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The Treatment of Monophasic Cycles with the Retroprogesterone Ro 4-8347

H.-D. TAUBERT and O. JÜRGENSEN

While studying the progestational effects of the new retroprogesterone Ro 4-8347, it was noted by STAMM et al. in 1968 that a relatively large number of women over 40 years of age, who underwent a hysterectomy for uterine myomas, showed corpora lutea at the time of surgery, when they had been pretreated with this compound in the first half of the menstrual cycle. This observation created considerable interest in the possibility of using this progestational agent as a stimulator of ovulation.

Ro 4-8347, chemically 6-chloro-9 β ,10 α -pregna-1,4,6-triene-3,20-dione, is a derivative of dydrogesterone, but has considerably higher progestational activity. Secretory transformation of an estrogen primed endometrium could be obtained by administration of as little as 2–4 mg/day given orally over a 10-day period (STAMM et al., 1968). Because retroprogesterones lack the thermogenic effect of progesterone and most of its synthetic analogues, the basal temperature curve is not affected by the administration of Ro 4-8347. There was no inhibitory effect on ovulation in doses of 2–6 mg/day. A partial suppression of total urinary gonadotropin excretion was only seen in approximately 50 % of menopausal women receiving 12 mg/day for 5 days (STAMM et al., 1968).

In the rabbit and in the rat, Ro 4-8347 proved to be a centrally and peripherally effective progestin. Ovulation could be inhibited in the rat by the daily application of 0.5 mg/kg per os. A dosedependent inhibition of rat uterine and ovarian weights was seen in unilaterally oophorectomized rats after oral administration of 0.5–10 mg/rat per day. This effect, however, did not differ from results obtained with equal doses of progesterone. Ro 4-8347 could be shown to have a definite pregnancy-maintaining action in the rat. When 5–10 mg/rat were given to animals which had been spayed on day 4 of pregnancy, the free blastocysts could be maintained in the state of delayed nidation, and the pregnancy would proceed to term after implantation had been induced, without further addition of estrogen (KESSLER and TAUBERT, unpublished results).

The study reported here was undertaken to assess the effectiveness of cyclically administered Ro 4-8347 in the induction of biphasic cycles in anovulatory women, and to determine whether this compound would affect pregnandiol excretion in mono- and biphasic cycles.

Methods and materials

In the years 1967 through 1969, 60 patients were treated with Ro 4-8347 for one or more cycles. Only those patients were included in the study who fulfilled the usual criteria for medical induction of ovulation (i.e. those who showed evidence of adequate estrogenic stimulation on the basis of the fern test of the cervical mucus, vaginal cytology, progesterone withdrawal bleeding, and who were judged according to a general physical examination to be otherwise healthy). All patients with genetic or anatomical causes of amenorrhea, and all women with inadequate endogenous estrogen production were excluded.

Ro 4-8347 was supplied in 2 mg tablets. In the majority of cases 2 mg were given twice daily for a 10-day period (in few instances 2 mg 3 times daily) either from day 5 through 14 or from day 17 through 26 of the cycle. In patients with amenorrhea, withdrawal bleeding was induced as a rule with medroxyprogesterone acetate or chlormadinone acetate. Occasionally, Ro 4-8347 was also used initially. Pregnanediol determinations were carried out on 24-hour urine specimens according to the method of ABRAHAM and TAUBERT (1968).

Results

A. Withdrawal bleeding

Withdrawal bleeding occurred per average 3.2 ± 1.8 days following the discontinuation of the compound in monophasic cycles. Since the life span of the corpus luteum did not necessarily overlap the period of Ro 4-8347 administration, the time interval between the onset of bleeding and intake of the last tablet varied rather widely in biphasic cycles. 3 out of 60 patients did not bleed upon administration of Ro 4-8347. In one instance delayed bleeding occurred. In the two remaining cases withdrawal bleeding could be induced by repeating the course of the therapy with a daily dosage of 8 mg/day.

