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The Use of Ro 4-8347 in Amenorrhea and Anovulation

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The new progestational agent Ro 4-8347 was found to have two main properties: a) a strong progestational effect primarily on the endometrium and b) a stimulating effect on gonadotrophin secretions. These two properties served as a basis for the clinical application of Ro 4-8347 in 82 cases of amenorrhea and anovulation.

Material and method

The patients may be divided into four groups:

Group a) included cases of sterility with *anovulatory cyclic menstruations*. In these cases, the routine sterility work-up excluded the male, tubal, peritoneal and cervical factors of sterility. Anovulation was diagnosed by vaginal smears, basal body temperature and endometrial biopsy. There were 33 such patients who received medication in 44 cycles.

Group b). Oligomenorrhea with anovulation. These were sterility patients whose only apparent reason for sterility was anovulation. Their menstrual cycles were irregular and prolonged, occurring between 5 and 12 weeks. There were 24 such cases which received 31 cycles of treatment.

Group c). Amenorrhea. These were 9 cases of primary and 6 cases of secondary amenorrhea. Except for 2 patients, they all presented some signs of ovarian function, i.e. estrogenic activity in their vaginal smear and withdrawal bleeding following the administration of progesterone.

Group d). Short-term amenorrhea. These were normally menstruating, presumably ovulating, patients who consulted us for a 4–14 days delay in their menstruation. In 10 such cases, Ro 4-8347 was given in order to induce a withdrawal bleeding and possibly ovulation.

Because of the unpredictable response to Ro 4-8347 in these cases, treatment was given according to one of several schedules. The "short course" consisted of a daily dose of 4–10 mg for a 2–6 day period. The "long course" consisted of a daily dose of 2–6 mg for periods of 10–20 days.

The response to treatment was evaluated by several criteria which included: the vaginal maturation index, basal body temperature, onset of bleeding in relations to the thermal shift, endometrial biopsy and the occurrence of pregnancy.

Results of treatment with Ro 4-8347 (Table I)

a) *Anovulatory cycles.* In 11 cases the "short course" of treatment was employed. Most of these cases received 8–10 mg of Ro 4-8347 daily for 5–6

Table I

Cases treated with Ro 4-8347

Clinical classification	Number of cases	Number of cycles	Summary of results
1. Anovulation and amenorrhea			
a) Anovulatory cycles.....	33	44	24 (56%) ovulatory cycles (short course 7/11, long course 17/33)
b) Oligomenorrhea	25	31	10 (30%) ovulatory cycles (short course 3/10, long course 7/10) 12 withdrawal bleeding
c) Amenorrhea	17	20	2 (10%) ovulatory cycles 9 withdrawal bleedings 7 increased estrone activities
d) Short-term amenorrhea ..	10	10	5 withdrawal bleedings
2. Normal cyclic menstruation	16	18	4 delayed ovulation 6 suppressed ovulations (BBT)
3. Meno-metrorrhagia	12	12	
4. Menopause	7	7	
5. Others	6	6	
Total	123	148	

days. The treatment was begun usually on days 10–14 of cycle, when signs of moderate to marked estrogenic activity were present. Here we relied greatly on the cervical mucus arborization as a convenient, quick, clinical test.

In 22 cases with 33 treatment cycles, the "long course" of treatment was employed. This consisted of 2–6 mg daily for 10–20 days. In 7 cases treatment began on day 5 of the cycle and lasted 20 days. Otherwise treatment started on days 10–14 of cycle and lasted for 10–14 days. The results in terms of ovulation were more or less the same in the 3 types of treatment.

"Short course": 7 out of 11 ovulated (60%)
"Long course", starting on day 5: 4 out of 7 ovulated (57%)
starting on day 10–14: 13 out of 26 ovulated (50%)

Only one of these patients became pregnant. In the cases receiving two courses or more of treatment, ovulation did not always recur (Table II).

b) *Oligomenorrhea.* In 10 of the 25 cases of oligomenorrhea, there were indications that ovulation occurred following Ro 4-8347. In 7 of the 10 cases the schedule used was that of 4–5 mg daily for 10–14 days starting 10–14

days after the last menstrual period. In 12 cases of this group a withdrawal bleeding set in 3–6 days after termination of treatment. In 11 out of 12 patients who had withdrawal bleeding the schedule used was the "short course" of 10 mg for 2–5 days. One of these patients in this group became pregnant (Table III).

c) *Amenorrhea.* In this group there were only 2 patients who responded to treatment by ovulating. One was a case of primary amenorrhea and one of secondary amenorrhea. In both cases the "long course" of treatment was used. In 7 cycles of treatment an increased estrogenic activity was found in vaginal smears soon after termination of Ro 4-8347 administration. In 9 of these cycles withdrawal bleeding took place.

d) *Short term amenorrhea.* All these cases received a "short course" of Ro 4-8347. In 5 cases withdrawal bleeding took place 3–4 days after the last day of treatment. In 1 case, which was an early pregnancy, the patient miscarried 5 days after the last day of "treatment". This we feel, is a purely coincidental occurrence. In the other 4 cases no bleeding or ovulation took place up to 10 days following treatment. There was no correlation between the degree of estrogenic activity and the occurrence of withdrawal bleeding (Table IV).

