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Article Title: Plasma levels of progesterone after vaginal, rectal or intramuscular administration of progesterone
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Name: Glaser, Rebecca
Status: Faculty
Address: SOUTHVIEW (via Kettering Hosp),
Site:
E-Mail Address: rglaser@woh.rr.com
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Department: School of Medicine

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Plasma levels of progesterone after vaginal, rectal, or intramuscular administration of progesterone

SVEN JOHAN NILLIUS*
ELOF D. B. JOHANSSON
Uppsala, Sweden

Plasma levels of progesterone were determined after vaginal, rectal, or intramuscular administration of 10 to 100 mg. of progesterone to 35 female volunteers. Progesterone was assayed by a competitive protein–binding technique. The absorption was very rapid by all three routes of administration, usually resulting in peak plasma levels of progesterone within the first 8 hr. after administration. The plasma levels remained elevated for longer periods of time than would be expected from the rapid rate of disappearance described for progesterone. Plasma levels corresponding to those encountered during the luteal phase of the menstrual cycle were attained with an intramuscular injection of 25 mg. of progesterone in oil or four times this dose by vaginal or rectal administration, while an intramuscular dose of 100 mg. resulted in a mean peak level corresponding to mid-pregnancy plasma levels of progesterone.

PROGESTERONE was synthesized in 1934, and it was soon used in the treatment of various gynecologic disorders. When, in the fifties, orally effective compounds with progestational activity (progestogens) became available, they soon largely replaced progesterone in the clinic. However, the biological effects of the progestogens differ in some respects from those of progesterone.[9] "Purists" have, therefore, directed interest back to progesterone as preferable in, for instance, the treatment of luteal phase insufficiency.

It has been shown earlier that progesterone is absorbed and physiologically effective after vaginal,[1] rectal,[2] and parenteral administration. In order to study the absorption of progesterone, previous investigators have used as end points either withdrawal bleeding in amenorrheic women, secretory transformation of the proliferative endometrium, urinary level of pregnanediol, or distribution of isotopically labeled progesterone.

When substituting for a deficiency in progesterone production, the aim should be to maintain physiologic blood levels of progesterone. It is then essential to know both the physiologic plasma levels during the menstrual cycle and pregnancy and the plasma levels following administration of progesterone. In the present study, plasma levels of progesterone after vaginal, rectal, or intramuscular administration of various doses of progesterone have been determined with the use of a rapid competitive protein–binding technique.[4, 10] Normal levels during the luteal phase of the menstrual cycle and during normal pregnancy determined by the same method have been described previously.[4, 5, 10]

From the Department of Obstetrics and Gynaecology (Head: Professor Carl Gemzell), University Hospital.

*This study was supported by the Ford Foundation (Grant No. 66-405 to Professor Carl Gemzell) and the Population Council. *Recipient of postdoctoral fellowship from the Ford Foundation.*

Material and methods

Subjects. Forty-three experiments were performed in 35 female volunteers. The majority, 25 subjects, were healthy women with regular periods working at the hospital. They received progesterone by vaginal, rectal, or intramuscular administration in doses from 10 to 100 mg. Three of these women participated in more than one experiment. Three women, investigated for amenorrhea of 3 to 10 months' duration, were given intramuscular injections of 50 mg. of progesterone. Seven subjects were postmenopausal women who were hospitalized for the treatment of uterine prolapse. They had been treated with 100 μg of ethinyl estradiol daily for four weeks and participated in a study on the effect of progesterone on the serum levels of the gonadotropins.* During continued estrogen treatment, they received either 10 or 100 mg. of progesterone intramuscularly.

The subjects were in good general health. They had no symptoms or signs of renal or hepatic insufficiency. In most of them, creatinine in serum was determined, and liver function tests (bilirubin, alkaline phosphatase, thymol turbidity, aspartate aminotransferase [Enzyme Commission 2, 6, 1, 1], and alanine aminotransferase activity [Enzyme Commission 2, 6, 1, 2]) were performed and found to be normal.

Blood samples were obtained by venipuncture. The blood was collected in heparinized tubes and centrifuged. The plasma was stored at −15° C. until analyzed.