B. Induction of ovulation

A biphasic temperature curve was considered to be presumptive evidence of ovulation having taken place. When the hyperthermic shift was equivocal, the cycle was classified as "questionably biphasic", and a total lack of response as "monophasic".

a) Therapeutic response and age of patients. The age of the 60 patients studied ranged from 17 to 38 years. The incidence of positive responses was not affected by the factor of age (Table I).

b) Hyperthermic shifts. Biphasic cycles were observed in 27 out of 60 (45%) patients in one or more cycles subsequent to the administration of Ro 4-8347. In 13 cases questionably biphasic basal temperature curves were seen (22%). The remaining 20 patients (33%) did not show a positive reac-

Table I
Therapeutic success and age of patients

Age of patients	Number	Bi-phasic	Mono-phasic	? Bi-phasic	Pregnancy
20	8	4	3	1	—
21–25	17	5	7	5	—
26–30	21	12	5	4	2
31–35	13	6	5	2	1
36–40	1	—	—	1	—
	60	27 (45%)	20 (33%)	13 (22%)	3

Table II
Therapeutic success and diagnosis

Diagnosis	Number	Bi-phasic	Mono-phasic	? Bi-phasic	Pregnancy
Primary amenorrhea	3	1	1	1	—
Secondary amenorrhea	19	4	10	5	—
Postpartum amenorrhea	2	—	—	2	—
Amenorrhea with galactorrhea	2	—	1	1	—
Primary oligomenorrhea	20	11	6	3	2
Secondary oligomenorrhea	10	8	1	1	1
Anovulatory eumenorrhea	4	3	1	—	—
	60	27 (45%)	20 (33%)	13 (22%)	3

tion. Treatments were given for a total of 225 cycles. Of these, 74 (33%) were biphasic, 21 questionably biphasic (9%), 120 (54%) monophasic, and 10 (4%) could not be properly evaluated.

c) *Occurrence of hyperthermia.* In 19 out of 27 patients with a positive response the first rise in the basal temperature was observed during or after the first treatment course, in 5 cases after the second, and in only 3 cases after the third course. A first positive reaction was never seen later than the third cycle.

d) *Long-term therapy.* 41 out of 60 patients received Ro 4-8347 for periods from 3 to 8 cycles. Of these, 23 (56%) out of 41 responded once or more than once with a biphasic basal temperature curve. These 23 favorably reacting patients were treated for a total of 114 cycles of which 68 (60%) were considered biphasic.

e) *Therapeutic effect and diagnosis.* The relationship between therapeutic effect and diagnosis has been summarized in Table II. 26 patients were

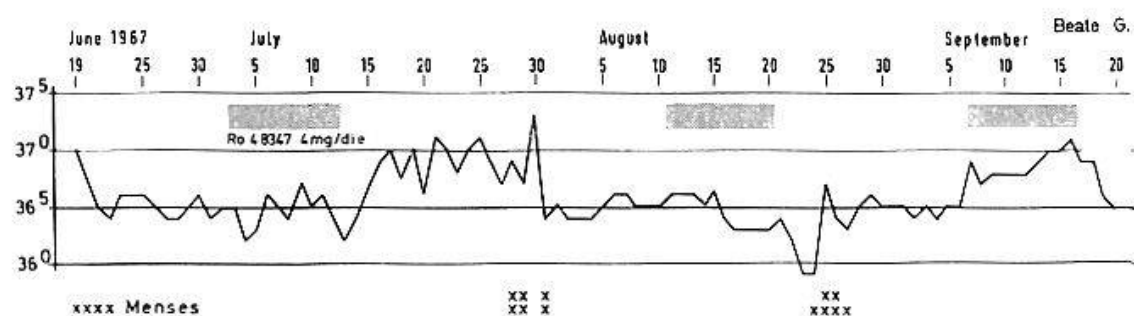


Fig. 1. Beate G., 21-year-old patient with primary amenorrhea. Wedge resection had been performed at age 18 without success. Biphasic cycles after administration of 4 mg Ro 4-8347 in the second half of the cycle. "Direct" response in the first, "delayed" response in the third treatment cycle.

present with various forms of amenorrhea, 30 with primary or secondary oligomenorrhea, and 4 with anovulatory eumenorrhea. The results depicted in Table II clearly indicate that patients with amenorrhea generally reacted much less favorably than those with oligomenorrhea or anovulatory cycles.

f) Types of response. Two types of hyperthermic response were noted. Most often there was withdrawal bleeding a few days after the discontinuation of therapy, followed by a rise in the basal temperature curve approximately two weeks later. This was referred to as a "delayed" response. In some cases a "direct" effect was noted. In such cases the hyperthermic shift of the basal temperature curve occurred during or subsequent to the administration of Ro 4-8347, but prior to the onset of bleeding. The 74 biphasic cycles of this series comprised 59 of the "delayed response" and 15 of the "direct response" types. Both occurred in the same patient at different times (Fig. 1).

