Further Investigations on the Induction of Uterine Haemorrhage by means of Progesterone

Second Report

BY

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As recently reported by us in this journal,[1] haemorrhages are produced during the intermenstrual stage in the normally menstruating women by means of parenteral administration of progesterone: intracyclical haemorrhage. If a woman is injected with 10 mg. of progesterone* daily during the post-menstrual stage, i.e. from the fifth to the ninth or from the seventh to the eleventh day of the cycle, a total dosage of 50 mg., haemorrhage sets in after an interval of 60 hours, that is on the twelfth or the fourteenth day of the cycle, and persists for 3 to 4 days. During the period when progesterone is given the patients notice swelling and pain in the breasts, as well as pain in the abdomen, all these symptoms subsiding as soon as the haemorrhage commences. The blood discharged in this intracyclic haemorrhage does not coagulate, a quality characteristic of true menstrual blood.

I. *Progesterone Administration in the Intermenstrual Stage.*

What is the effect of progesterone if injected in the intermenstrual stage, that is at a time when the woman, after follicular rupture, is already under the influence of the progesterone formed endogeneously in the corpus luteum? In our first report we have

* As we have previously reported elsewhere, the same effect can be achieved with the oral administration of pregnen-in-on-ol as is noted with the parenteral administration of progesterone. In a normally menstruating woman we produced intracyclic haemorrhage with 300 milligrams of pregnen-in-on-ol. The same dose produced a haemorrhage in a case of secondary amenorrhoea without any preliminary treatment with oestrogenic hormone.

already described two such cases. In the first case progesterone had been given from the eleventh to the fifteenth days of the cycle, and on the eighteenth day the onset of the haemorrhage was observed during an operation for myoma of the uterus. In the second case the hormone had been injected from the twelfth to the sixteenth day of the cycle. Haemorrhage, however, did not take place precociously before the normal period of menstruation. We treated four other patients in a similar manner, injecting 50 mg. of progesterone in two patients from the eleventh to the fifteenth day, in one from the twelfth to the sixteenth day of the cycle, and in one from the fifteenth to the nineteenth day. (Table I and Fig. 1.) Precocious bleeding could not be produced in any of these patients, and the haemorrhage did not occur before the normal menstrual period. There is, therefore, a characteristic difference in the action of progesterone depending on the cyclic phase in which it is administered. If progesterone is given in the post-menstrual stage the haemorrhage occurs in the intermenstruum; if it is given during the intermenstruum, there is no effect whatsoever. Haemorrhage occurs only if there is an interval between the administration of progesterone and the period when it is formed endogeneously. If the exogeneous administration of progesterone merges with the period of the formation of progesterone in the corpus luteum, there is no haemorrhage.

Subsequent menstruation occurs at the normal term (*cf.* Table I, Cases 1, 3, and 4). The use of progesterone during the second half of the cycle, therefore, does not interfere with the ovarian cycle.

II. *Prevention of the Intracyclic Haemorrhage through Follicular Hormone.*

By administration of 50 mg. of progesterone in the post-menstrual stage a haemorrhage during the intermenstruum is brought about: intracyclic haemorrhage. The oestrone level which is physiologically present during the intermenstrual stage does not prevent the haemorrhage; if, however, additional amounts of oestrogenic hormone are given the inhibitory action becomes effective. In five patients we injected, subsequent to 5 days' treatment with 50 mg. of progesterone (10 milligrams equals 100,000 international units of oestradiolbenzoate) daily for 4 days; the total dose, therefore, amounting to 40 mg. (Fig. 2). The intracyclic haemorrhage which had previously appeared subsequent to progesterone administration after an interval of 60 hours did not occur in any of these patients (*cf.* Table II).

CASE No. 1. Progesterone had been given from the fourth day to the eighth day of the cycle, oestradiolbenzoate from the ninth day to the twelfth day. If progesterone only hade been given the haemorrhage would have occurred on the eleventh day of the cycle. It did not, however, occur before the fifty-second day, and was, therefore, delayed by 41 days. (Fig. 2.)

CASE No. 2. Progesterone had been given from the fifth to the ninth day of the cycle, oestradiolbenzoate from the tenth to the thirteenth days. If progesterone only had been given, we should have expected the onset of the haemorrhage on the twelfth day of the cycle. It occurred, however, on the fifty-third day, and was, therefore, delayed by 41 days. The uterine mucosa, as ascertained by histological examination of a strip, was in the menstrual stage of development.

CASE No. 3. Progesterone had been given from the fifth to the ninth days, oestradiolbenzoate from the tenth to the thirteenth days of the cycle. If progesterone only had been given the haemorrhage would have been expected on the twelfth day. It occurred, however, on the nineteenth day, and was, therefore, delayed by 7 days. Examination of the mucous membrane revealed a pseudo-menstrual bleeding occurring from a proliferative mucosa.

CASE No. 4. Progesterone had been given from the seventh to the eleventh days and oestradiolbenzoate from the twelfth to the fifteenth days of the cycle. If progesterone only had been given bleeding would have been expected on the fourteenth day; it occurred, however, on the forty-fourth day, and was, therefore, delayed by 30 days. Histological examination showed a progestational mucosa, demonstrating, therefore, that we were dealing with a true menstrual haemorrhage.

CASE No. 5. Progesterone had been given from the eighth to the twelfth days, and oestradiolbenzoate from the thirteenth to the sixteenth days of the cycle. If progesterone only had been given we should have expected the onset of the haemorrhage on the fifteenth day. It did not occur, however, before the twenty-fourth day, and was, therefore, delayed by 9 days.

