Fibrinolytic Activity during Pregnancy

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MAKI, M., SOGA, K. and SEKI, H. *Fibrinolytic Activity during Pregnancy.* Tohoku J. exp. Med., 1980, 132 (3), 349-354 — It has been a general concept that fibrinolytic activity is diminished during pregnancy. However, increase in FDP (fibrin/fibrinogen degradation products by plasmin digestion) which indicates accelerated fibrinolytic activity is also observed during pregnancy. To clarify these conflicting findings, α -2-plasmin inhibitor and FDP, sensitive indicators of fibrinolytic activity, were studied during pregnancy. Decrease in plasmin inhibitor and increase in FDP were found during pregnancy suggesting that fibrinolytic activity is accelerated during pregnancy. Since FDP level was higher in blood samples from the uterine vein than those from the artery, the accelerated fibrinolysis characterized by decrease in plasmin inhibitor and increased FDP, might be reflection of local event. On the other hand, systemic blood remains still hypofibrinolytic in normal pregnant condition. — fibrinolysis; pregnancy; FDP (fibrin/fibrinogen degradation products); α -2-plasmin inhibitor

Depressed fibrinolytic activity during pregnancy characterized by, for example, increases in euglobulin clot lysis time, plasminogen and α -1-trypsin inhibitor, has been reported by various investigators. However, increase in serum FDP (fibrin/fibrinogen degradation products by plasmin digestion) which suggests acceleration of fibrinolytic activity was observed with advance of gestational ages. There has been no evidence to explain these conflicting findings. This paper describes new information of the fibrinolytic activity during pregnancy by determination of FDP and α -2-plasmin inhibitor which are the most sensitive indicators of fibrinolytic activity in blood.

MATERIALS AND METHODS

Blood samples were obtained from volunteers of normal healthy non-pregnant, pregnant women with various gestational ages and from the umbilical cord of new-borns.

Reagents. (1) FDPL-Kit (Teikoku Zoki Co.) (2) Antiplasmin assay Kit (Daiichi Kagaku Co.) (3) Antiserum against α -2-plasmin inhibitor was obtained by courtesy of Dr. Aoki from Jichi Medical School.

Methods. (1) Serum FDP were determined by latex agglutination method (FDPL-Kit). (2) Plasmin inhibitor was assayed by chromogenic substrate (S-2251) method (Teger-Nilsson et al. 1977). (3) α -2-plasmin inhibitor was determined by single radial immunodiffusion technique.

RESULTS

Correlation between plasmin inhibitor determined by chromogenic substrate and α -2-plasmin inhibitor by immunological method

Plasmin inhibitor was determined by the two methods on various plasma samples including umbilical cord blood. There was a close correlation between plasmin inhibitor determined by chromogenic substrate and α -2-plasmin inhibitor by immunological method (Fig. 1). The antiplasmin assayed by chromogenic substrate, therefore, indicates mainly concentration of α -2-plasmin inhibitor.

Fig. 1. Correlation between plasmin inhibitor determined by chromogenic substrate method and α -2-plasmin inhibitor determined by immunoassay.

Changes in α -2-plasmin inhibitor during pregnancy and puerperium

Alpha-2-plasmin inhibitor was determined immunologically on the plasma samples obtained from non-pregnant healthy control, normal pregnant in each trimester, parturient and puerperal women. The results are shown in Fig. 2. Concentration of α -2-plasmin inhibitor was gradually decreased with advance of gestational ages. It reached the minimum during labor, and returned to the normal level 30 days after delivery.

Changes in plasmin inhibitor during pregnancy and puerperium

Plasmin inhibitor determined with chromogenic substrate changed as in the α -2-plasmin inhibitor (Fig. 3). However, the change was less sensitive than that obtained by immunological assay. This less sensitivity might be produced by other serine protease inhibitors, especially by α -1-trypsin inhibitor which increases markedly during pregnancy.