g) Duration of cycle, luteal phase, and date of ovulation. In the delayed type biphasic cycles the average interval between the menses was 28.5 ± 5.1 days. The rise of the basal temperature curve occurred on the average on day 14.8 ± 4.5 , and the mean length of the hyperthermic phase was 137 ± 2.6 days.

h) Effect of Ro 4-8347 in the first half of the cycle. 9 patients were treated with 2 mg Ro 4-8347 twice daily from day 5 through 14. Withdrawal bleeding occurred as early as day 12 and as late as day 34. In 4 cases biphasic responses were noted subsequent to withdrawal bleeding. 2 patients received 4 mg of Ro 4-8347 per day from day 5 through 24. In one case the temperature rose on day 18 and remained elevated until day 32. The second patient showed a monophasic reaction.

C. Pregnancies

36 out of 60 patients desired to have children, 17 of which responded with biphasic cycles (47.2%). 3 pregnancies were observed, conception having taken place in treatment cycles 1, 6, and 7 respectively. 2 patients had immature deliveries in the sixth month of pregnancy, complicated by

bleeding since the early months of pregnancy and isthmo-cervical insufficiency. The third patient went to term and delivered a healthy infant.

D. Side effects

The number of side effects was minimal. Some patients noted bleeding even during the last days of therapy. In one instance an ovarian cyst of approximately 5 cm diameter was noted in the fourth treatment cycle. It receded within two weeks without therapy. A second patient developed seborrhoeic dermatitis after the fifth cycle of therapy. A cause and effect relationship could not, however, be definitely established.

E. Effect on pregnandiol excretion

The effect of Ro 4-8347 on pregnandiol as a parameter of luteal function was studied. An analysis of 32 paired pregnandiol values from the first and second half of the cycle failed to show any effect of the compound in the dosages used upon pregnandiol excretion in biphasic and monophasic cycles.

Discussion

The concept of regulating anovulatory ovarian function by means of cyclic progestin therapy is intellectually attractive, because there is little doubt that progesterone secreted by the corpus luteum affects the hypothalamic-pituitary axis by a negative feed-back mechanism. The action of progesterone on ovulation in species as different as the rat, the rabbit, and the cow has been adequately summarized by COWIE and FOLLEY (1955). In these species progesterone has been shown to stimulate ovulation under properly chosen conditions. In the estrous rabbit, progesterone seems to increase the sensitivity to environmental stimuli. It is possible that the declining level of progesterone results in a lowering of the neural threshold concerned with the release of LH (KAWAKAMI and SAWYER, 1959). ELLINGTON et al. (1964) and also McDONALD and CLEGG (1967) could clearly show that progesterone has an effect on the production and the release of gonadotropins in sheep. They found that increasing amounts of gonadotropins were released on the fifth and sixth day of daily injections of 20 mg progesterone per sheep, and regardless of the length of treatment the same phenomenon could be observed 5-6 days after the end of treatment. Similar data are not yet available for the human, but it was suggested as early as 1959 by HASKINS that ovulation could be induced in the human by intravenous injection of 17 α -OH-progesterone-capronate. His observation was however limited to only one patient.

An increase in urinary LH excretion in healthy women following the injection of 200 mg progesterone was described by McARTHUR et al. (1961). More recently BUCHHOLZ et al. (1964) published extensive data on the interrelationship of progesterone secretion and the regulation of ovulation. The latter authors could show that the injection of 200 mg progesterone was

followed within 24 hours by a significant rise in gonadotropin excretion in the urine. A preovulatory rise in progesterone secretion from the Graafian follicle described by several authors has also been interpreted as an indication of the role of progesterone in mediating ovulation via the pituitary (DIBBELT and BUCHHOLZ, 1953; ZANDER, 1958; ZANDER et al., 1958, 1967). The existence of a rise in progesterone secretion prior to the mid-cyclic peak of LH has, however, been recently disputed (LIPPSETT, 1968).

The results of the study presented here confirm the reports of other authors on the effectiveness of Ro 4-8347 as a progestational agent. It proved to be remarkably free of undesirable side effects, the only significant observation being occasional break-through bleeding during the last 2-3 days of medication which could be easily prevented by increasing the dose in the following treatment cycle.

