Published in final edited form as:
J Matern Fetal Neonatal Med. 2008 December ; 21(12): 855–869. doi:10.1080/14767050802361872.

Tissue Factor and Its Natural Inhibitor in Preeclampsia and SGA

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Abstract

Objective—Tissue factor (TF), the major activator of the extrinsic pathway of coagulation, is abundant in the placenta and decidua. The aim of this study was to determine the maternal plasma concentrations of TF and its primary inhibitor, tissue factor pathway inhibitor (TFPI), in women who delivered small for gestational age (SGA) neonates, and in preeclampsia.

Study Design—A cross-sectional study included the following groups: 1) women with normal pregnancies (n=86); 2) patients who delivered SGA neonates (n=61); and 3) women with preeclampsia (n=133). Maternal plasma concentrations of TF and TFPI were measured by a sensitive immunoassay. Non-parametric statistics were used for analysis.

Results—1)Women with preeclampsia had a significantly higher median plasma concentration of TF than patients with a normal pregnancy (median: 1187 pg/ml; range: 69–11675 vs. median: 291.5 pg/ml; range: 6.3–2662.2; p<0.0001, respectively); 2) Similarly, TFPI concentrations were higher in preeclampsia than in normal pregnancy (median: 87.5ng/ml; range 25.4–165.1 vs. median: 66.1 ng/ml; range: 14.3–86.5; p<0.0001, respectively); 3) Surprisingly, mothers with SGA neonates had a lower median maternal plasma concentration of TF (median: 112.2 pg/ml; range: 25.6–1225.3) than women with a normal pregnancy (p<0.0001).

Conclusion—1) Maternal plasma concentrations of TF in patients with preeclampsia, but not in those who delivered an SGA neonate, were higher than in women with normal pregnancies; 2) While the role of immunoreactive plasma TF in coagulation remains controversial, our observations suggest that changes are present in the context of complications of pregnancy.

Keywords

inflammation; coagulation; TFPI-1; TFPI-2; placenta; microparticles

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INTRODUCTION

Preeclampsia and small for gestational age (SGA) are considered two of the "Great Obstetrical Syndromes"[1] that complicate pregnancy, either as an isolated or a combined pathology. Moreover, the presence of fetal growth restriction in patients with preeclampsia is regarded as criteria for the severity of the disease[2,3].

SGA and preeclampsia share similar underlying mechanisms of disease: 1) increased maternal leukocyte activation as a sign of systemic maternal inflammation has been reported in patients who developed preeclampsia[4–20] and in women who delivered an SGA neonate [21–25]; 2) an increased activation of the coagulation cascade, reflected by the higher maternal plasma concentrations of thrombin-antithrombin complexes[10,26–30]; 3) abnormal placental implantation, manifested as a failure of transformation of the spiral arteries, shallow trophoblast invasion and spiral artery atherosis[31–43]; 4) an antiangiogenic state[44–70] characterized by elevated maternal plasma concentrations of soluble vascular endothelial growth factor receptor-1[71–78] and soluble endoglin[44,79–81] that decrease the activity of vascular endothelial growth factor and reducing the angiogenic activity. However, there is also an approach suggesting that preeclampsia and SGA are different entities, and several mechanisms have been proposed to explain the differences between preeclampsia and SGA, including maternal infectious disease [82–90], maternal obesity (which is associated with a higher degree of insulin resistance) [91], and a different degree of systemic maternal inflammation [25,91–93].

Tissue factor (TF), the major activator of the coagulation cascade, is involved also in the underlying mechanisms implicated in preeclampsia and SGA, such as systemic inflammation[94–97], placental implantation[98,99], and angiogenesis[100–105]. During normal pregnancy, TF is abundant in the uterine decidua[106,107], resulting in an efficient hemostatic mechanism that is activated both during implantation[108] and after delivery[109]. In addition to its tissue form, TF can be found in the maternal plasma as blood-born TF. The maternal plasma concentrations of TF during normal pregnancy are compatible with the non-pregnant state[110,111] and increase during labor[112].

Tissue factor pathway inhibitor (TFPI), the main physiological inhibitor of the TF pathway of coagulation, is a three Kunitz domain glycoprotein which inhibits thrombin generation through the inhibition of activated factor X and factor VIIa (FVIIa)/TF complex[113,114]. The mean maternal plasma concentrations of total TFPI have been reported to increase during the first half of pregnancy until 20 weeks of gestation, subsequently staying relatively constant until term[115], and to decrease during labor[112].

