ENDOTHELIAL FUNCTION IN NEWBORN INFANTS FROM PREECLAMPTIC PREGNANCIES

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SUMMARY

Preeclampsia (PE) is a characteristic hypertensive disorder of human pregnancy that is potentially dangerous for both mother and fetus. It is widely accepted that the fibrinolytic system is altered in PE, and is likely to result from the underlying endothelial dysfunction observed in this syndrome. A significant increase in PAI-1 antigen as well as in tPA antigen has been observed in PE and these may work as markers of endothelial dysfunction.

Our aim was to evaluate hemostatic variables in normal and PEc pregnancies at delivery, both in maternal and umbilical cord blood (UCB). We measured the antigen plasma levels of tissue plasminogen activator (tPA) and of plasminogen activator inhibitor type 1 (PAI-1), both markers of hemostatic and endothelial function disturbances, and fibrin fragment D-dimer.

Maternal blood from uncomplicated (n=42) and PEc pregnancies (n=44) were collected before delivery, and UCB immediately after delivery of the placenta. We found significantly higher values for PAI-1 and tPA in PEc women when compared with normal pregnant women, but no significant difference was found for D-dimer. In UCB, only tPA was significantly higher in PEc cases. In women with PE, proteinuria (marker of PE severity) correlated positively and significantly with tPA (r=0.44, P= 0.003) and PAI-1 antigen levels (r=0.58, P< 0.001). An inverse relationship between maternal tPA antigen levels and fetal birth weigh in PE (r=-0.63, P< 0.001) was also observed.

In summary, tPA and PAI-1 levels are higher in PEc women, suggesting endothelial dysfunction, and correlate with the severity of PE. Furthermore, these PEc hemostatic changes seem to have impact in fetal circulation. We suggest that tPA may be a good marker of fibrinolytic impairment and of endothelial dysfunction, particularly in the maternal circulation, and that the impact of raised tPA levels in the neonates from PEc mother deserves further studies.

INTRODUCTION

Preeclampsia (PE) is a characteristic hypertensive disorder of human pregnancy that is potentially dangerous for both mother and fetus. It is widely accepted that the fibrinolytic system is altered in PE, and is likely to result from the endothelial dysfunction observed in this syndrome[1]. A significant increase in plasminogen activator inhibitor type 1 (PAI-1) antigen as well as in tissue plasminogen activator (tPA) antigen has been observed in PEc pregnant women and these may work as markers of endothelial dysfunction.

Our aim was to evaluate hemostatic variables in normal and PEc pregnancies at delivery, both in maternal and umbilical cord blood (UCB). We measured the antigen plasma levels of tPA and of PAI-1, both markers of hemostatic and endothelial function, and fibrin fragment D-dimer.

MATERIALS AND METHODS

Approval for the study was given by the Ethics Committee of the Hospital S. João, Porto. PE was defined according to established criteria as a systolic/diastolic blood pressure of at least 140/90 mmHg (after 20 weeks gestation) and proteinuria of at least 1+ (30mg/dl) on dipstick testing, both on 2 occasions, 4 to 6 hours apart[2].

Blood was collected from normal (*n= 42*) and PEc pregnant women (*n= 44*) before delivery and UCB was obtained after delivery of the placenta.

PAI-1 and tPA antigen and D-dimer levels were evaluated by using enzyme-linked immunoadsorbent assays (Biopool).

STATISTICS

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 13.0 for Windows (SPSS Inc, Chicago). Kolmogorov-Smirnov analyses were used to test if the results were normally distributed. Clinical data are presented as mean ± standard deviation (data normally distributed) or median (interquartile range). Comparisons between groups were made by Student's unpaired *t* test. Data not normally distributed were compared by the Mann-Whitney *U* test and the Wilcoxon Signed Ranks test. The proportion of small for gestational age (SGA) cases was compared between normal and PEc pregnancies by Chi-square test. The strength of the association between the substances was estimated by Spearman's rank correlation coefficient. *P*-values below 0.05 were considered statistically significant.

RESULTS

Clinical characteristics of the studied groups are presented in Table I.