Progesterone administration. Progesterone (pregn-4-ene-3, 20-dione) dissolved in arachidic oil (25 mg. per milliliter) was supplied by ACO, Sweden. This solution was diluted with arachidic oil to a concentration of 5 mg. per milliliter and used for the administration of doses of 10 mg. The intramuscular injection was given deep in the gluteal muscles. Suppositories, containing either 25 or 100 mg. of progesterone, were made by mixing progesterone with cocoa fat.

*Nillius and Wide: Acta Endocr. In press.

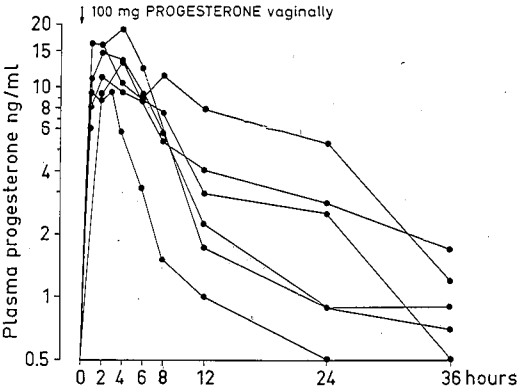

Fig. 1. Plasma levels of progesterone after vaginal administration of 100 mg. of progesterone in suppository form to six women in the follicular phase of the menstrual cycle.

The progesterone was administered at 8 A.M. In the women with regular periods, it was given on Day 7 of the menstrual cycle except in the group who received 25 mg. of progesterone in suppository form. This suppository was administered preovulatory to four women on Day 11, 12, or 13 of the menstrual cycle.

Progesterone assay. Progesterone in the plasma was determined with the use of the competitive protein–binding technique of Neill and associates[10] as modified by Johansson.[4] All samples from the same experiment were assayed simultaneously in duplicate.

For the calculation of differences between mean values, a formula based on the t distribution was used (see standard textbooks in statistics).

Results

Vaginal administration. The administration of 100 mg. of progesterone in suppository form vaginally to six women of fertile age resulted in a rapid increase of the plasma levels of progesterone (Fig. 1). Individual peak levels of 9.5 to 19.0 ng. per milliliter (geometric mean 13.5 ng. per milliliter) were attained within the first 4 hr. after the administration. During the next 8 hr., there was a gradual fall in the plasma levels. After 24 hr., plasma levels of progesterone were above follicular phase levels in three of the six women.

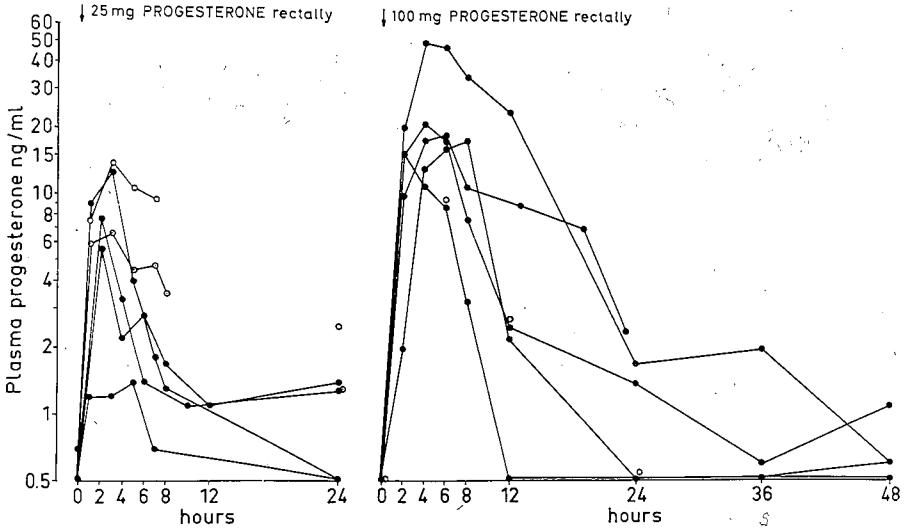

Fig. 2. Plasma levels of progesterone after rectal administration of 100 mg. of progesterone in suppository form to two groups of six women in the follicular phase of the menstrual cycle.