There are two types of TFPI. TFPI-1 is found in the maternal circulation and fetal blood, platelets, endothelial cells and other organs[116,117], while TFPI-2, the major form of TFPI in the placenta[118–123], was first isolated as Placental Protein 5 (PP5)[124,125]. During pregnancy, the maternal plasma TFPI-2 concentrations increase gradually, reach a plateau at 36 weeks of gestation, and subside after delivery[124,126–130].

Maternal plasma concentrations of TF and free TFPI are higher in women with preeclampsia than in patients with a normal pregnancy[131–133]. However, the differences in the maternal plasma concentrations of TF and TFPI between patients with preeclampsia and those who delivered an SGA neonate, as well as the differences between patients who delivered an SGA neonate and women with a normal pregnancy, have been poorly studied. Therefore, the aim of this study was to determine and compare the changes in the maternal plasma concentration of TF, TFPI, and the TFPI/TF ratio in patients with preeclampsia, SGA neonate, and women with normal pregnancies.

METHODS

Study groups and inclusion criteria

A cross-sectional study was conducted and included patients in the following groups: 1) women with normal pregnancies (n=86); 2) patients who delivered SGA neonates without preeclampsia (n=61); and 3) patients with preeclampsia (n=133). Women with normal pregnancies met the following criteria: 1) no medical, obstetrical, or surgical complications at the time of the study; 2) gestational age ranging from 20 to 41 weeks; and 3) delivery of a term infant, appropriate for gestational age, without complications. Patients with multiple pregnancies or fetuses with congenital and/or chromosomal anomalies were excluded.

Samples and data were retrieved from our bank of biological samples and clinical databases. Many of these samples have previously been employed to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concentrations in non-pregnant women, normal pregnant women, and those with pregnancy complications. All women provided an informed consent prior to the collection of maternal blood. The *Eunice Kennedy Shriver* Institutional Review Boards of both Wayne State University and the National Institute of Child Health and Human Development (NICHD/NIH/DHHS) approved the collection and utilization of samples for research purposes.

Clinical definitions

Preeclampsia was defined in the presence of hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least two occasions, 4 hours to 1 week apart) and proteinuria (≥ 300 milligrams in a 24 hour urine collection or one dipstick measurement ≥ 2+).[2] A small for gestational age neonate was defined as birthweight below the 10^{th} percentile[134]. Placental histologic findings were classified according to a diagnostic schema proposed by Redline et al[135].

Sample collection and human tissue factor (TF) immunoassay

All blood samples were collected with a vacutainer into 0.109M trisodium citrate anticoagulant solution (BD; San Jose, CA, USA). The samples were centrifuged at 1300 *g* for 10 minutes at 4°C and stored at −70°C until assay. Maternal plasma TF concentrations were determined by sensitive and specific immunoassays obtained from American Diagnostica (Greenwich, CT, USA), which recognizes TF-apo, TF, and TF-FVII complexes. The assays were conducted according to the manufacturer's recommendations. The calculated coefficient of variation (CV) in our laboratory was 5.3%, and the sensitivity is 10 pg/mL.

Human tissue factor pathway inhibitor TFPI immunoassay

Concentrations of TFPI in maternal plasma were determined by sensitive and specific immunoassays obtained from American Diagnostica (Greenwich, CT, USA). The TFPI ELISA employs a murine anti-TFPI monoclonal as the capture antibody. This capturing antibody is directed against the Kunitz-1 domain of the TFPI molecule, therefore detecting both TFPI-1 and TFPI-2, and measuring the total TFPI plasma concentrations. The assay was conducted according to the manufacturer's recommendations. The calculated CV in our laboratory was 6.6%, and the sensitivity was approximately 10 ng/mL. The correlation between TFPI antigen concentrations and functional activity was approximately $r^2 = 0.785$.

