8347 was unpredictable, and in cases with repeated treatments, none was recurrent. Ovulation was induced by the "long course" of treatment as well as the "short course" with almost equal frequency.

Summary

The effects of Ro 4-8347 on the vaginal mucosa as well as the endometrium were studied in a series of 79 cases with various functional disorders. The features of Ro 4-8347 activity could be defined as follows:

a) *A progestational effect.* This was especially marked and often exclusively on the endometrium and to a smaller degree on the vaginal mucosa.

b) *A gonadotrophin stimulating effect.* This effect was expressed by one of two cytologic forms. The first was a prolonged follicular phase with increased estrogenic activity and delayed ovulation which occurred in cases of normal ovulatory cycles or as increased estrogenic activity in oligo- and amenorrhea cases. The second form was the induction of ovulation in cases of anovulation with normal cycles or in oligomenorrhea.

1. Haskins A. L.: Progesterone in the induction of ovulation. in: Ovulation (ed. by R. B. Greenblatt), p. 158. J. B. Lippincott Co., 1966.
2. Rothschild I. and Koh N. H.: The effects of a single pre-ovulatory injection of progesterone on indices of ovulation in women. J. clin. Endocr. *11*, 789 (1951).
3. Stamm O., Caveng B., Gerard J. and Keller M.: Ovulationsauslösung mittels Retrosteroid Ro 4-8347. Z. Geburtsh. Gynäk. *169*, 225 (1968).

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