PEc pregnancy, when compared with normal pregnancy, presented significantly higher blood pressure; similar maternal age and body mass index (BMI) and significantly lower gestational age and newborn weight.

Comparing normal with PEc pregnant women, we observed significantly higher PAI-1 and tPA levels for PEc group.

We found that tPA was also significantly higher in UCB from PEc pregnancy, when compared with normal pregnancy. TPA levels were significantly higher in pregnant women (normal and PEc) than in UCB.

We also observed that in the PEc group, proteinuria (a marker of PE severity) correlated positively with maternal PAI-1 levels (Fig 1) and maternal tPA levels (Fig 2). We also found a significant positive correlation between maternal tPA and maternal D-dimer in normal pregnancy (Fig 3) and a significant inverse relationship between maternal tPA antigen levels and fetal birth weight in PE (Fig 4).

Table I – Clinical data of normal and preeclamptic groups at delivery [mean ± SD or median (IQR)].

	Normal	Preeclamptic	P
Maternal characteristics:			
Gestational Age (wk)	38.5 (38.0; 39.3)	37.0 (34.3;38.0)	< 0.001
BMI (kg/m^2)	29.2 (27.2; 30.8)	29.8 (26.8; 33.0)	0.15
Age (y)	30.4 ± 5.7	29.7 ± 5.2	0.61
Blood Pressure (mm Hg):			
Systolic	119.9 ± 11.5	155.0 ± 14.9	< 0.001
Diastolic	69.0 ± 7.2	97.4 ± 6.3	< 0.001
Fetal characteristics:			
Birth weight (kg)	3.4 (3.0; 3.7)	2.6 (1.9; 3.1)	< 0.001
SGA (n)	0 (0%)	6 (13.6%)	< 0.01

BMI – Body Mass Index; **SGA** – Small for Gestational Age

Table 2 – PAI-1, tPA and D-dimer data in maternal and fetal blood, in normal and preeclamptic cases

	Maternal		P	Fetal		P
	Normal (n = 42)	PEc (n = 44)		Normal (n = 40)	PEc (n = 44)	
D-dimer (ng/ml)	538.2 (391.2; 822.8)	488.5 (313.0;1091.3)	0.99	200.4 (101.6; 492.5)	190.7 (104.1; 588.3)	0.96
PAI-1 (ng/ml)	119.1 (86.8; 177.4)	173.8 (119.8; 211.3)	0.003	99.7 (52.2; 175.7)	58.3 (36.9; 123.1)	0.10
tPA (ng/ml)	9.7 (7.3; 13.3)	20.9 (14.0; 27.0)	<0.001	3.4 (2.2; 5.3)	4.8 (3.1; 10.1)	0.02
PAI-1/tPA	11.9 (8.4; 14.5)	7.6 (5.7; 10.4)	<0.001	23.0 (11.3; 68.1)	9.6 (4.5; 35.2)	0.006
Platelets (x10^9/l)	178.0 (142.0; 203.5)	197.5 (141.0; 238.5)	0.25	271.0 (210.3; 299.8)	218.0 (200.5; 271.0)	0.056

PEc, Preeclamptic

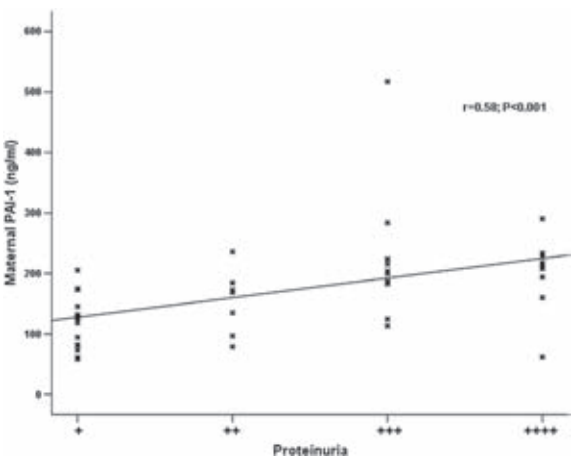

Figure 1 – Proteinuria *vs* maternal PAI-1.