Statistical analysis

Plasma concentrations of TF and TFPI were not normally distributed. Thus, Kruskal-Wallis test with post-hoc analysis was used for comparisons of continuous variables. Comparison

of proportions was performed by Chi-square and Fisher's exact tests. The Spearman's rho test was used to detect a correlation between the concentrations of TF, TFPI, and TFPI/TF ratio to the gestational age at sample collection in women with a normal pregnancy. Multiple logistic regression analysis was performed to investigate the association between TF, TFPI, and their ratio to preeclampsia. A p value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 12 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table I displays the demographic and clinical characteristics of the study groups. Patients with preeclampsia had higher rates of primiparity and cesarean deliveries, as well as higher median gestational age at sample collection, lower median gestational age at delivery, and lower median birthweight, than women with normal pregnancies. Similarly, women who delivered an SGA neonate had a higher median gestational age at sample collection and a lower median gestational age at delivery and neonatal birthweight than women in the normal pregnancy group. Women with preeclampsia had a lower gestational age at delivery and a higher rate of cesarean section than women who delivered an SGA neonate. There was no correlation between maternal plasma TFPI/TF ratio to the gestational age at blood sample collection in patients with a normal pregnancy (r=0.030, p=0.79).

Changes in the median plasma concentrations of TF, TFPI, and TFPI/TF ratio in the different study groups

Of the 86 patients in the normal pregnancy group, 79 (91.9%) had detectable immunoreactive TF in the plasma. Maternal plasma TF concentrations were significantly higher in patients with preeclampsia than in women with a normal pregnancy (median: 1187 pg/ml; range: 69–11675 vs. median: 291.5 pg/ml; range: 6.3–2662.2; p<0.0001, respectively), as well as from patients with an SGA neonate (median: 1187 pg/ml; range: 69–11675 vs. median: 112.2 pg/ml; range: 25.6–1225.3; p<0.0001, respectively). In contrast, the median maternal plasma TF concentrations were significantly lower in women in the SGA group than in those in the normal pregnancy group (median: 112.2 pg/ml; range: 25.6–1225.3 vs. median: 291.5 pg/ml; range: 6.3–2662.2; p<0.0001, respectively) (Figure 1).

Maternal plasma TFPI concentrations were significantly higher in patients with preeclampsia than in women with a normal pregnancy (median: 87.5 ng/ml; range 25.4–165.1 vs. median: 66.1 ng/ml; range: 14.3–86.5; p<0.0001, respectively). However, there were no significant differences in the median maternal TFPI concentrations between women in the SGA and normal pregnancy groups (median: 63.6 ng/ml; range 22.3–133.5 vs. median: 66.1 ng/ml; range: 14.3–86.5; respectively, p=0.8) (Figure 2).

Patients with preeclampsia had a significantly lower median maternal plasma TFPI/TF ratio than both women with normal pregnancies (median: 68.9; range: 9.7–969.9 vs. median: 221.5; range: 25.4–3355.3; p<0.0001, respectively) and women who delivered an SGA neonate (median: 68.9; range: 9.7–969.9 vs. median: 586.8; range: 53.7–2335.9; p<0.0001, respectively). In contrast, women who delivered an SGA neonate had significantly higher median maternal plasma TFPI/TF ratio than women with a normal pregnancy (median: 586.8; range: 53.7–2335.9 vs. median: 221.5; range: 25.4–3355.3; p<0.0001, respectively) (Figure 3).

We have constructed two multivariate logistic regression models to determine the association between maternal plasma TF and TFPI concentrations and preeclampsia. In the first model, maternal plasma concentrations of TF and TFPI, as well as the delivery of an SGA neonate, were all independently associated with the development of preeclampsia

(Table II). In the second model, the maternal plasma TFPI/TF ratio was introduced instead of the plasma concentrations of TF and TFPI. (Table III) The TFPI/TF ratio and the gestational age at delivery were negatively associated with the development of preeclampsia, while the gestational age at sample collection had a positive association with preeclampsia. The delivery of an SGA neonate was not associated with the development of preeclampsia in this model.

Placental lesions in patients with preeclampsia and SGA and their association with the changes in TF, TFPI concentrations and their ratio (TFPI/TF)

Placental histology was available from 88% (117/133) of patients in the preeclampsia group and 80.3% (49/61) of patients from the SGA group. The specific histologic findings are presented in Table IV. Increased syncytial knots were more frequent in placentae of patients with preeclampsia than in those of patients in the SGA group [55.6% (65/117) vs. 32.7% (16/49), p=0.01; respectively].