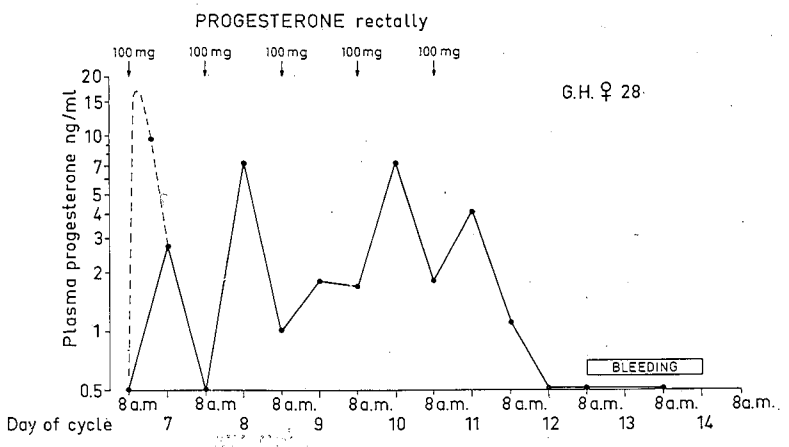

Fig. 3. Plasma levels of progesterone before, during, and after five days of daily rectal administration of 100 mg. of progesterone in suppository form to a woman in the follicular phase of the menstrual cycle. The broken curve shows schematically the absorption curve after rectal administration of 100 mg. of progesterone.

Rectal administration. Administration rectally of suppositories containing either 25 or 100 mg. of progesterone to two groups of six women of fertile age resulted in a similar response (Fig. 2). Peak plasma levels of progesterone were obtained within the first 8 hr. after administration, followed by a gradual decline to normal follicular phase levels. One of the subjects who received a 25 mg. suppository showed a very small increase in the plasma level of progesterone. The individual peak levels after the 25 mg. suppository varied between 1.4 and 13.8 ng. per milliliter (geometric mean 6.4 ng. per milliliter), and after the 100 mg. suppository levels were between 15.0 and 51.9 ng. per milliliter (geometric mean 22.5 ng. per milliliter). The rectal dose of 100 mg. of progesterone resulted in slightly higher plasma levels than the corresponding dose administered vaginally, but the difference between the geometric mean peak levels was not statistically significant ($P > 0.05$).

Plasma concentrations of progesterone

Table I. Progesterone concentrations in plasma after intramuscular administration of 100 mg. of progesterone in oil to twelve women

				Progesterone concentrations in plasma (ng./ml.)									
				Hours after administration									
Subject	*Age*	*Length*	*Weight*	*0*	*2*	*4*	*6*	*8*	*12*	*24*	*36*	*48*	*72*
E. L.	20	169	67	0.2	51.1	55.5	73.3	35.5	45.5	9.9	6.1	2.8	—
B. H.	23	159	55	0	35.6	37.5	55.5	88.8	74.4	14.4	11.8	5.6	—
K. S.	24	168	53	0.5	24.4	23.3	32.3	34.4	24.4	25.5	15.6	12.2	8.9
G. A.	25	163	58	1.4	58.0	51.1	47.5	96.6	—	—	—	—	—
C. E.	26	165	61	1.5	35.2	35.5	60.5	69.9	—	—	—	—	—
K. B.	28	168	57	0.6	141.0	95.5	67.8	104.3	—	—	—	—	—
G. H.	28	170	60	0.5	68.8	74.4	104.0	46.2	53.0	26.0	10.0	8.6	—
S. Å.	33	170	62	0.5	64.4	113.1	72.1	35.5	18.9	7.2	1.4	0.9	0.5
A. L. E.	53	164	97	0.6	4.2	14.2	16.4	13.3	23.1	13.1	—	3.0	—
S. E.	54	162	62	0	56.1	73.3	67.7	50.6	32.2	9.5	—	2.2	0.5
L. L.	58	175	74	0	58.5	56.3	56.0	37.5	28.0	14.4	—	2.8	—
R. E.	67	159	74	1.4	15.0	27.0	18.4	15.5	27.8	18.2	—	8.9	—
Gemetric mean concentrations				—	39	46	50	44	33	14.2	7.0	4.0	—

after daily rectal administration of suppositories containing 100 mg. of progesterone to a woman in the follicular phase of the menstrual cycle are shown in Fig. 3. Progesterone was administered every 24 hr. for five days. Blood samples were obtained every 12 hr. It was not possible to maintain a stable elevated plasma level of progesterone with this dosage. There was, however, a tendency to a cumulative effect during the five days of treatment. The rise and fall in the plasma levels of progesterone coincided with pronounced early-pregnancy–like symptoms such as nausea, "depression," etc. These symptoms were most marked between noon and 4 P.M.