These observations demonstrate that:

1. The intracyclic haemorrhage is prevented by oestrogenic hormone.

2. The duration of this inhibitory action varies from 2 to 41 days. In two of the cases (Nos. 3 and 5) the haemorrhage occurred during the course of the cycle; in three cases (Nos. 1, 2 and 4) it was postponed, thus bringing about artificial amenorrhoea. This observation need not surprise us, since follicular hormone, at least 70,000 m.u., is able to inhibit menstruation (Zondek[2]). The follicular hormone inhibits the secretion of the luteinizing hormone

of the anterior pituitary (prolan B), thus disturbing the development of the corpus luteum. There is, therefore, an insufficient production of progesterone, which in its turn prevents the progestational transformation of the uterine mucosa. Protracted treatment with large doses of hormone (60 mg. of oestradiolbenzoate during 60 days) results in hormonal sterilization of women, and, without the formation of corpus luteum the ovaries appear like those of an old woman (Zondek[3]). The oestrogenic hormone, consequently, can bring about:

(a) inhibition of the haemorrhage-producing action of progesterone;

(b) inhibition of the gonadotropic secretion of the anterior pitituary.

Summary.

1. Progesterone, if administered during the post-menstrual stage, induces intermenstrual haemorrhages in the normally menstruating woman: intracyclic haemorrhage.

2. Progesterone is not effective if given in the intermenstrual stage, i.e. during, or subsequent to the rupture of the follicle, at a time, therefore, when the woman is already under the influence of the endogeneously produced corpus luteum hormone. The intracyclic haemorrhage, therefore, does not occur if there is not an interval between the exogeneous administration and the endogeneous production of the corpus luteum hormone.

3. The oestrone level which is physiologically present during the intermenstrual stage does not prevent the intracyclic haemorrhage; if, however, additional amounts of oestrogenic hormone are given the inhibitory action becomes effective. The oestrogenic hormone interferes with the haemorrhage-producing effect of the corpus luteum hormone, as well as with the gonadotropic mechanism of the anterior pituitary.

4. Pregnen-in-on-ol given *per os* has the same effect as has progesterone given parenterally.

Progesterone, progestine, and oestradiolbenzoate (dimenformone) were kindly supplied to us by N. V. Organon Oss.

TABLE I.

Progesterone administration in the inter-menstruum.

	No. 1 J.	No. 2 M.	No. 3 K.	No. 4 M.
Progesterone treatment day of the cycle ...	11 to 15	11 to 15	12 to 16	15 to 19
Bleeding: day of the cycle ...	26 to 30	27 to 29	28 to 31	25 to 27
Following bleeding: day of the cycle ...	54	—	55	49
Interval between the two haemorrhages	28	—	27	24

TABLE II.

Inhibition of the intracyclic haemorrhage through follicular hormone.

	No. 1 K.	No. 2 N.	No. 3 J.	No. 4 N.	No. 5 N.
50 mg. of progesterone, day of the cycle	4 to 8	5 to 9	5 to 9	7 to 11	8 to 12
40 mg. oestradiolbenzoate, day of the cycle	9 to 12	10 to 13	10 to 13	12 to 15	13 to 16
Haemorrhage, day of the cycle	52 to 55	53 to 56	19 to 22	44 to 47	24 to 30
Uterine mucosa	—	Mens.	Psuedo-menstrual	Mens.	—
Inhibition through oestradiol-benzoate, in days	41	41	7	30	9
Following haemorrhage, days after	24	30	30	—	—

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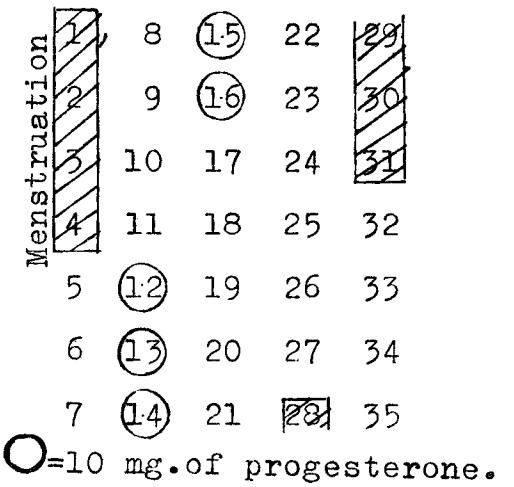

FIG. 1.

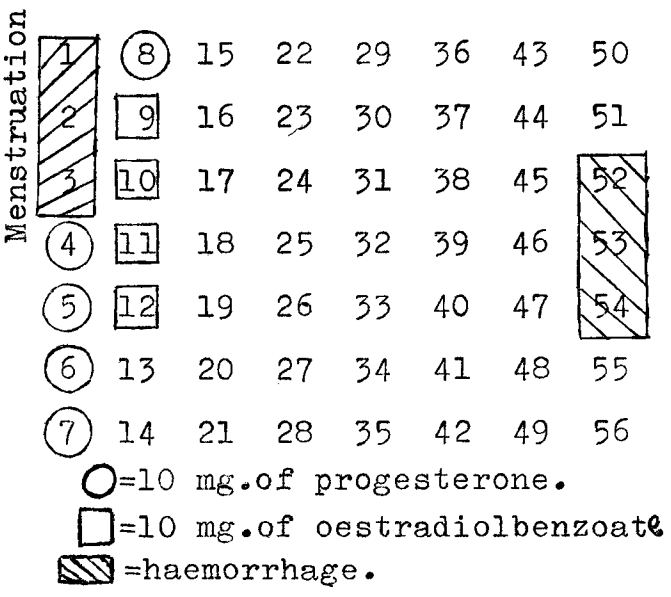

FIG. 2.