PLASMA FIBRINOLYTIC ACTIVITY AND MENSTRUAL CYCLE

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Blood discharged during menstruation does not clot; it has a further capacity to lyse added fibrin (Smith and Smith, 1945; Albrechtsen, 1956). This phenomenon stimulated investigation of the fibrinolytic activity of circulating blood of women during menstruation (Smith and Smith, 1945; Willson and Munnell, 1946; Beller, *et al.* 1964). Astrup (1958) speculated that these cyclic increases in fibrinolytic activity may give relative resistance to atherosclerosis to women during their fertile life. Sex hormones have been found to influence the fibrinolytic potential of circulating blood (Gillman and Naidoo, 1958; Gillman, *et al.* 1958; Jensen, 1960; Brackman and Astrup, 1964; Donayre and Pincus, 1965; Robinson and Lebeau, 1965).

In view of the above information, it was thought that fibrinolytic activity of blood obtained at random points in the menstrual cycle of women may not represent a true "normal" value in these subjects and such a sampling may conceal differences in enzyme activity between men and women. In an attempt to obtain information on such possible periodical variations, fibrinolytic activity in the blood was studied in women at two points in their menstrual cycle — about the 14th day when ovulation was expected and the 28th day just before the onset of menstruation. Conclusions of these experiments were briefly reported earlier (Ramachandra Rao, 1964).

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Material and Methods

The subjects were 14 healthy young women of ages ranging from 22 to 33 years. Two samples of venous blood were taken from each volunteer on days which were to approximate the 14th and the 28th day of their cycles. From the date of onset of the next menstruation (or when this was not available, based on an assumed 28th day cycle), the actual day of blood collection was back calculated. Sometimes the periods started earlier than expected so that the samples of blood were collected during the menstruation. Fibrinolytic activity was measured both as euglobulin clot lysis time (ELT) and as dilute plasma clot lysis time (DPLT) as described earlier (Ramachandra Rao, 1964 a).

Results

It is seen from Table 1 that blood samples representing the middle of the cycle were collected between the 13th and the 17th day to approximate the day of ovulation. The range of days for the premenstrual period was longer — 25th to 3rd day of next cycle; two samples collected for this period were found to have been on the 28th day of 38-day and 58-day

TABLE I
Plasma Fibrinolytic Activity in Women

Subject No.	Day of menstrual cycle	Length of cycle (days)	Date of blood collection	DPLT	ELT
1	28	38	21-9-63	29	8.50
,,	14	?	14-10-63	84	30.00
2	17	28	21-9-63	50	10.00
,,	2	28	4-10-63	51	5.75
3	28	28	21-9-63	63	11.00
,,	15	?	7-10-63	135	3.50
4	28	58	24-9-63	17	9.50
,,	6	?	31-10-63	29	4.00
5	15	26	24-9-63	60	9.50
,,	2	?	7-10-63	84	12.50
6	28	28	24-9-63	17	11.00
,,	14	?	7-10-63	135	8.50
7	27	28	26-9-63	30	6.00
,,	15	?	11-10-63	28	4.50
8	13	25	26-9-63	15	4.00
9	14	27	30-9-63	30	14.00
,,	25	27	11-10-63	84	8.00
10	15	29	30-9-63	30	12.50
,,	25	29	11-10-63	....	13.50
11	14	30	30-9-63	17	5.00
,,	25	30	11-10-63	28	5.50
12	15	30	4-10-63	29	6.50
,,	27	30	16.10-63	15	4.75
13	14	27	7-10-63	36	5.25
,,	3	27	22-10-63	16	6.00
14	17	?	14-10-63	84	30.00
,,	5	?	31-10-63	350	5.50
Range				15-350	3.5-30.0
Median				33	8.0

DPLT—Dilute plasma lot clysis time in hours ;

ELT — Plasma euglobulin clot lysis time in hours

? — Not known.

cycles (delayed menstruation) and two others on the fifth and sixth days of continuing menstrual flow. The range of values for ELT (3.5 to 14 hours) was approximately the same for both periods. Two very high values of 30 hours were recorded for ELT. Similarly three high values (135, 135 and 350 hours) have been recorded for DPLT. There is no explana-

tion for these data. Data were analysed statistically (Student's 't' test) for differences between periods. The differences both for DPLT and ELT were found not to be significant. This remained true even after eliminating the aberrant high values.