Changes in the median maternal plasma concentrations of TF, TFPI, and TFPI/TF ratio in patients with preeclampsia were associated with the following placental lesions: 1) Mural hypertrophy of decidual arteries (MHD) was associated with a higher median maternal plasma TF concentration [patients with MHD: median: 1678 pg/ml; range: 876–1876 pg/ml vs. patients without MHD: median: 1177 pg/ml; range: 69.8–11675 pg/ml, p=0.042]; 2) Distal villous hypoplasia (DVH) was associated with a lower median maternal plasma TFPI concentration [patients with DVH: median: 70.4 ng/ml; range: 25.4–124.9 ng/ml vs. patients without DVH: median :88.7 ng/ml; range: 42.7–163.9 ng/ml, p= 0.011); 3) Remote villous infarcts were associated with a lower median maternal plasma TF concentration [patients with remote villous infarcts 845 pg/ml (102.5–1876 pg/ml) vs. patients without remote villous infarcts 1245 pg/ml (69.8–11675 pg/ml), p=0.01] and a higher median TFPI/TF ratio [patients with remote villous infarcts 95.70 (31.3–661.5) vs. patients without remote villous infarcts 64.8 (9.7–969.9), p=0.02]. In contrast, there was no association between the maternal plasma median concentrations of TF, TFPI and TFPI/TF ratio and specific placental lesions in the SGA group.

DISCUSSION

Major findings of the study

1) Women with preeclampsia have a significantly higher median maternal plasma TF and TFPI concentrations than women with a normal pregnancy and women who delivered an SGA neonate. 2) The median maternal plasma TFPI/TF ratio was significantly lower in patients with preeclampsia than in patients with a normal pregnancy. 3) TF, TFPI and TFPI/TF ratio were independently associated with preeclampsia. 4) Among patients with preeclampsia, those who had MHD lesions had a higher median TF plasma concentration, and those with distal placental villous hypoplasia had a lower median maternal plasma TFPI concentration. 5) Women who delivered an SGA neonate had significantly lower maternal plasma TF concentrations than patients with a normal pregnancy.

Differences between preeclampsia and SGA and changes in maternal plasma TF concentrations

This study's observation that the median maternal plasma TF concentration of patients with preeclampsia are significantly higher than of those who delivered SGA neonates, and that the latter had a significantly lower median TF plasma concentrations than women with normal pregnancies are novel. Preeclampsia and SGA share many maternal and placental pathological features, and it was proposed that along with recurrent abortions, these obstetrical syndromes may be different phenotypes of the same underlying disease[31,93].

However, it is not clear why some women will manifest the maternal phenotype of the disease (preeclampsia) with or without fetal involvement, while others will have only the fetal phenotype (growth restriction).

Recent epidemiologic studies[82,136] suggest that preeclampsia and SGA are distinct entities. The multinational epidemiologic study[82] conducted by the World Health Organization—included 39,615 pregnancies—compared the maternal risk factors and perinatal outcome of pregnancies complicated by preeclampsia, gestational hypertension, unexplained SGA neonates, and a reference group of normal pregnancies[82]. Maternal age above 40 years, pregestational maternal morbidity such as chronic hypertension, diabetes, renal and cardiac disease, as well as urinary tract infection during pregnancy were independent risk factors for preeclampsia, but not for SGA. In contrast, chronic respiratory disease was an independent risk factor only for the delivery of an SGA neonate. Preeclampsia was associated with increased risk for preterm delivery before 37 and 32 weeks of gestation. Unexplained SGA, however, had a protective effect against preterm delivery[82]. The authors suggested that “preeclampsia and unexplained intrauterine growth restriction, often assumed to be related to placental insufficiency, seem to be independent biologic entities,”[82] thus contradicting the notion that preeclampsia and SGA are a different spectrum of the same disease. This is in support of the current study; in spite of the similar placental histopathologic findings in the preeclampsia and SGA groups, a significant association between placental mural hypertrophy of decidual arterioles and higher median maternal plasma TF concentration was observed only in the preeclampsia group.

Collectively, the evidence presented above suggests that preeclampsia is primarily a systemic maternal disease that in some cases is associated with fetal growth restriction, while SGA is primarily a fetal disease in which the systemic changes in the maternal compartment may not be as prominent as in preeclampsia. In fact, some of them are even in the opposite direction, as in the case of the maternal TF plasma concentrations reported herein.

