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Alternations of Maternal and Cord Plasma Hemostasis in Preeclampsia Before and After Delivery

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Objective: The aim of this study was to investigate the role of hemostatic factors in the pathogenesis of preeclampsia. *Materials and Methods*: Maternal and cord plasma concentrations of tissue factor (TF), tissue factor pathway inhibitor (TFPI), von willebrand factor (vWF), soluble P-selectin (sP-selectin), fibrinopeptide A (FPA), D-dimer, and antithrombin III (AT-III) were measured by enzyme-linked immunosorbent assay (ELISA) in 46 women with preeclampsia and 40 normotensive pregnant women before and after delivery. *Results*: The maternal plasma concentrations of TF, vWF, and sP-selectin were higher, but lower concentrations of TFPI, AT-III, and D-dimer were observed in women with preeclampsia compared to normotensive pregnant women before and after delivery. Compared with maternal plasma, fetal plasma concentrations of TF concentrations were increased significantly in both groups, whereas vWF, FPA, TFPI, AT-III, and D-dimer were decreased. Compared with normotensive pregnancy, fetal plasma concentrations of TF were markedly increased in preeclampsia, accompanied with a higher vWF and a lower sP-selectin and D-dimer levels. Furthermore, fetal plasma TF concentrations were more significantly increased in women with high blood pressure and severe proteinuria. *Conclusions*: Imbalance in the coagulation/fibrinolysis equilibrium, especially alterations in the extrinsic pathway of coagulation and anticoagulation, may play an important role in the pathogenesis of preeclampsia. In addition, fetal alteration of TF may be involved in the pathogenesis of fetal complications of preeclampsia.

Keywords Coagulation, Fibrinolysis, Tissue factor, Preeclampsia, Thrombophilia.

INTRODUCTION

Preeclampsia affects about 7% of first pregnancies and is one of the leading causes of maternal and neonatal mortality and morbidity worldwide (1). The

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clinical hallmarks of the disorder include hypertension, proteinuria, and edema. In advanced stages, clinical symptoms include cerebral edema, renal failure, and the hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome (1).

Studies over the last decade have provided exciting new insights into potential mechanisms underlying the pathogenesis of preeclampsia. The initiating event in preeclampsia is generally regarded to be placental ischemia/hypoxia, which in turn results in the elaboration of a variety of factors from the placenta that generates widespread dysfunction of the maternal vascular endothelium (2). Alterations in the hemostatic system resulting in the pathological hypercoagulability and thrombophilias may contribute to the clinical spectrum of preeclampsia (3,4). However, the role of the endothelium dysfunction in hypercoagulability and thrombophilias and the importance of the various critical molecules of hemostatic system in the development of proteinuria and hypertension during preeclampsia remain to be elucidated.

Normal pregnancy is associated with extensive changes in all aspects of hemostasis, resulting in a shift towards hypercoagulability, which in turn provides maintenance of placental functions and limits blood loss during labor (5). The hemostatic changes in preeclampsia are even more prominent with impaired endothelial functions, increased coagulation and platelet activation, and decreased anticoagulation and fibrinolysis (6–8). However, the key changes leading to the pathological hypercoagulability and thrombophilias are still unclear, with all published studies only explored alterations in two or three aspects of hemostasis in a small number of patients.

Coagulation proteins are expressed early in fetal life. mRNA for endothelial proteins, including the von Willebrand factor (vWF), thrombomodulin (TM), tissue factor (TF), and the TF pathway inhibitor (TFPI) can be detected 4 weeks post conception (9). However, the hemostatic system differs markedly between fetuses, neonates, and adults, and fetal and neonatal thrombotic abnormalities in both normal pregnancy and complicated pregnancy are poorly understood (10,11). Tay et al. (12) have reported that the levels of TF and D-dimer in cord blood were significantly higher than that in adults in normal pregnancy, whereas TFPI level was lower. In preeclampsia, some important coagulation and fibrinolysis factors are found to be altered in newborns (13).

Therefore, in order to investigate the role of hemostatic system in the pathogenesis of preeclampsia, we studied the changes of impaired endothelial functions (vWF), platelet activation (soluble P-selectin [sP-selectin]), coagulant activation (TF and fibrinopeptide A [FPA]), anticoagulant activation (TFPI and antithrombase III [AT-III]), and fibrinolytic activation (D-dimer) in maternal and cord blood from preeclamptic and normotensive pregnant women before and after delivery.