It is noteworthy that very few patients complained of any side-effects of the drug. There were some who complained of vertigo and various gastrointestinal symptoms of mild nature.

Discussion

In summing up the effects of Ro 4-8347 medication in cases of anovulatory cycles, oligo- and amenorrhea, we should consider 3 types of reactions: 1. ovulation, 2. increased estrogenic activity, and 3. withdrawal bleeding.

Ovulation was induced by Ro 4-8347 in over 50% of cases of anovulatory cycles, in 30% of cases of oligomenorrhea and in 10% of cases of amenorrhea. Most of these ovulations followed the "long course" of treatment of 4–5 mg for 10–14 days. It is noteworthy that only in 2 cases did pregnancy follow ovulation. Some follicular activity appears to be a prerequisite for the occurrence of ovulation. In fact, in only 3 cases did ovulation follow Ro 4-8347 medication with a vaginal smear of less than 10% superficial cells.

All this points to the ability of Ro 4-8347 to induce increased gonadotrophin secretion, especially luteinizing hormone. Further evidence of this stimulatory effect may be found in the cases of amenorrhea in which an increased estrogenic activity was observed shortly after Ro 4-8347 medication. We have been employing short progesterone treatment of 100 mg intramuscularly, in cases of oligomenorrhea resulting in an occasional occurrence of ovulation. However, the desired response was not always a recurrent one, and we have no criteria for predicting the outcome of this treatment. Similar observations have been reported by other authors. The only prerequisite for a positive response has been a strong estrogenic activity as expressed by a strongly positive arborization test of cervical mucus.

Table 11

Ro 4-8347 in anovulation

No., name		Maturation index before	Daily dose (mg)	Begins on day	During days	Vaginal smear after treatment	BBT after treatment	Bleeding after Ro 4 (during days)	Side-effects	Ovulation
1	F. R.	0/60/40	10	14	5	luteal effect	biphasic	yes (9)	no	yes
2	R. T.	0/72/28	4	7	5	moderate estrogenic effect	biphasic	no (10)	no	yes
3	M. S.		8	10	5		biphasic	yes (3)	no	yes
4	G. M.		10	14	5		biphasic	yes (5)	no	yes
5	C. R.		10	14	5		monophasic	yes (6)	no	no
6	G. A.		10	10	5		monophasic	no (10)	no	no
7	Z. Y.		10	12	5		biphasic	no (10)	no	yes
8	G. Z.	0/32/68	10	14	5		possible rise	no (10)	no	yes
9	A. Z.		10	10	5		monophasic	yes (5)	no	no
10	F. Y.	0/78/22	4	8	6	short luteal phase	biphasic	no (10)	no	yes
11	B. S.		8	14	7		monophasic	no (10)	no	no
12	H. R.	0/88/12	4	12	10	delayed luteal effect	biphasic	yes (7)	no	yes
12 a	H. R.		4	9	10	delayed luteal effect	biphasic	yes (7)	no	yes
13	M. E.	0/62/38	4	9	10	slight estrogenic effect	monophasic	no (10)	no	no
14	S. D.	0/64/36	5	14	10	luteal effect	biphasic	yes (4)	no	yes
15	S. S.	0/86/14	6	14	10	no modified cytolysis	monophasic	yes (3)	no	no
16	H. S.	0/91/9	4	14	10	estrogen deficiency	monophasic	yes (6)	no	no
17	G. M.		2	14	10		biphasic	yes (5)	no	yes
18	B. S.	0/37/63	5	11	10	luteal effect	biphasic	yes (5)	no	yes
19	D. P.	0/80/20	6	14	10	no luteal effect	monophasic	yes (4)	no	no
20	A. R.	0/48/52	4	11	10	not modified	monophasic	yes (5)	no	no
21	Y. S.	0/89/11	6	12	10	not modified	monophasic	yes (4)	no	no