Differences in the maternal systemic response between patients with preeclampsia and women who delivered SGA neonates

The maternal systemic inflammatory response of patients with preeclampsia includes changes in markers of endothelial cells[137–140] and leukocyte activation[4,25,93,141], complement split products,[142] as well as thrombin generation that represent activation of the coagulation cascade [10,26–29,143]. The following changes can also differentiate between patients with preeclampsia and those who delivered an SGA neonate:

Differences in the profile of maternal systemic leukocyte activation in patients with preeclampsia and those who delivered an SGA neonate—Maternal systemic leukocyte activation has been reported in women with a normal pregnancy, patients with preeclampsia,[4,25,93,141] and those with SGA neonates[22,25,93]. Indeed, patients with preeclampsia had a significant delay in neutrophils apoptosis than patients who delivered SGA neonates, and those with normal pregnancies[93]. However, maternal plasma concentrations of neutrophils activation markers, CD11b and $CD62_L$, did not differ significantly between patients with preeclampsia and those who delivered SGA neonates[25].

There is a substantial body of evidence showing the increased monocyte activation in preeclampsia in comparison to normal pregnancy[4–6,144–151]. Peripheral blood monocytes from the uterine vein of patients with preeclampsia showed a higher degree of activation in comparison to those obtained from their cubital vein. The authors proposed that the passage through the placental bed activates the maternal monocyte in patients with

preeclampsia[144].A recent study reported that preeclamptic patients have higher monocyte metabolic activity and oxidative burst than women who delivered an SGA neonate[92]. This is in accord with our findings, since during systemic inflammation activated monocytes express TF on their membrane[97,152–156] and shed micro-particles which contain TF into the plasma[94,96,152,157–162]. Hence, the increased monocyte activation among patients with preeclampsia can be a possible source for the elevated maternal plasma TF concentrations in these individuals.

Differences in the profile of circulating endothelial cells adhesion molecules in patients with preeclampsia and those who delivered an SGA neonate— Circulating endothelial cell adhesion molecules were reported to be higher in the plasma of patients with preeclampsia[137–140] and those who delivered an SGA neonate[137,139] than in the case of women with normal pregnancies. However, patients with preeclampsia had a different expression pattern of endothelial cell adhesion molecules than women who delivered SGA neonates, and maternal plasma concentrations of intercellular cell adhesion molecule-1 were higher in preeclamptic patients than in patients who delivered an SGA neonate[22] and women with a normal pregnancy [137,139,140].

Differences in the maternal plasma complement split products profile in patients with preeclampsia and those who delivered an SGA neonate—Patients with preeclampsia had higher median maternal plasma concentrations of C5a than patients with SGA neonate and women with a normal pregnancy[142]. Moreover, patients who delivered an SGA neonate had lower median maternal C4a plasma concentrations than women with a normal pregnancy[142]. This correlates with the changes in maternal plasma TF concentrations observed in this study. The association between C5a and TF activation and expression has been previously reported:[163,164] 1) C5a induces a 4.9-fold increase in TF activity and a 3.8-fold increase in tissue factor mRNA expression by endothelial cells[163]; 2) the administration of C5a to animals increases the procoagulant activity of alveolar macrophages by 5- to 6-fold through TF activation[164]; and 3) serum from patients with antiphospholipid syndrome induced the expression of TF by neutrophils of healthy individual and increased the extrinsic pathway procoagulant activity of these neutrophils, in a complement dependent manner through the C5a receptor[165]. In addition, the C5a–induced TF expression by neutrophils contributes to the neutrophils oxidative burst, and was associated with antiphospholipid-related fetal injury in mice[166]. Thus, the higher maternal plasma C5a concentrations reported in patients with preeclampsia when compared to those who deliver an SGA neonate may contribute to an increased TF expression and activation of neutrophils in these patients. Moreover, this association may serve as a possible explanation as to why the same placental lesions were associated with elevated median TF plasma concentration in patients with preeclampsia, but not in those who delivered an SGA neonate.