MATERIAL AND METHODS

Patients

Forty-six women with preeclampsia and 40 age-matched healthy women with singleton pregnancy in third trimester and underwent elective cesarean

section were recruited from June 2005 to September 2006 for the study. Eligible pregnant women delivered at the Obstetrics and Gynecology Hospital and Zhongshan Hospital of Fudan University and the Second Huaxi Hospital of Sichuan University. The indications of elective cesarean section were preeclampsia, abnormal fetal position, premature rupture of membrane, and social problems. Inclusion criteria were preeclampsia for study group and normal pregnancy without any signs of obstetric complications for control. Exclusion criteria were diabetes mellitus, chronic hypertension, kidney diseases, liver disease, cardiovascular disease, and blood disease.

Preeclampsia was defined as the development after 20 weeks of gestation of either systolic blood pressure (SBP) more than 140 mm Hg or a diastolic blood pressure (DBP) more than 90 mm Hg on two occasions at least 6 h apart with previously normal blood pressure, and proteinuria of either more than 300 mg per 24 hours or 2++ or greater on urine dipstick . A neonate was defined as small for gestational age (SGA) when the birth weight was below the 10th percentile for gestational age for Chinese according to the reference range proposed by Zhang (14). Neonatal asphyxia was defined by the Apgar scores at 1 minute equal to 7 or below.

The protocol was approved by the ethics committees of the Obstetrics and Gynecology Hospital of Fudan University. Informed consent after full explanation of the objectives of the study was obtained from all the women participating in this study.

Sample Collection

Maternal peripheral blood were taken by sterile venipuncture and collected directly into tubes containing citrate on the day of selective cesarean section, and days 1 and 5 postpartum. The samples were centrifuged at 3000 rpm for 10 min at 4°C (Beckman CS-15R centrifuge) and plasma was collected, aliquoted, and stored at –80°C until assayed. Umbilical cord blood was taken at the time of delivery by umbilical vein venipuncture. Plasma was collected, processed, and stored as described above.

ELISA Assays

The concentrations of plasma TF, TFPI, vWF, sP-selectin, FPA, D-dimer, and antithrombase III (AT-III) were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions (TF, TFPI, vWF, FPA, and D-dimer: American Diagnostica; sP-selectin: R&D Systems; AT-III: Assaypro, USA). Briefly, samples were loaded into 96 flat-bottom microwells coated with a monoclonal antibody against TF, TFPI, vWF, FPA, D-dimer, sP-selectin, or AT-III. After washing away any unbound substrate, an enzyme-linked polyclonal antibody specific for above antigens was added to the wells. A substrate solution was then added to the wells and color developed in the samples in proportion to the quantity of targets present. The reaction was quenched with 0.5 M H_2SO_4 and the absorbance was measured using a plate reader at 450 nm and the actual concentration was calculated with a standard curve. All plasma samples were performed in duplicate.

Statistical Analysis

All data are presented as mean ± standard error (SE). The Student *t* test was conducted to evaluate the differences between groups. Statistic package SPSS for Windows 10.0 (Statistical Analysis System, Chicago, IL, USA) was used for data analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics

Table 1 summarizes the clinical features of 46 women with preeclampsia and 40 normotensive pregnant women. Women with preeclampsia delivered at earlier gestational age (36.5 ± 3.1 versus 39.1 ± 1.2 weeks, $p < 0.01$) and had lower neonatal birth weight than control (2691 ± 136 versus 3257 ± 56 g, $p < 0.01$), which were characterized by significantly high blood pressure and severe proteinuria. The incidences of SGA and neonatal asphyxia were significantly increased in preeclampsia as compared with normotensive pregnancy (30.4 versus 2.5%, $p < 0.01$; 8.7% versus 0%, $p < 0.01$; respectively). Maternal age, parity, postpartum hemorrhage, and routine laboratory findings of hemostasis were similar between the two groups.

Maternal Plasma Concentrations of the Hemostatic Parameters in Preeclamptic and Normotensive Pregnancy Before and After Delivery

The maternal plasma concentrations of TF, vWF, and sP-selectin were significantly higher in preeclampsia than in normotensive pregnancy before and after delivery($p < 0.05$). Lower trends of concentration of TFPI, AT-III, and D-dimer were observed in the preeclampsia group, although these changes were no statistically significance. In addition, the maternal plasma levels of

Table 1: Clinical characteristics and laboratory findings of hemostasis in forty-six women with preeclampsia and forty normotensive pregnant women.