The data showed variations in the individuals (of varying magnitude) from period to period. The changes between periods were not consistent in all the individuals. So it could not be said that there was a physiological change in the fibrinolytic potential of the individual with the progress of the cycle. Three women during menstruation had showed lower ELT, but two others during the same period gave higher figures for ELT.

In some instances, there were discrepancies in periodical fluctuations measured as DPLT and ELT. These discrepancies in variations may be attributed to the methods. It is possible, for instance, that the levels of inhibitors are raised with no changes in the levels of the fibrinolytic components (activators, plasminogen and plasmin). In such a case, the DPLT (where due to the dilution of plasma, the inhibitors are only reduced, but not altogether eliminated) is raised, but the ELT remains the same (due to the total removal of the inhibitors during the preparation of the euglobulins). On the other hand, when the active components of the fibrinolytic system are increased with no changes in the levels of the inhibitors, both DPLT and ELT may show lower values. If both the active and the inhibitory factors of the fibrinolytic system are raised, the ELT will fall, but the change in DPLT will depend on the relative balance between the two sets of factors.

Discussion

There are only two previous reports (Smith and Smith, 1945; Willson and Munnell, 1946) on the changes in blood fibrinolytic activity in women. Both these reports show an increase in fibrinolytic activity during menstruation compared to the intermenstruum. Cliffton (1958) mentions similar findings of Daniel and Florian. The present data do not support any such consistent trend. Recently, Beller, *et al.* (1964) confirmed the present findings.

Just before the time of ovulation (about the 12th day), blood progesterone levels begin to increase and reach a gradual peak after ovulation by about the 18th day and fall to minimal levels just before menstruation, continuing thus till the 12th day of the next cycle (Harper, 1961). In these experiments, the fibrinolytic potentials determined on about the 17th or 18th day did not considerably differ from the values in the same volunteer at other times.

Estrogen withdrawal (as it occurs during menstruation) increases the fibrinolytic activity in the uterus (Page *et al.* 1951). A distinct fall in plasma fibrinolytic potential has been reported in the later stages of pregnancy (Biezenski and Moore, 1958; Gillman *et al.* 1959; Chiplunkar and Sirsi, 1963; Badhe *et al.* 1965) during which time both estrogen and progresterone levels are high. Shaper *et al.* (1965) speculate that changes in circulating fibrinolytic activity in pregnancy may have something to do with changes in the levels of sex hormones in the circulation.

During menstruation, the progesterone levels are low and during the last stages of pregnancy they are high (along with high levels of estrogen), but during both these periods, the fibrinolytic potential is low.

The above discussion suggests that the circulating fibrinolytic potential in a woman is not dependant on only her estrogen or progesterone levels; other factors also may be important.

Conclusions from the present data are not final, primarily because of the difficulty in determining the actual day of ovulation. Bell and Loraine (1965) found that ovulation in normal women may occur any time between the 10th day and the 20th day in a cycle of 28 days. Thus, it appears necessary to be certain in each woman about the actual day of ovulation, determined by urinary levels of estrogens or small changes in body temperature. This would show changes in blood fibrinolytic activity in relation to the major phases of the menstrual cycle. Alternatively, a number of determinations of blood fibrinolytic activity throughout the menstrual cycle can give some conclusive evidence. Such repeated determinations of plasma fibrinolytic activity by Beller, *et al.* (1964) confirm the present results.

Summary

The circulating fibrinolytic potential in 14 healthy young women determined as plasma euglobulin clot lysis time and dilute plasma clot lysis time did not vary significantly from the middle to the end of the menstrual cycle. Of the five women studied during menstruation only three showed an increased plasma fibrinolytic activity; in the remaining two, changes were marginal.

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