Pathophysiology of Plasmin System

III. A Contribution to the Mechanism of Incoagulability of Menstrual and Intraperitoneal Blood

By

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It is evident that menstrual and intraperitoneal blood are both lacking in fibrinogen and are in the fluid state. Although a number of reports¹⁻³⁾ dealing with the reason why menstrual blood is fluid have been done hitherto, little is known regarding the mechanism by which intraperitoneal blood becomes fluid in such cases as ectopic pregnancy. In this paper, a mechanism will be discussed based on the results obtained from experiments wherein the equilibrium between plasmin (activator) and inhibitor seems to be of considerable importance.

MATERIALS AND METHODS

Samples of menstrual blood were collected by suction from the uterine cavity and sometimes from the vagina. Blood samples from the peritoneal cavity were collected from patients with ectopic pregnancy at the time of surgical treatment. These blood samples were mixed with 3.8% sodium citrate in the proportion of 9:1. In each case, venous blood was also collected in the usual manner. Citrated plasma was obtained by centrifuge at 3,000 r.p.m. for 10 minutes and used for this experiment.

Endometrial samples were obtained by curettage. Peritoneal and omental samples were taken from the patients at the time of laparotomy. These tissues were cleansed of contaminated blood by rapid washing with physiological saline solution. The tissue, weighing 100 mg., was suspended in 5 ml. of freshly prepared 1 M potassium thiocyanate solution and minced by blender. It was then allowed to stand in a refrigerator for 24 hours and centrifuged. The supernatant fluid was used for the plasminogen activator assay by using the standard fibrin plate method.

Tyrosine content in 0.1 ml. of the tissue extracts was measured by the

phenol reagent method.

The activity of tissue plasminogen activator was calculated by the following formula.

$$\text{Activity} = \frac{\text{Lysed area of fibrin plate (mm}^2\text{)}}{\text{Tyrosine content in 0.1 ml. of tissue extract (}\mu\text{g.)}}$$

Fibrinogen content of the blood samples was qualitatively estimated by thrombin addition.

The proteolytic activity of the euglobulin fraction without any artificial activating procedure (latent activity) was measured by the caseinolytic and fibrinolytic (standard fibrin solution) methods and inhibitor assay (as trypsin inhibitor) as was described in the previous report.⁴⁾

RESULTS

Assay results of plasmin system of 12 cases of menstrual blood and 10 cases of intraperitoneal blood with ectopic pregnancy are summarized in Table I.

TABLE I. Assay Results of Plasmin System of Menstrual and Intraperitoneal Blood

Exp. No.	Menstrual blood			Intraperitoneal blood		
	Euglobulin fraction method		Inhibitor (%)	Euglobulin fraction method		Inhibitor (%)
	Caseinolytic activity ($\mu\text{g.}$)	Fibrinolytic activity ($\mu\text{g.}$)		Caseinolytic activity ($\mu\text{g.}$)	Fibrinolytic activity ($\mu\text{g.}$)	
1	215			10	44	0
2	124			0	53	3
3	96			15	40	0
4	127			0	98	5
5	152	104	0	16	52	10
6	253	128	0	9	45	0
7	70	88	8	18	48	6
8	212	105	3	21	88	10
9	114	100	10	18	48	6
10	154	101	6	17	43	8
11	242	121	0			
12	200	103	0			
Average	164.9	106.3	3.4	12.4	56.7	5.5

All samples of menstrual blood were completely lacking in fibrinogen content. Both caseinolytic and fibrinolytic activity of the euglobulin fraction of menstrual plasma were very high, and these high values were comparable with the values obtained by streptokinase fully-activated euglobulin fraction (whole activity) of venous blood. The supernatant of menstrual plasma after the elimination of the euglobulin fraction showed much lower inhibitory action on trypsin as compared with normal venous blood.

Fibrinogen was also found to be absent in all cases of intraperitoneal blood. The most remarkable finding regarding the intraperitoneal blood was that it was essentially free from the inhibitory action on trypsin. Both caseinolytic and fibrinolytic activity of the euglobulin fraction of intraperitoneal blood were unexpectedly low, and these activity values were almost similar to that of normal venous blood.

The assay results of plasminogen activator of endometrial (Table II), peritoneal and omental tissue (Table III) extracts gave high values.