	Preeclampsia n = 46	Normotensive pregnancy n = 40	*p* value
Maternal age (years)	29.0 ± 0.9	28.8 ± 0.7	>0.05
SBP (mm Hg)	153 ± 1.9	114 ± 1.8	<0.01
DBP (mm Hg)	102 ± 2.0	73 ± 1.2	<0.01
Proteinuria (+)	2.3 ± 0.2 (1–4)	0	<0.01
Parity (n)	0 (0–3)	0 (0–1)	>0.05
Gestational age (weeks)	36.5 ± 3.1	39.1 ± 1.2	<0.01
Postpartum hemorrhage (mL)	260 ± 32	207 ± 16	>0.05
Birth weight (g)	2691 ± 136	3257 ± 56	<0.01
SGA(%)	14 (30.4%)	1 (2.5%)	<0.01
Neonatal asphyxia (%)	4 (8.7%)	0 (0%)	<0.01
PT (s)	10.3 ± 0.2	11.4 ± 0.2	>0.05
INR	0.86 ± 0.01	0.92 ± 0.02	>0.05
APTT (s)	28.6 ± 0.4	27.5 ± 0.5	>0.05
FB (g/L)	3.9 ± 0.1	4.3 ± 0.2	>0.05

Note: SBP = systolic blood pressure; DBP, diastolic blood pressure; SGA, small for gestational age.

TF, vWF, and sP-selectin were decreased significantly, whereas TFPI and D-dimer levels were increased significantly in both groups in the first day after delivery. However, there was no significant difference in FPA concentrations between the two groups (Figure 1).

Fetal Plasma Concentrations of the Hemostatic Parameters in Preeclamptic and Normotensive Pregnancies

Compared with maternal plasma, fetal plasma concentrations of TF were significantly increased in both groups ($p < 0.05$), whereas the fetal concentrations of vWF, FPA, TFPI, AT-III, and D-dimer were increased significantly. However, fetal plasma concentrations of sP-selectin was lowered in preeclampsia but elevated markedly in the normal control group.

Compared with in normotensive pregnancy, fetal plasma concentrations of TF in preeclampsia were markedly increased; however, the changes of fetal plasma TFPI, FPA, AT-III, sP-selectin, and D-dimer were not significantly different between two groups (Figure 2).

Relationship Between the Clinical Data and the Hemostatic Parameters

The maternal plasma TF was significantly positively related with SBP, DBP, and proteinuria ($r = 0.218$, $p < 0.05$; $r = 0.234$, $p < 0.05$; $r = 0.225$, $p < 0.05$, respectively). And also, a significant positive relationship was also observed between sP-selectin and proteinuria ($r = 0.229$, $p < 0.05$), and between TF and vWF ($r = 0.227$, $p < 0.05$). No marked relationships were observed between other clinical features and the hemostatic parameters (data were not show).

According to the relationships between the hemostatic parameters and SBP, we further divided these pregnant women into two groups: high blood pressure group (SBP ≥ 160 mm Hg) and low blood pressure group (SBP < 160 mm Hg). Maternal plasma TF concentrations were significantly increased in the high blood pressure group than in the low blood pressure group before and after delivery. Other hemostatic markers were not changed significantly before and after delivery between two groups (Table 2).

Similarly, all participants were divided into high proteinuria group for proteinuria at least ++ and low proteinuria group for proteinuria less than ++. The maternal plasma levels of TF and sP-selectin were increased significantly in the high proteinuria group, compared with the low proteinuria group before and after delivery (Table 3).

