Von Willebrand Factor and ADAMTS13
A Candidate Couple for Preeclampsia Pathophysiology

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Objective—The goal of this study was to search for an association between a desintegrin-like and metalloprotease thrombospondin type 1 motif, member 13 (ADAMTS13) levels and the occurrence of preeclampsia, its characteristics (time-onset and severity), and its consequences (occurrence of fetal growth restriction or preterm delivery).

Methods and Results—We studied 140 pairs of women in a case-control study with 3 matching criteria: maternal age, gestational age, and ethnic origin. We measured ADAMTS13 activity using a fluorescence resonance energy transfer assay with the fluorescence resonance energy transfer-VWF73 peptide. ELISA was used to assess protein antigen levels: ADAMTS13, von Willebrand Factor (VWF), interleukin-6, C-reactive protein, P-selectin, and thrombospondin-1. The lowest levels of ADAMTS13 (activity ≤70% or antigen ≤592 ng/mL) were significantly associated with preeclampsia (odds ratios [OR] [95% confidence interval] of 4.2 [1.1 to 15] and 14.3 [1.7 to 123], respectively). This association was independent of VWF levels and preeclampsia risk factors but dependent on interleukin-6 and C-reactive protein levels for ADAMTS13 activity. Levels of ADAMTS13 activity (≤57%) were significantly associated with early-onset preeclampsia (OR=2.5 [1.1 to 5.8]). Severe preeclampsia was associated with the highest levels of P-selectin (>57 ng/mL) (OR=3.4 [1.2 to 9.7]).

Conclusion—Preeclampsia is associated with decreased levels of ADAMTS13, independently of VWF. This decrease is quantitative, occurs early, and seems to be dependent on inflammation. Our results suggest that ADAMTS13 could participate in the pathophysiology of preeclampsia. (Arterioscler Thromb Vasc Biol. 2011;31:1703-1709.)

Key Words: hypertension ■ pregnancy ■ ADAMTS13 ■ preeclampsia ■ von Willebrand factor
that in normal plasma) is observed in most patients with thrombotic thrombocytopenic purpura and is caused by either mutations of the ADAMTS13 gene or by inhibitory antibodies against ADAMTS13.9 Thrombocytopenic purpura is a thrombotic microangiopathy characterized by VWF-mediated platelet thrombi disseminated in the microcirculation, responsible for end-organ ischemia. Recent findings suggest a potential role of 2 proteins, P-selectin (P-sel) and thrombospordin-1 (TSP-1), in the regulation of ADAMTS13 protease activity toward VWF. These 2 molecules colocalize with VWF in Weibel-Palade bodies and platelet α granules.10,11 P-sel levels are increased in women with PE,12,13 whereas TSP-1 has not yet been measured in a large number of pregnant women with or without PE. In addition, inflammatory cytokines seem to inhibit ADAMTS13 proteolytic activity,14 or its expression in hepatic stellate cells and endothelial cells.15 In particular, interleukin-6 (IL-6), levels of which are increased in PE,16,17 inhibits ultralarge VWF strings cleavage by ADAMTS13 under flowing conditions.14 As VWF levels are increased in PE and because placental microcirculation offers optimal conditions to activate that protein, we hypothesized that decreased levels of ADAMTS13 could participate in the pathophysiology of PE. The aim of this study was to search for an association between ADAMTS13 levels and the occurrence of PE. Thus, we measured, in a case-control study, ADAMTS13 (activity and antigen [Ag]); its substrate VWF; the potential regulators of its activity, IL-6, P-sel, and TSP-1; and C-reactive protein (CRP), a marker of inflammation.

**Methods**

**Patients**
In this study, 140 case-control matched pairs were randomly chosen among the 184 pairs of the Search for an Association Between CX3CR1 and V2491 Polymorphism, Preeclampsia and Endothelial Injury (ECLAXIR) study. The ECLAXIR study was a multicenter case-control study for which 368 white pregnant women were enrolled between May 2003 and October 2007.18 The cases were pregnant women with PE, who were enrolled at time of diagnosis. They were matched with normotensive pregnant women (controls) for maternal age (±2 years), gestational age (±2 weeks), and ethnic origin (European or Maghrebian). Controls who developed PE after enrollment were excluded.