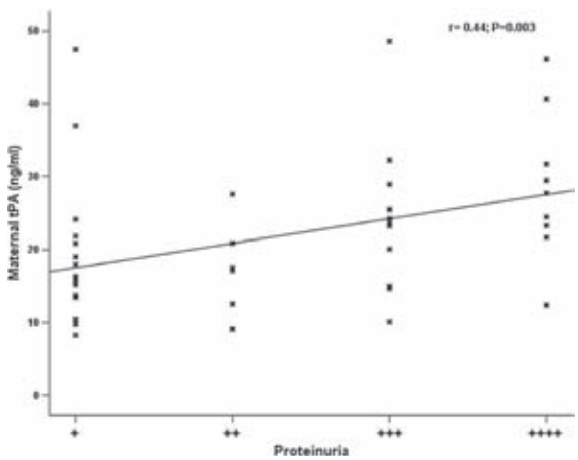

Figure 2 – Proteinuria *vs* maternal tPA.

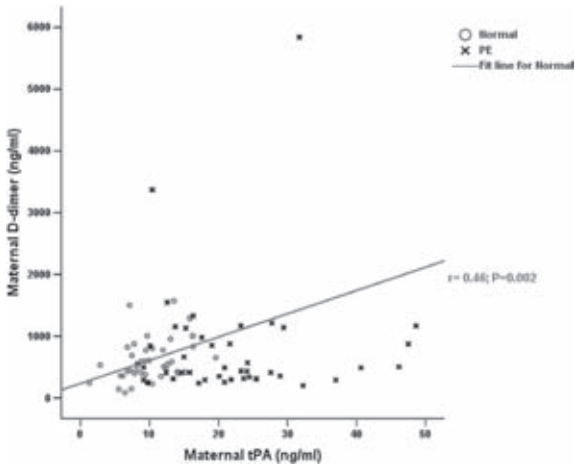

Figure 3 – Maternal tPA *vs* maternal D-dimer.

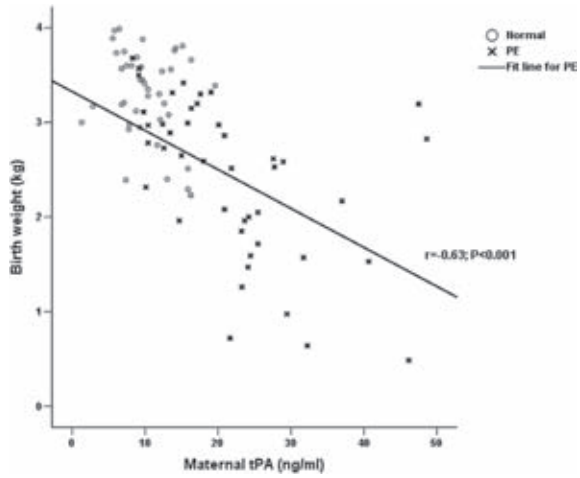

Figure 4 – Maternal tPA *vs* birth weight.

DISCUSSION AND CONCLUSION

Our data suggest that the significant rise of tPA and PAI-1 in PEc women, when compared with normal pregnant women, may reflect endothelial dysfunction. Similar findings for tPA were observed in PEc newborns, suggesting also some degree of endothelial dysfunction. Actually, a significant positive correlation was observed between mother's and newborn's tPA values, suggesting that the endothelial dysfunction occurring in mothers is linked to the same disturbance in their newborns.

Moreover, tPA and PAI-1 may provide markers of the severity of PE, considering their significant positive correlations with proteinuria.

In summary, tPA and PAI-1 levels are higher in PEc women, suggesting endothelial dysfunction, and correlate with the severity of PE. Furthermore, these PEc hemostatic changes seem to have impact in fetal circulation. We suggest that tPA may be a good marker of fibrinolytic impairment and of endothelial dysfunction, particularly in the maternal circulation, and that the impact of raised tPA levels in the neonates from PEc mothers deserves further studies.

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