22	W. R.	0/90/10	6	14	10	no modified cytolysis	monophasic	yes	(4)	no	no
23	H. D.	0/74/26	5	12	10	slight luteal effect cytolysis	monophasic			no	no
24	P. A.	0/72/28	5	13	10	luteal effect cytolysis	biphasic	yes	(2)	no	yes
25	R. S.	0/96/4	8	13	10	modified estrogenic effect	biphasic	yes	(4)	no	yes
26	B. M.	0/57/43	6	12	10	luteal effect	biphasic	yes	(5)	no	yes
27	D. N.	0/64/36	5	14	10	luteal effect	biphasic			no	pregnancy
27 a	D. N.	0/80/20	4	10	14	not modified	monophasic	yes	(3)	no	no
28	R. A.	0/74/26	2	10	14	not modified	monophasic	yes	(6)	no	no
22 a	W. R.	0/85/15	4	10	14	not modified	monophasic	yes	(1)	no	no
23 a	H. D.	0/74/26	4	10	14	slight luteal effect cytolysis	monophasic	yes	(6)	no	no
29	B. H.	0/73/27	4	12	14	luteal effect	biphasic	yes	(4)	no	yes
30	C. R.	0/78/22	5	10	14	strong luteal effect	biphasic	yes	(3)	no	yes
31	L. S.	0/60/40	5	12	14	delayed estrogenic effect	monophasic	yes	(4)	no	no
32	A. A.		4	12	14		biphasic	yes	(2)	no	yes
12 a	H. R.		4	8	14		biphasic	yes	(4)	no	yes
12 a	H. R.		2	5	20	slight luteal effect	biphasic	yes	(4)	no	yes
8 a	G. Z.		2	5	20		monophasic	spotting during treatment			no
33	T. Y.		4	5	20	luteal effect, delay in ovulation	biphasic	yes	(2)	no	yes
15 a	S. S.	0/77/23	6	5	20	no luteal effect	monophasic	yes	(5)	no	no
26 a	B. M.	0/93/7	2	5	20	luteal effect	biphasic	yes	(5)	no	yes
25 a	R. S.	0/94/6	4	5	20	no luteal effect	biphasic	yes	(3)	no	yes
24 a	P. A.	0/94/6	4	5	20	slight luteal effect	monophasic	yes	(4)	no	no

Table III

Ro 4-8347 in oligomenorrhea

No., name		Maturation index before	Daily dose (mg)	Begins on day	During days	Vaginal smear after treatment	BBT after treatment	Bleeding after Ro 4 (during days)	Side-effects	Ovulation
1	M. L.	0/93/7	10		2	not modified		no	no	
2	F. H.	0/73/27	6		2	poor luteal effect		yes (5)	no	
3	L. A.	0/65/35	10		2	slight luteal effect		yes (6)	no	
4	F. E.	0/78/22	10		2			yes (4)	no	
5	Z. Y.		10	11	2		biphasic	yes (15)	no	yes
6	F. M.	0/58/42	10		3	estrogenic effect		yes (4)	no	
7	B. R.		6		3			yes (5)	no	
8	D. R.	0/40/60	5		3			yes (5)	no	
9	I. E.	0/64/36	10		3	slight luteal effect		yes (5)	no	
10	F. G.		10		3		biphasic	yes (10)	no	yes
11	T. S.	0/79/21	10		3	slight luteal effect		yes (5)	no	
12	T.	0/71/29	4	7	4	not modified	monophasic	yes (5)	no	
13	A. M.	0/59/41	4	21	5	estrogenic effect		yes (3)	no	
14	K. L.	0/64/36	4		5	not modified		no	no	
15	L. S.		10		5			yes (4)	no	
16	M. F.		10	14	7		biphasic	yes (5)	no	yes
17	P. Z.	0/90/10	4	12	10	not modified		spotting	no	
18	G. Y.	0/56/44	2	8	10	luteal effect cytolysis	monophasic	yes (5)	no	
19	L. A.		2	7	10			bleeding during treatment		
20	S. M.	0/66/34	4	*	10	luteal effect		yes (2)	no	
21	A. M.		5	13	10		biphasic	yes (4)	no	yes

22	S. S.	0/88/12	4	16	10			yes (12)	no	
23	H. B.	0/84/16	4	13	10			yes (15)	no	
24	Y. E.	0/96/4	2		10	cytolytic smear		yes (6)	no	
24 a	Y. E.	0/98/2	5	11	12	not modified	biphasic	yes (4)	no	yes
19 a	L. A.		5	11	12			bleeding during treatment		
25	R. B.	0/70/30	5	15	14	luteal effect	biphasic			pregnancy
16 a	M. F.		5	11	14		biphasic	yes (3)	no	yes
17	Y. E.	cytolytic smear	4	5	20		biphasic	yes (4)	no	yes
5 a	Z. Y.	do.	2	9	20	luteal effect	biphasic	yes (1)	no	yes
8 a	D. R.	0/40/60	4	16	20	luteal effect	biphasic	yes (5)	no	yes