Placental microparticles and monocyte activation in patients with preeclampsia

It has been proposed that placental micro-particles may be the mediators of the increased maternal systemic inflammation observed during normal pregnancy, as well as the exaggerated systemic maternal inflammation reported in patients with preeclampsia[167–169]. Microparticles are cellular particles of different sizes in the order of 100 nm that are shed into the plasma by platelets, leukocytes, granulocytes, erythrocytes, endothelial [170] and trophoblast cells[167,168,171]. While present in the normal state, they are also associated with cellular activation, apoptosis, inflammation, and coagulation[172]. The smaller microparticles are called exosomes (30–100nm) and are originated from intracellular mutivesicular bodies that can be derived from dendritic cells and are part of their normal activity[173]. A recent study reported that women with preeclampsia, particularly if the

condition was developed before 34 weeks of gestation, had a significantly higher maternal plasma concentration of placental microparticles than women with a normal pregnancy who were matched for gestational age[174]. In contrast, women in the fetal growth restriction group had a lower median plasma concentration of microparticles than women with a normal pregnancy, though this difference was not statistically significant[174]. It has been proposed that apoptotic and necrotic placental debris may activate monocytes in normal pregnancy and that excessive placental debris may be associated with the systemic maternal inflammation observed in preeclampsia[5,19]. Indeed, a supernatants from endothelial cells co-cultured with syncytiotrophoblast microparticles activated monocytes in vitro[93]. Thus, the differences in the concentrations of trophoblast microparticles in the maternal serum among patients with preeclampsia, SGA, and women with a normal pregnancy may be related to the differences in maternal monocyte activation and in TF plasma concentrations observed in these patients.

Of note, VanWijkk et al[143] reported that the total number of microparticles presenting TF did not differ between patients with preeclampsia and those with a normal pregnancy. A post hoc analysis of these results revealed that their study was under powered to detect a significant difference in the number of TF presenting microparticles[143]. Moreover, the authors did not differentiate between the sources of the microparticles that were measured, which can influence the procoagulant activity of the microparticles[143]. We therefore argue that a larger study is needed to determine whether patients with preeclampsia have a higher expression and secretion of TF expressing microparticles by activated monocytes than patients with SGA and those with a normal pregnancy.

What is the role of immunoreactive TF in the maternal plasma?

The procoagulant activity of immunoreactive TF in the maternal plasma (blood born TF) is a topic of debate[97,152,175–178]. Blood born TF has very little or no procoagulant activity[152], and only the administration of exogenous active TF generated a whole blood and plasma clot after the inhibition of the contact factor (factor XIIa)[152]. On the other hand, it has been proposed that blood born TF does not initiate the coagulation cascade, but rather propagate clot formation by attaching to activated platelets and further enhancing the coagulation process[175–178]. In addition, patients with preeclampsia, but not those with a normal pregnancy or non-pregnant women, had a significant reduction in their thrombin generation by microparticles after treatment with anti-FVII antibodies[143]. The authors concluded that a higher proportion of thrombin generation is derived from the extrinsic pathway of coagulation in patients with preeclampsia[143].

What are the plasma and placental changes in TFPI concentrations in normal and complicated pregnancies?

TFPI is the main inhibitor of TF, and the maternal plasma concentration of immunoreactive TFPI is 500 to 1000 times higher than that of TF[179]. Our observation that total TFPI plasma concentrations are higher in patients with preeclampsia than in women with a normal pregnancy is in accord with previous reports[131,133].

In contrast to the changes in the maternal plasma, a lower placental extract of total TFPI concentrations and TFPI mRNA expression was reported in pregnant women with vascular complications of pregnancy (preeclampsia, eclampsia, placental abruption, fetal growth restriction, and fetal demise) in comparison to women with normal pregnancies[180]. A different study also demonstrated a lower placental TFPI-2 immunoreactivity in patients with preeclampsia, though not in patients with fetal growth restriction[181].

TFPI/TF ratio: an additional marker for coagulation activity?