Intramuscular administration. Administration intramuscularly of 100 mg. of progesterone in oil to eight women in the follicular phase of the menstrual cycle and to four postmenopausal women resulted in a rapid increase in the plasma levels of progesterone (Table I and Fig. 4). High plasma levels (geometric mean 39 ng. per milliliter) were found two hours after administration, and the peak levels were usually obtained within 8 hours. The geometric mean of the individual peak levels was 68 ng. per milliliter. The elevated levels persisted in most subjects for at least 48 hours. Blood samples 72 hr. after progesterone administration were taken in only three subjects, and in two of them the plasma level of progesterone was below 1 ng. per milliliter. Five of the eight women of fertile age experienced a small vaginal bleeding 72 to 96 hr. after progesterone administration.

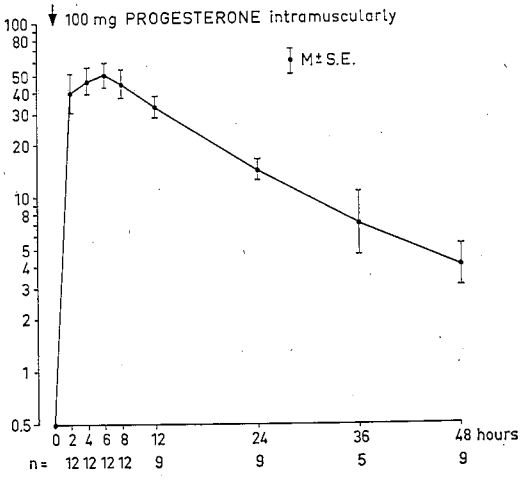

Fig. 4. The mean plasma level of progesterone after intramuscular administration of 100 mg. of progesterone in oil to eight women in the follicular phase of the menstrual cycle and to four postmenopausal women. The geometric means and standard error of the means are plotted in the figure.

The intramuscular administration of 50, 25, and 10 mg. of progesterone in oil gave a similar pattern (Figs. 5, 6, and 7). The individual peak levels which were usually found within the first 8 hr. after administra-

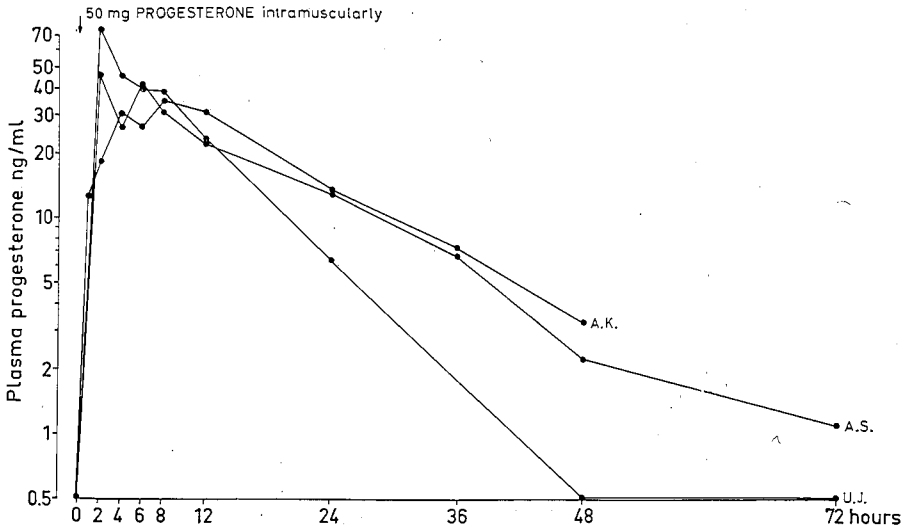

Fig. 5. Plasma levels of progesterone after intramuscular administration of 50 mg. of progesterone in oil to three amenorrheic women.