TABLE II. Activity of Plasminogen Activator of Endometrial Extracts

Exp. No.	Diagnosis	Phase of cycle	Age	Activity
1	Fibroid	Proliferative	51	3.36
2	Endometrial hyperplasia	Proliferative	36	3.64
3	Fibroid	Proliferative	37	1.11
4	Fibroid	Proliferative	41	4.11
5	Fibroid	Proliferative	40	5.34
6	Fibroid	Proliferative	50	1.07
7	Pelvic peritonitis	Proliferative	40	1.37
8	Fibroid	Secretory	38	6.00
9	Fibroid	Secretory	42	7.25
10	Fibroid	Secretory	40	8.08

TABLE III. Activity of Plasminogen Activator of Peritoneal and Omental Extracts

Exp. No.	Diagnosis	Activity	
		Peritoneum	Omentum
1	Fibroid	2.98	
2	Fibroid	4.32	
3	Fibroid	5.04	
4	Fibroid	4.29	
5	Stomach cancer	4.73	
6	Intestinal cancer	1.63	
7	Peritoneal adhesion	7.69	16.6
8	Ovarian cyst	2.70	3.32
9	Retro-displacement of the uterus		4.29
10	Ovarian cyst		5.52
11	Endometriosis		4.83
Average		4.17	6.91

DISCUSSION

According to the recent work of Albrechtsen^{2,3}), it has been claimed that the fluidity mechanism of menstrual blood can be attributed to the consumption of fibrinogen by endometrial plasminogen activator. However, by what mechan-

ism fibrinogen becomes lacking in menstrual blood is as yet uncertain. It may result from fibrinolysis, or perhaps from fibrinogenolysis. Maki, Kikuchi and Saito⁵⁾ noted that the recalcification time of normal citrated plasma was markedly shortened by the addition of saline extract of endometrial tissue. Therefore, the presence of a significant amount of thromboplastic material in the endometrial tissue can be presumed. Accordingly, it is supposed that the menstrual blood from the endometrium coagulates initially by the influence of such thromboplastic material, and secondarily is lysed by the fibrinolysis. In the causation of menstrual blood fluidity, it is presumed that fibrinogenolysis is less important than fibrinolysis because fibrin is far more easily digestible by plasmin than is fibrinogen.

In cases of ectopic pregnancy, the fluid blood is found occasionally along with intraperitoneal clots; however, the volume of fluid blood is too great to be explained on the basis of merely transudate from the coagulum. The role of fibrinolysis in producing fluid blood in the peritoneal cavity is, therefore, presumed in the same fashion as menstrual blood. The values of caseinolytic and fibrinolytic activity of the euglobulin fraction from the peritoneal cavity blood were relatively low; however, the extracts of peritoneal and omental tissues gave high activity of plasminogen activator. These values of the plasminogen activator were comparable with that of endometrial tissue which was generally believed to be an organ containing large quantities of plasminogen activator. In addition, all blood samples from the peritoneal cavity showed almost no potency of antitryptic activity.

As viewed from our concept of plasmin (activator)-inhibitor ratio,⁶⁾ there must be fibrinolysis in the intraperitoneal blood. Furthermore, it may be presumed that the fibrinolysis may be enhanced by the contact of blood with peritoneum and omentum both of which contain a significant amount of plasminogen activator. Mechanical enhancement by the motion of the intestines and by changes of body position must also be considered.

A possible role of the plasminogen activator on the surface of body cavities may be in the prevention of adhesion formation. For example, the rarity of occurrence of adhesions in the uterine cavity, inspite of the high frequency of wounds caused by menstruation, abortion and delivery, may be due to the high concentration of plasminogen activator in the endometrium.

A possible mechanism of the causation of the fluidity of menstrual and intraperitoneal blood has been discussed.

SUMMARY

1. All menstrual blood samples were capable of high potency caseinolytic and fibrinolytic activity in their euglobulin fraction. All samples lacked fibrinogen and had low inhibitory action on trypsin. A significant amount of

plasminogen activator in 1 M potassium thiocyanate extracts was detected on the standard fibrin plate. This fibrinolysis may play a very important role in maintaining fluidity of the menstrum.

2. Blood samples obtained from the peritoneal cavity in cases of ruptured ectopic pregnancy had relatively low proteolytic activity in their euglobulin fraction. All samples lacked fibrinogen and had no potency of inhibitory action on trypsin. It is also suggested that the fluidity mechanism of the intraperitoneal blood is due to fibrinolysis and this fibrinolysis is enhanced by peritoneal plasminogen activator.

References

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