The finding that the ratio of TFPI/TF in patients with preeclampsia is significantly lower than normal pregnancy and SGA is novel, as it suggests that the significant increase in TFPI plasma concentrations observed in preeclampsia may not be sufficient to compensate for the higher plasma TF concentration observed in these patients, and the overall balance is of a procoagulant state. Therefore, the TFPI/TF ratio may represent a good indicator for the severity of a procoagulant state in the context of pregnancy complications. The following evidence supporting this view was reported in patients with disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP), which are both complicated by consumption coagulopathy resulting from a hypercoagulable state: 1) TFPI plasma concentrations are higher in patients with DIC than in healthy individuals[178,179,182]; 2) patients with pre-DIC state have higher TF/TFPI ratio than patients with DIC, and patients with DIC who had a poor outcome also had a higher TF/TFPI ratio than those with a good outcome[179]; and 3) patients with TTP have lower TFPI concentrations than healthy controls[178], as well as a significant increase in TFPI/TF ratio after treatment[178]. The authors propose that this reflects an improvement in the hypercoagulable state associated with TTP[178]. Therefore, the observation that an increase in TFPI plasma concentrations may be of benefit in reducing the activation of the coagulation cascade in the presence of a hypercoagulable state has relevant therapeutic implications.

A possible intervention that can change the TFPI/TF ratio and reduce its systemic effect is the administration of heparin/low molecular weight heparin (LMWH), which augments the secretion and production of TFPI by the endothelial cells[183–188], leading to an increase in the plasma concentrations of TFPI-1 and TFPI-2[183–185,187–200]. Moreover, heparin binds factor Xa and TFPI-1 simultaneously, bringing them into proximity, which enhances factor Xa inhibition by TFPI-1.[113,114,201,202] Indeed, patients with recurrent abortions (of which 86.7% (26/30) had a thrombophilic mutation) that were treated with LMWH had a significantly higher total placental TFPI mRNA expression and protein concentrations than placentae of untreated patients with gestational vascular complications[180]. Therefore, the TFPI/TF ratio may serve as a marker for an increased prothrombotic activity, and the administration of LMWH might be of benefit in the case of patients with low concentrations of TFPI or a low TFPI/TF ratio.

In summary, the marked increase of plasma TF concentrations observed in patients with preeclampsia may reflect the maternal systemic inflammatory response associated with preeclampsia. Moreover, although the median maternal plasma TFPI concentrations are higher in patients with preeclampsia than in women with a normal pregnancy, the ratio of TFPI/TF is significantly lower and can be considered as a marker for the presence of a hypercoagulable state in these patients.

Acknowledgments

This research was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

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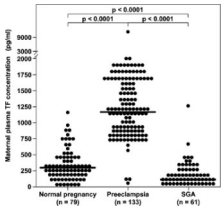

Figure 1.
Comparison of median maternal plasma tissue factor (TF) concentration between patients with normal pregnancy (n=79), preeclampsia (n=133), and women who delivered an SGA neonate (n=61).

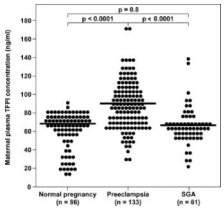

Figure 2.
Comparison of median maternal plasma tissue factor pathway inhibitor (TFPI) concentration between patients with normal pregnancy (n=86), preeclampsia (n=133), and women delivered an SGA neonate (n=61).

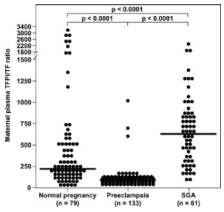

Figure 3.

Comparison of maternal plasma tissue factor pathway inhibitor (TFPI)/ tissue factor (TF) ratio between women with normal pregnancy (n=79), preeclampsia (n=133), and who delivered an SGA neonate (n=61).

Table I

Demographic and clinical characteristics of the study population

	Normal pregnancy (n=86)	Preeclampsia (n=133)	SGA (n=61)
Maternal age (years)	24 (21–27)	25(20–31)	25 (20–30)
Gravidity€			
1	18(21.4%)	45(34.1%)	12 (20.3%)
2–5	53(63.1%)	71 (53.8%)	39 (66.1%)
≥6	13(15.5%)	16 (12.1%)	8 (13.6%)
Parity§			
1	46 (54.1%)	96 (72.7%)*	38 (63.3%)
2–5	38(44.7%)	32 (24.3%)	21 (35%)
≥6	1 (1.2%)	4(3%)	1 (1.7%)
Ethnic origin £			
African-Americans	67 (80.7%)	110(83.9%)	51(87.9%)
Caucasian	11(13.3%)	14 (10.7%)	4(6.9%)
Hispanic	2 (2.4%)	5(3.8)	1(1.7%)
Asian	3(3.6%)	1(0.8%)	1(1.7%)
Other	0	1(0.8%)	1(1.7%)
Gestational age at blood collection (weeks)	31.1 (27.4–35)	34.3* (30.2–37.5)	37 * (31.0–38.3)
Gestational age at delivery (weeks)	39.6 (38.4–40.7)	34.4*@ (31.1–37.6)	37.4* (33.6–39)
Neonatal birthweight (grams)	3343 (3050-3700)	1880* (1200–2680)	2085* (1365–2505)