DISCUSSION

In this study, we firstly investigated the alterations of the overall hemostasis in preeclampsia, including impaired endothelial functions, platelet activation, coagulant and anticoagulant system, and fibrinolytic system in maternal and fetal plasma before and after delivery. We observed a significant higher concentration of clotting factors (TF, vWF, and sP-selectin), but a lower concentration of anticoagulant factors (TFPI, AT-III) and fibrinolytic factor (D-dimer) in preeclampsia as compared with normotensive pregnancy before and after delivery. In accordance with the attenuation of clinical symptoms after delivery, a decline of coagulation and an enhancement of anticoagulation

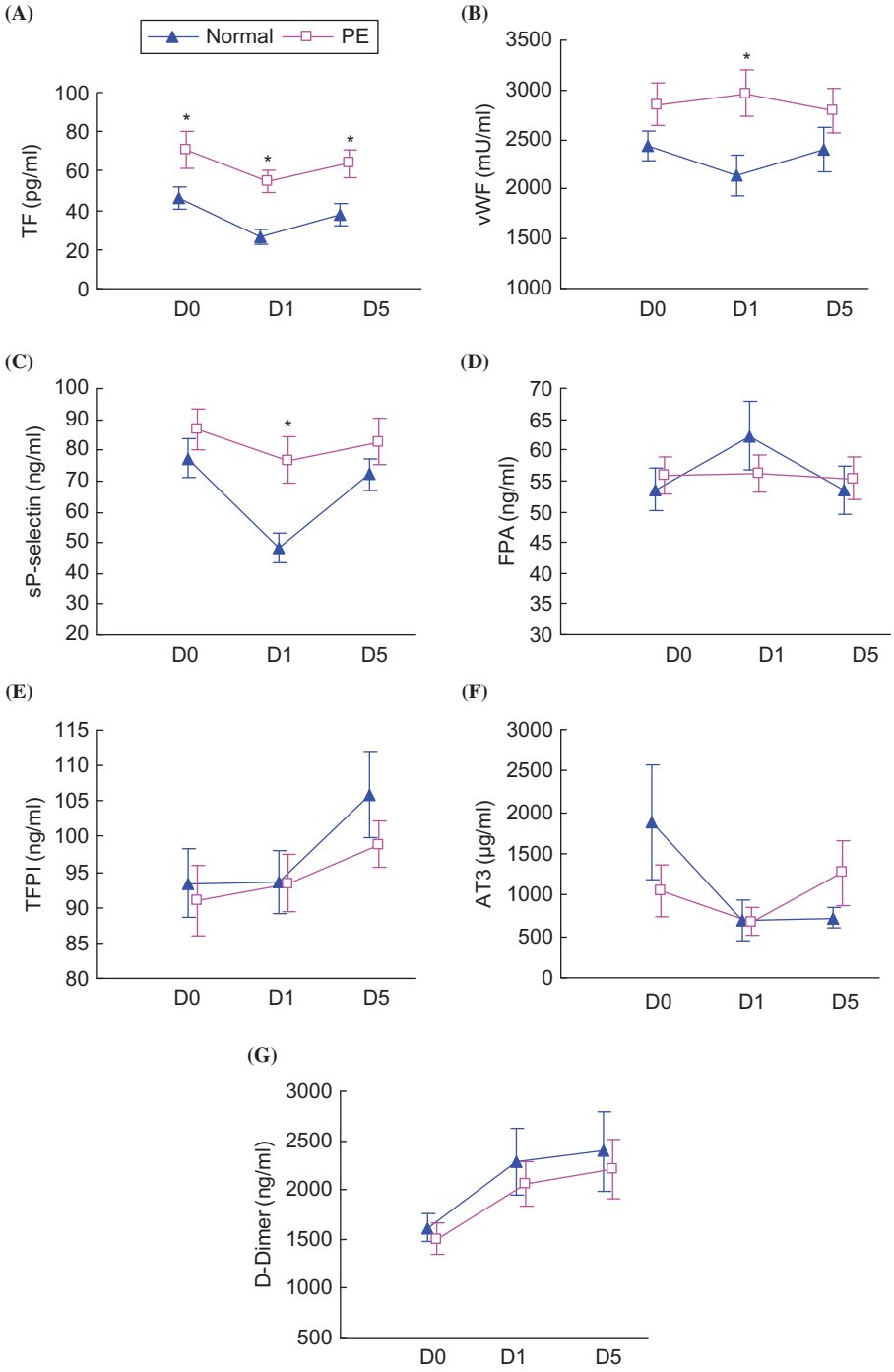

Figure 1: Maternal plasma concentrations of TF (A), vWF (B), sP-selectin (C), FPA (D), TFPI (E), AT-III (F), and D-dimer (G) in preeclampsia and normotensive pregnancy at different time (D0 indicates at delivery; D1, 1 day after delivery; and D5, 5 days after delivery). TF concentrations were significantly increased in preeclampsia as compared with normotensive pregnany before and after delivery (open squares indicates preeclampsia, close triangles indicates normotensive pregnancy; *$p < 0.05$).