* with ethinylestradiol

Table IV

Ro 4-8347 in amenorrhea

No., name		Diagnosis	Maturation index before treatment	Daily dose (mg)	Begins on day	During ... days	Vaginal smear after treatment	BBT after treatment	Bleeding after Ro 4-8347 (during ... days)	Side-effects	Ovulation
1	F. Y.	short term	0/83/17	10		4	not modified		* yes (4)	no	
2	M. S.	short term	0/81/19	10		2			yes (4)	no	
3	B. E.	short term	0/95/5	10		2			no	no	
4	B. N.	short term	0/74/26	10		2	estrogenic effect		no	no	
5	Y. O.	short term	0/94/6	10		2	not modified		yes (4)	no	
6	D. I.	short term	0/80/20	10		2			yes (3)	no	
7	L. S.	short term	0/85/15	10		2			yes (3)	no	
8	G. F.	short term	0/90/10	10		3	cytolysis		no	no	
9	S. S.	short term	0/85/15	5		4			incomplete abortion (5)		
10	D. A.	short term	0/85/15	10		4			yes (4)	no	
1	F. Y.	secondary		10		2			yes (5)	no	
2	L. M.	secondary	0/75/25	10		3	luteal effect		yes (6)	no	
3	G. A.	secondary	0/82/18	10		3	estrogenic effect		no	no	
3 a	G. A.	secondary	0/91/9	6		14	estrogenic effect		no	no	
4	A. S.	secondary	0/90/10	4		5	estrogenic effect		no	no	
5	F. Y.	secondary	0/66/34	2	15	14	luteal effect	biphasic	spotting during treatment		yes
6	B. D.	secondary	40/60/0	5	22	20	not modified	monophasic	no	no	

1	K. L.	primary	0/91/9	10		2	not modified		no	no	
2	S. S.	primary	0/98/2	10	19	2	not modified		no	no	
3	S. G.	primary	0/80/20	10		3	luteal effect		yes (7)	no	
4	G. R.	primary	0/84/16	10		3	not modified		no	no	
5	C. R.	primary	0/88/12	6		3	not modified		no	no	
6	K. A.	primary	0/80/20	10		3	slight luteal effect		yes (5)	no	
6 a	K. A.	primary	0/90/10	4		5	not modified		yes (6)	no	
7	S. S.	primary	0/62/38	4	9	5	luteal effect		yes (3)	no	
8	S. H.	primary	0/61/39	8	11	10	luteal effect	biphasic	yes (3)	no	yes
8 a	S. H.	primary	0/86/14	6		14	estrogenic effect		yes (4)	no	
9	A. R.	primary	0/90/10	5	14	14	not modified	monophasic	no	no	
10	S. M.	primary	0/82/18	6		14	slight luteal effect		yes (2)	no	
11	M. L.	primary	0/11/23	6		14	estrogenic effect		yes (4)	no	
11 a	M. L.	primary		6		20	estrogenic effect		yes (1)	no	

* + progesterone 100 mg

The Ro 4-8347 induced ovulation also in cases with minimal estrogenic activity. However, the response to its administration was both unpredictable and non-recurrent. A rational approach to treatment with Ro 4-8347 will be possible only when the precise mechanism of its activity is made clear.

The relatively low pregnancy rate, 2 in 37 ovulatory cycles, was discouraging. This may be improved by a more repeated use of this retrosteroid. We have not seen any case of ovarian overstimulation syndrome following treatment with retrosteroid.

Summary

The retroprogestational agent Ro 4-8347 was given in 85 cases of amenorrhea and anovulation in various dose schedules.

In 33 cases of anovulatory cyclic menstruation Ro 4-8347 induced ovulation in 24 out of 44 cycles of treatment (56%). Of 25 cases with oligomenorrhea, ovulation was induced in 10 out of 31 cycles of treatment (30%) and of 17 cases of amenorrhea, 2 ovulatory cycles were obtained in 20 cycles of treatment. Only 2 patients of this series became pregnant following treatment.

The "long course" of treatment consisting in the administration of 2–6 mg daily for 10–20 days gave better results than the "short course" of 4–10 mg daily for 2–6 days.

No case of ovarian overstimulation has been observed following treatment, and other side-effects were minimal.

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