If one would consider the biphasic basal temperature curve to be a reliable sign of ovulation, which it clearly is not, Ro 4-8347 would have to be considered to be a relatively effective inducer of ovulation in comparison to other progestins. A presumptive rate of ovulation of 45% is certainly much lower than the ovulation rate with clomiphene, but it is also noticeably higher than a placebo effect, which according to CUDMORE and TUPPER (1966) must be calculated in a study of this kind to be approximately 25%. There appears to be no advantage in using Ro 4-8347 in the first half of the cycle as is usually done with clomiphene, because mid-cycle bleeding will almost invariably occur. The low rate of pregnancy was somewhat disappointing and very much at variance with results presented by DAPUNT in 1968. The question remains unanswered as to whether or not all biphasic basal temperature curves actually represented corpora lutea or to a certain extent might have been a reflection of the secretory activity of luteinized follicles. Another possible explanation for the low pregnancy rate can be found in a histologic study by STAMM et al. (1968). He observed a partial secretory transformation of the endometrium by Ro 4-8347 even without previous priming with estrogens. This could be an indication for an indirect estrogenic effect of this drug mediated through the pituitary. Since the luteal effect was mainly limited to the endometrial glands, and a pseudo-decidual reaction was exceptional, further studies should be carried out to determine whether or not this compound creates optimal conditions for the implantation of the blastocyst. Because pregnandiol levels in urine were not interfered with by the administration of Ro 4-8347 in both ovulatory and anovulatory cycles, it was assumed that this compound did not affect the function of the corpus luteum directly. Pregnandiol excretion values in urine were found to be not different from those registered in healthy women.

The introduction of clomiphene and related compounds into the management of disturbed ovarian function greatly widened the therapeutic spectrum of the gynecologist. Since clomiphene, however, cannot be used for long-term therapy and its use is still fraught with a relatively high rate of complications, it definitely cannot be considered to be a panacea for the

treatment of anovulatory patients who are not desirous of conceiving or who are not married. It has been shown in an exhaustive study by SOUTHAM and RICHART (1967) that there is a direct relationship between the onset and duration of disturbed menstrual function and the later state of fertility. It appears, therefore, mandatory to develop therapeutic agents which could be used on a long-term basis, would induce regular menstrual periods, and possibly would stimulate ovulation in a considerable proportion of normogonadotropic patients. On the basis of the results obtained with Ro 4-8347 in 60 patients, it seems justified to consider the cyclic administration of this compound to young girls and unmarried women with anovulatory cycles with a certain degree of optimism.

So far it remains unknown which site of action of Ro 4-8347 is involved in inducing ovulation in the anovulatory female. Possibly a similar hypothesis as described above might apply to its effect on the hypothalamic-hypophyseal axis in the human.

Summary

1. 60 women, aged 17 through 38, were treated cyclically with the retroprogesterone Ro 4-8347.

2. 27 out of 60 patients showed in 74 out of 225 cycles a biphasic basal temperature curve, 13 patients showed questionable biphasic curves, the remainder did not respond at all.

3. 3 out of 17 patients who wished to become pregnant and responded with biphasic basal temperature curves conceived. Two delivered premature infants, 1 went to term.

4. Ro 4-8347 was shown not to affect pregnandiol excretion in ovulatory and anovulatory cycles.

5. It was proposed that Ro 4-8347 could be of particular value in the treatment of anovulation in unmarried women and young girls.

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Diskussion

J. STAEMMLER: Herr Dr. DAPUNT und Herr Dr. STAMM, haben Sie Überstimulierungserscheinungen nach Verabreichung von Ro 4-8347 beobachtet?

O. DAPUNT: Ich habe in einem Fall ein zystisches Ovar beobachtet und in einem Fall eine verlängerte hypertherme Phase, ohne dass die Patientin Beschwerden oder vergrösserte Ovarien geboten hätte. Diesen zweiten Fall habe ich hier gezeigt.

O. STAMM: Unter 50 Behandlungen hatten wir 2 Fälle: einmal ein orangengrosses Ovar bei einem Stein-Leventhal und einmal ein pflaumengrosses Ovar. Beide haben sich spontan resorbiert. Eine intraperitonäale Blutung hat es nicht gegeben. Das ist der grosse Vorteil dieser Behandlung gegenüber dem Clomiphen: sie können den Leuten während sechs Monaten eine Behandlung verschreiben und brauchen sie sozusagen nie zu kontrollieren.

L. MARTINI: The major difference between the results of the treatment, here reported, and those obtained with clomiphene is that apparently there are no cases of multiple pregnancies with the Roche steroid.

J. HAMMERSTEIN: What about other side effects. Are there any?

Different investigators reply "no".