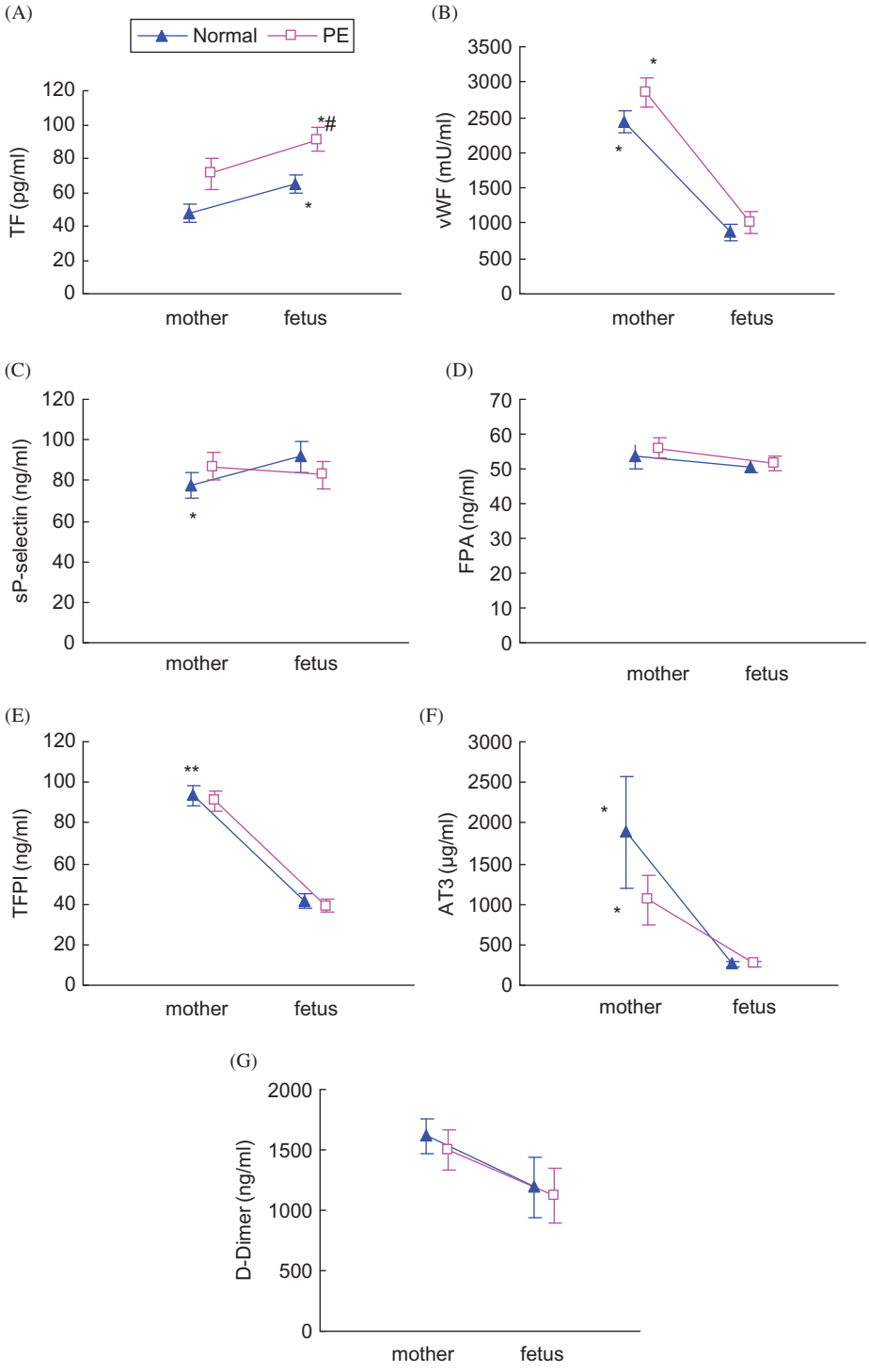

Figure 2: Maternal and umbilical plasma concentrations of TF (A), vWF (B), sP-seletin (C), FPA (D), TFPI (E), AT-III (F), and D-dimer (G) in preeclampsia and normotensive pregnancy just after delivery (open squares indicates preeclampsia, close triangles normotensive pregnancy). Compared with maternal concentrations, fetal concentrations of TF were significantly increased, whereas vWF, TFPI, and AT-III concentrations were significantly decreased in both groups (*$p < 0.05$). Compared with normotensive pregnancy, fetal concentrations of TF were significantly increased in preeclampsia ($^{\#}p < 0.05$).