Fig. 2. α -2-Plasmin inhibitor during pregnancy, labor and puerperium. Figures in parentheses indicate the numbers of cases studied.

* $p < 0.001$. N.S., not significant.

Fig. 3. Plasmin inhibitor during pregnancy and puerperium. Figures in parentheses indicate the numbers of cases studied.

* $0.05 < p < 0.1$, † $p < 0.001$. N.S., not significant.

Serum FDP level during pregnancy

Table 1 shows that serum FDP level was slightly increased during pregnancy and moderately during labor and early stage of puerperium.

Comparison of fibrinolytic activity between blood samples obtained from the uterine vein and artery

Blood samples were obtained during cesarean section. After delivery of baby, but before delivery of the placenta, the uterus was drawn from the abdominal

TABLE 1. *Percent distribution of serum FDP level during pregnancy, labor and puerperium*

	Non-pregnant	Trimester			Labor	Days after delivery	
		1st	2nd	3rd		1-2	7
Number of cases	20	20	32	32	42	30	15
FDP ($\mu\text{g/ml}$)							
20-40			3	34	24	27	20
10-20		25	38	25	28	27	13
5-10	100	75	59	41	12	13	67
<5

Fig. 4. Comparison of serum FDP level between arterial and venous blood samples during cesarean section.

cavity, and blood samples were obtained from the uterine vein and artery. The samples were subjected to thrombelastography and FDP assay. No detectable fibrinolytic activity was demonstrated on thrombelastography in both arterial and venous blood samples. Higher level of FDP was observed in blood samples from the uterine vein than those from the artery (Fig. 4).

DISCUSSION

Several lines of evidence that suggest diminished fibrinolytic activity during pregnancy have been reported by various investigators. The euglobulin clot lysis time is about 2 times longer in pregnant than that of non-pregnant woman. Plasminogen level is increased to approximately 200% of non-pregnant (Maki et al. 1965). Plasminogen increase is often accompanied by lowered fibrinolytic activity (Maki et al. 1969). Alpha-1-trypsin inhibitor which exerts inhibitory action not

only on trypsin but also on plasmin, is increased markedly during pregnancy (Saito et al. 1978). Astedt found that the fibrinolytic activity in the vein wall was diminished in late pregnancy (Astedt 1972).

The placenta has been shown to contain urokinase inhibitor (Uszynski and Abildgaard 1971). Decrease in tissue plasminogen activator of the kidney was found in pregnant rat, guinea pig, and rabbit (Maki 1967). These findings indicate that the fibrinolytic activity during pregnancy is diminished. However, there is another evidence that suggests accelerated fibrinolytic activity, that is, the increase in serum FDP during pregnancy. We have had no clear explanation for these conflicting findings. In order to resolve this problem, we studied the α -2-plasmin inhibitor during pregnancy and serum FDP content of the uterine vein and artery blood. Alpha-2-plasmin inhibitor reacts with plasmin at 1:1 molar ratio, and inhibits plasmin almost instantaneously (Aoki et al. 1977, Müllertz 1979). Alpha-2-plasmin inhibitor-plasmin complex disappears subsequently from the circulation, resulting in decreased concentration of the inhibitor by consumption. Therefore, α -2-plasmin inhibitor is the most sensitive indicator of fibrinolytic activity in the circulation. As already mentioned, α -2-plasmin inhibitor was decreased significantly during pregnancy with slight increase in FDP. This indicates that fibrinolytic activity is accelerated during pregnancy. Since FDP level was higher in blood samples from the uterine vein than those from the artery, the elevated fibrinolytic activity is probably the result from local, but not from systemic event. Tendency to form thrombi in the intervillous space even in normal pregnancy is well known. The thrombi are lysed by plasmin, resulting in FDP increase and consumption of α -2-plasmin inhibitor. The local thrombosis and thrombolysis seem to occur continuously and chronically during pregnancy without inducing systemic fibrinolysis.

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