Data are presented as median (inter-quartile range) or numbers (%)

SGA: small for gestational age

€ = Normal pregnancy (n=84); Preeclampsia (n=132); SGA (n=59)

§ = Normal pregnancy (n=85); Preeclampsia (n=132); SGA (n=60)

£ = Normal pregnancy (n=83); Preeclampsia (n=131); SGA (n=58)

* $p<0.05$ in comparison to normal pregnancy

@ $p<0.05$ in comparison to SGA

Table II

Multiple logistic regression analysis of the association of maternal plasma tissue factor pathway inhibitor and tissue factor concentrations and preeclampsia

Factor	OR (95% CI)
Gestational age at sample collection wk	1.002 (0.996–1.007)
Gestational age at delivery wk	1.11 (0.92–1.34)
Tissue factor pg/mL	1.004 (1.004–1.005)
Tissue factor pathway inhibitor ng/mL	1.076 (1.055–1.097)
Neonatal birthweight g	1 (0.996–1.007)
Small for gestational age neonate	7.366 (2.585–20.988)

OR: odds ratio; CI: confidence interval

Table III

Multiple logistic regression analysis of the association of maternal plasma tissue factor pathway inhibitor / tissue factor ratio and preeclampsia

Factor	OR (95% CI)
Gestational age at sample collection wk	3.64 (1.34–9.9)
Gestational age at delivery wk	0.186 (0.057–0.608)
TFPI/ TF ratio	0.955 (0.934–0.977)
Neonatal birthweight g	1 (0.998–1.001)
Small for gestational age neonate	0.747 (0.083–6.711)

TFPI/ TF- Tissue factor pathway inhibitor/ Tissue factor

OR: odds ratio; CI: confidence interval

Table IV

A comparison of placental histologic lesions between patients with preeclampsia and patients who delivered an SGA neonate

Placental histologic findings	Preeclampsia (n=117)	SGA (n=49)	p value
Findings consistent with amniotic fluid infection			
Chorioamnionitis, maternal response	7 (6%)	4 (8.8%)	0.73
Funisitis, fetal response	2 (1.7%)	4 (8.8%)	0.05
Findings consistent with maternal under perfusion			
Remote villous infarcts	23 (19.7%)	5 (10.2%)	0.18
Recent villous infarcts	7 (6%)	0	0.11
Increased syncytial knots	65 (55.6%)	16 (32.7%)	0.01
Villous agglutination	16 (13.7%)	8 (16.3%)	0.64
Increased intervillous fibrin	29 (24.8%)	9 (18.4%)	0.42
Decreased placental weight	------	------	
Distal villous hypoplasia	32 (27.4)	8 (16.3%)	0.17
Persistent muscularization of basal plate arteries	4 (3.4%)	2 (4.1%)	1
Mural hypertrophy of decidual arterioles	9 (7.7%)	4 (8.2%)	1
Acute atherosis of basal plate arteries/ decidual arterioles	17 (14.5%)	3 (6.1%)	0.19
Findings consistent with fetal vascular thrombo-occlusive disease			
Early villous stromal-vascular karyorrhexis	1(0.9%)	0	1
Exclusively small foci	6(5.2%)	1 (2%)	0.67
Variable size foci	1(0.9%)	2(4.1%)	0.19
Fetal thrombotic vasculopathy	1(0.9%)	1(2%)	0.48
Thrombi, large fetal vessels	0	1(2%)	0.29
Intimal fibrin cushions, large fetal vessels	------	---------	
Fibromuscullar sclerosis, Intermediate size fetal vessels	-------	---------	
Chronic villitis with obliterative fetal vasculopathy	9(7.7%)	6(12.2%)	0.38

Data are presented as numbers (%) (it is better to present percentage (numbers)