Table 2: Concentrations of hemostatic parameters in different systolic blood pressure groups.

	Delivery		1 day after delivery		5 days after delivery	
	SBP < 160	**SBP ≥ 160**	**SBP < 160**	**SBP ≥ 160**	**SBP < 160**	**SBP ≥ 160**
DD (ng/mL)	1552.35 ± 112.85	1624.39 ± 326.49	2137.48 ± 207.02	2192.65 ± 440.44	2237.63 ± 286.81	2523.08 ± 407.47
TF (pg/mL)	54.19 ± 6.20	81.32 ± 10.39*	36.27 ± 4.47	71.20 ± 8.12**	44.17 ± 4.21	88.71 ± 15.69**
TFPI (ng/mL)	91.30 ± 3.89	97.05 ± 7.29	91.90 ± 3.18	98.80 ± 7.59	99.96 ± 3.66	110.11 ± 5.83
PS (ng/mL)	81.12 ± 5.10	86.90 ± 12.69	64.25 ± 6.25	73.15 ± 10.19	78.71 ± 5.35	76.07 ± 12.18
VWF (mU/mL)	2617.27 ± 145.71	2840.66 ± 336.35	2474.93 ± 176.78	3275.32 ± 438.49*	2495.78 ± 181.40	3212.13 ± 333.27
FPA (ng/mL)	53.26 ± 2.50	62.22 ± 5.45	59.36 ± 3.21	55.19 ± 5.31	51.98 ± 2.64	65.65 ± 7.03*
AT-III (μg/mL)	1602.29 ± 436.51	707.17 ± 197.67	755.35 ± 180.73	462.51 ± 80.93	1074.06 ± 279.84	887.17 ± 263.41

Note: SBP = systolic blood pressure; DD = D-dimer; TF = tissue factor; TFPI = tissue factor pathway inhibitor; PS = sP-selectin; vWF = von Willebrand factor; FPA = fibrinopeptide A; AT-III = antithrombin III. *$p < 0.05$, ** $p < 0.01$, compared between two groups of SBP < 160 mm Hg and SBP ≥ 160 mm Hg.

Table 3: Concentrations of hemostatic parameters in different proteinuria groups.

	Delivery		1 day after delivery		5 days after delivery	
	PU < ++	**PU ≥ ++**	**PU < ++**	**PU ≥ ++**	**PU < ++**	**PU ≥ ++**
DD (ng/mL)	1537.42 ± 123.41	1626.93 ± 217.08	2085.78 ± 236.83	2259.40 ± 311.35	2392.47 ± 340.00	2115.90 ± 304.41
TF (pg/mL)	51.44 ± 4.82	75.08 ± 14.03*	38.61 ± 4.72	53.47 ± 8.33	45.20 ± 4.66	65.63 ± 10.75*
TFPI (ng/mL)	91.50 ± 3.99	93.96 ± 6.88	91.51 ± 3.76	96.65 ± 4.98	102.37 ± 4.47	101.02 ± 4.09
PS (ng/mL)	75.29 ± 5.19	97.60 ± 9.39*	52.01 ± 4.74	89.19 ± 9.74**	69.63 ± 4.62	93.32 ± 10.03*
vWF (mU/mL)	2623.69 ± 152.60	2724.90 ± 264.70	2528.51 ± 226.47	2869.45 ± 270.17	2564.15 ± 201.62	2763.56 ± 279.05
FPA (ng/mL)	53.11 ± 2.69	58.24 ± 4.31	59.44 ± 4.00	56.85 ± 3.24	54.31 ± 3.27	55.11 ± 4.35
AT-III (μg/ml)	1680.24 ± 530.62	958.26 ± 183.41	764.66 ± 224.47	566.62 ± 105.66	667.54 ± 91.37	1673.04 ± 589.84

Note: PU = proteinuria, *$p < 0.05$, **$p < 0.01$, compared between two groups of severe and mild proteinuria.

and fibrinolysis towards a imbalance of coagulation and fibrinolysis, providing further evidence that the imbalance in the coagulation/fibrinolysis equilibrium may play an important role in the pathogenesis of preeclampsia (8,15,16).