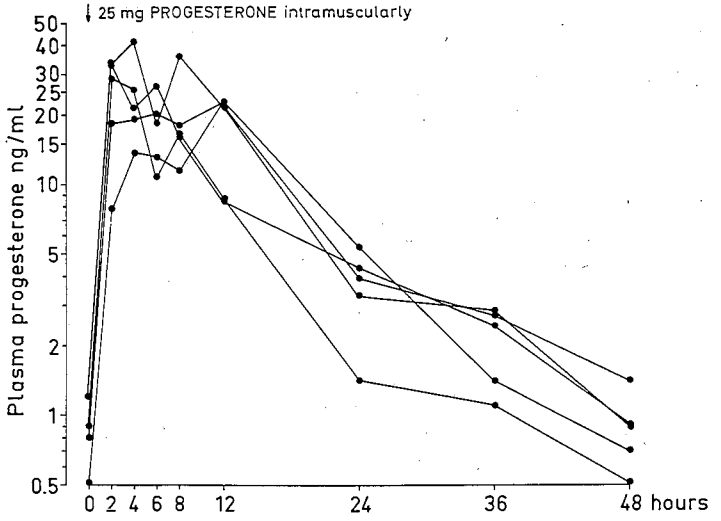

Fig. 6. Plasma levels of progesterone after intramuscular administration of 25 mg. of progesterone in oil to five women in the follicular phase of the menstrual cycle.

tion averaged (geometric means) 50, 28, and 7 ng. per milliliter, respectively. The elevated levels after the 50 mg. dose persisted for at least 48 hr. in two of the three amenorrhoeic women. Judged by the 24 hr. urinary excretion of total estrogens, these two women had a basal endogenous estrogen production, and both later experienced withdrawal bleeding. The 25 mg. dose resulted in elevated levels for about 36 hr. and the 10 mg. dose elevated levels for about 24 hr.

A 33-year-old woman volunteered for five experiments during a one-year period. Progesterone was administered intramuscularly, rectally, and vaginally in doses between 10 and 100 mg., always on Day 7 in the menstrual cycle. The results are shown in Fig. 8. The general appearance of the progesterone curves is similar to that of corresponding dos-

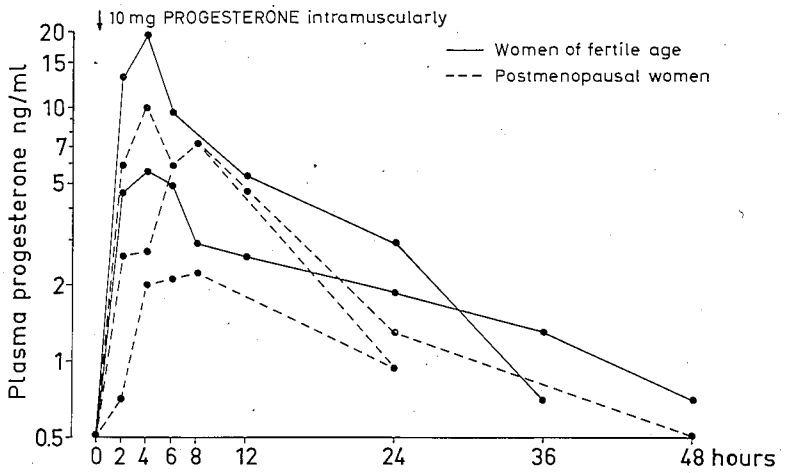

Fig. 7. Plasma levels of progesterone after intramuscular administration of 10 mg. of progesterone in oil to five women.

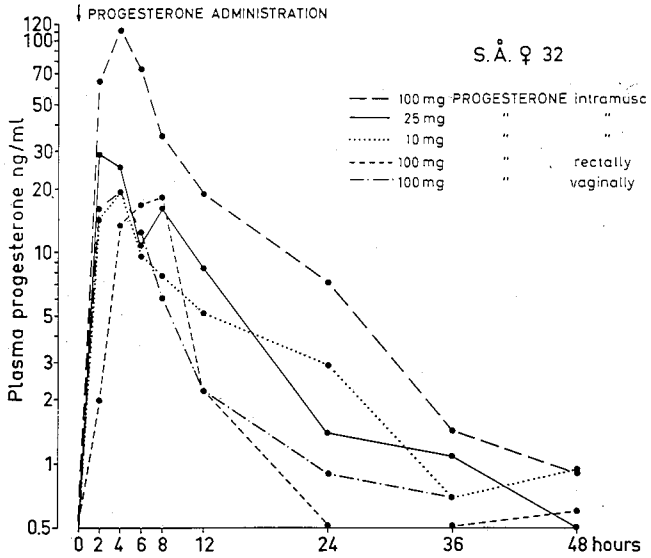

Fig. 8. Plasma levels of progesterone after intramuscular administration of 10, 25, and 100 mg. of progesterone in oil and after vaginal and rectal administration of 100 mg. of progesterone in suppository form to the same subject on Day 7 in the follicular phase of five different menstrual cycles.

ages in previous figures. However, the elevated plasma levels of progesterone persisted for shorter periods of time in this woman than in most of the other subjects.