The initiation phase of blood coagulation is triggered by the extrinsic pathway, whereas amplification requires the intrinsic pathway; and TF is the key initiator of the coagulation cascade (17). Elevated plasma levels of TF are frequently observed in patients with cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and TF may indeed be involved in the pathogenesis of atherosclerosis by promoting thrombus formation (18).

Few studies investigated the changes of TF in preeclampsia and paradoxical results existed in the previous reports. Lopez-Ramirez et al. (19) found that similar concentration of TF in severe preeclampsia and normal pregnant women, whereas TFPI increased significantly in severe preeclamptic placentas. However, Bellart et al. (20) reported the plasma level of TF and the ratio fibrinopeptide A:D-dimer were increased in preeclampsia women. A significant increase in TF protein and mRNA in placentas and decidual cell in preeclamptic women (21–23) has been reported. In our study, an elevated level of TF and a lowered level of TFPI were observed in women with preeclampsia, accompanied with a significantly increase in plasma vWF. And also, a significant positive relationship was found between TF and vWF. Moreover, plasma TF concentration was significantly increased in women with severe preeclampsia, characterized by higher blood pressure and severe proteinuria. In preeclampsia, lipid peroxides and blood oxidative imbalance could lead to injury of endothelial cells as reflected by an elevated level of vWF (24). We suggested that the elevated expression of TF in women with preeclampsia was mediated by impairment of endothelial cells and was partially responsible for the severity of preeclampsia. TF may play a key role in the pathogenesis of preeclampsia by initiating the extrinsic pathway of coagulation.

The coagulation system of the neonate differs markedly in many ways from that of the adult. Our study showed that fetal concentrations of TFPI and AT-III were significantly decreased whereas TF level was significantly increased as compared with maternal plasma in normotensive pregnancy, which is in line with earlier observations (12,25). Our finding supported the notion that a more evident hypercoagulabale state existed in cord blood to avoid the neonates injury at delivery (12,25,26).

Tanjung et al. (27) reported that no significant differences were seen in hemostatic parameters, including tissue- (t-PA), urokinase- (u-PA) type plasminogen activator, AT-III, plasminogen activator inhibitor (PAI)-I, and PAI-II between the neonates of normotensive pregnancy and preeclampsia. The new finding of our study is that fetal concentration of TF was significantly increased in preeclampsia, although no significantly differences were observed in the other hemostatic parameters, including vWF, sP-selectin, FPA, TFPI, AT-III, and D-dimer, between the neonates of preeclampsia and normotensive pregnancy. The changes of TF means the fetus has much more severe hypercoagulability and thrombophilias in preeclampsia, which may be associated with the fetal complications of preeclampsia. It has been reported that pregnant women with hemostatic abnormalities or thrombophilias have

increased risks to develop fetal complications such as fetal growth restriction and pregnancy loss (28–30). Di Paolo et al. (31) reported that the abnormal uterine and umbilical artery Doppler waveforms were significantly associated with only TF expression, which was markedly increased, in preeclamptic women with fetal growth restriction.

Perinatal arterial ischemic stroke (PAS), one of the top 10 causes of death before the first birthday, is the severe complication of preeclampsia. The high risk factors for PAS were linked with thrombophilias, including preeclampsia, fetal growth restriction (FGR), and history of thrombosis, infertility, or the antiphospholipid syndrome (26,32,33). We therefore speculated that alteration of fetal TF may be involved in the pathogenesis of fetal complications secondary to preeclampsia, e.g., FGR and PAS. The possible explanation is that the extrinsic pathway of coagulation initiated by the elevated level of TF, which in turn resulting in intravascular clotting and fibrin deposition in placental and fatal vessels and an increased frequency of placental ischemia and thrombosis in fetus.

In conclusion, our study suggests that the imbalance in the coagulation/fibrinolysis equilibrium was an important physiopathologic change in preeclampsia. The alterations in the extrinsic pathway of coagulation and anticoagulation, especially the changes of TF, may play a key role in the pathogenesis of preeclampsia.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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