With the exception of the early-pregnancy–like symptoms experienced by one subject during repeated rectal administration of progesterone suppositories, no local or systemic side effects were observed after the administration of progesterone either vaginally, rectally, or intramuscularly.

Comment

The direct measurement of progesterone in plasma after vaginal, rectal, or intramuscular administration shows in confirmation with earlier studies, reviewed by Langecker,[8] that progesterone is readily ab-

sorbed by these three routes of administration. The absorption was found to be very rapid, resulting in high plasma levels of progesterone within the first two hours and peak levels usually within eight hours. Plasma levels corresponding to those encountered during the luteal phase of the menstrual cycle were attained with an intramuscular injection of 25 mg. of progesterone in oil while an intramuscular dose of 100 mg. resulted in a mean peak level corresponding to mid-pregnancy plasma levels of progesterone. However, there was a considerable individual variation.

The elevated levels persisted for longer periods of time than would be expected from the rapid rate of disappearance described for progesterone. In nonpregnant women, the half-life time has been reported to be 20 to 29 min.[12, 14] This can possibly be explained by the fact that when the progesterone concentration in plasma rises to high levels during the absorption a considerable amount of the administered progesterone diffuses into the fat tissue of the body as shown by Plotz and Davis[11] and Zander and colleagues.[15] The progesterone deposited in the fat tissue then diffuses back into the bloodstream when the plasma levels decline, and a depot effect is thus obtained. The disappearance curve after intramuscular administration was found to fall more slowly than after vaginal or rectal administration, indicating that the intramuscular site of injection also serves as a depot for progesterone besides the fat tissue.

The vaginal or rectal administration of 100 mg. of progesterone in suppository form resulted in plasma levels in the range usually encountered during the luteal phase of the menstrual cycle. This means that with vaginal or rectal administration of progesterone about four times the intramuscular dose is required to reach corresponding plasma levels. There was no significant difference between the mean peak levels obtained after vaginal or rectal administration of 100 mg. of progesterone. The elevated levels usually persisted for less than 24 hr., suggesting that it is necessary to administer progesterone vaginally or rectally every 12 hr., to maintain a stable physiologic luteal phase level of progesterone in plasma.

The depot effect obtained with an intramuscular injection of progesterone has proved to be useful in clinical work. The prevention of anovulatory bleeding problems can be effectively managed by cyclic administration of 25 to 50 mg. of progesterone in oil intramuscularly,[3] and a single injection of 50 mg. of progesterone in oil is still the quickest way of testing the endogenous estrogen effect on the endometrium in amenorrheic women.[13] For the treatment of progesterone deficiency during a defective luteal phase, Jones[7] advocates the use of natural progesterone instead of synthetic progestational agents. This seems to be the treatment of choice, especially since a recent report[6] indicates that some of the progestogens, such as norethindrone, norgestrel, and chlormadinone acetate, especially in large doses, exert a luteolytic effect when given during the luteal phase of the menstrual cycle. Jones[7] recommends vaginal administration of 50 mg. of progesterone in suppository form or alternatively intramuscular injection of 12.5 mg. of progesterone in oil daily during the luteal phase. In light of the results from the present study, these seem to be fairly low dosages, but all our subjects were devoid of their own luteal activity when investigated and repeated administration was only used in one case.

From the results of the present investigation, the following recommendations may be made. To ensure physiologic luteal phase levels of progesterone in plasma, a daily intramuscular dose of 25 mg. of progesterone in oil or four times this dose by vaginal or rectal administration is needed. When daily administration is utilized, a certain cumulative effect will be obtained. The total daily vaginal or rectal dose should be divided into two doses to obtain a stable elevated plasma level of progesterone.

We are indebted to Mrs. Margareta Larsson for skillful technical assistance and to Mrs. Birgit Häggqvist for expert drawing of the illustrations.

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