Written informed consent was obtained from each woman before enrollment and blood sampling. The ECLAXIR study was approved by the ethics committee (Comité de Protection des Personnes dans la Recherche Biomédicale) of Hôpital Bichat-Claude Bernard (Paris, France). Further use of the samples in the ADAMSIE study was approved by the ethics committee (Comité de Protection des Personnes, Ile-de-France IX) of Hôpital Henri Mondor (Créteil, France). PE was defined according to the American Congress of Obstetricians and Gynecologists19 as elevated blood pressure (≥140/90 mm Hg) occurring after 20 WG with previously normal blood pressure, and proteinuria (≥0.3 g in a 24-hour urine specimen).

Severe PE was defined by the American Congress of Obstetricians and Gynecologists19 as the presence of at least 2 of the following criteria: blood pressure ≥160/110 mm Hg in 2 measurements 4 hours apart while the patient is on bed rest; proteinuria ≥5 g in a 24-hour urine specimen; oliguria of less than 25 mL per hour; cerebral or visual disturbances; pulmonary edema or cyanosis; epigastric pain; impaired liver function defined as serum aspartate aminotransferase concentrations ≥70 IU/L; thrombocytopenia defined as platelet count lower than 100 Giga/L; fetal growth restriction defined as a z-score lower than −1.88. This value, calculated according to Salomon et al,20 is equivalent to a birth weight below the third percentile for gestational age. PE was defined as early if gestational age at diagnosis was <34 weeks.

**Blood Sampling**
Venous blood was collected from all subjects at the time of enrollment (time of PE diagnosis for cases and matched gestational age for controls), before any treatment, into a 1:10 final volume of 3.8% sodium citrate. Platelet-poor plasma was obtained by centrifugation at 2500 g for 20 minutes, and samples were stored at −80°C until testing.

**Laboratory Assays**
ADAMTS13 activity was measured using the method of Kokame et al21 using commercial recombinant fluorescence resonance energy transfer-VWF73 peptide (Peptide Institute Inc, Osaka, Japan) according to the manufacturer’s instructions.

ELISA methods were used to assess protein Ag levels: ADAMTS13 (Immubind ADAMTS13 ELISA, American Diagnostica Inc, Stamford, CO), VWF (Asserachrom vWF-Ag, STAGO, Asnières-sur-Seine, France), soluble P-selectin (Human s-P Select CD62P immunoassay, R&D Systems, Minneapolis, MN), TSP-1 (Human Thrombospondin-1 Quantikine ELISA kit, R&D Systems), and IL-6 (Human IL-6 Quantikine HS, R&D Systems). CRP levels were determined by immunonephelometry using a high-sensitivity method with the Cardiophase hsCRP kit from Dade Behring Inc (Deerfield, IL). Specific activity of ADAMTS13 was calculated with the ratio of ADAMTS13 activity/Ag.

**Statistics**
Categorical variables were described using frequency and percentage; continuous variables were described using quartiles. Correlation studies were carried out using the Spearman rank test. Quantitative values were compared between cases and controls using the signed rank test. As the laboratory data were not normally distributed (except for VWF), ADAMTS13 activity and Ag and VWF Ag levels were divided in tertiles based on the distribution of the control group. The measure of association between ADAMTS13 and VWF levels and the occurrence of PE was assessed using conditional logistic regression models, whereas the measure of association with time-onset and severity of PE or occurrence of fetal growth restriction or preterm delivery was assessed using unconditional logistic regression. Multivariate analysis was performed according to forward stepwise model selection procedure. The odds ratios (OR) and their 95% CIs were calculated using the lowest tertile of the control group as the reference for VWF Ag and the highest tertile of this group as the reference for ADAMTS13 levels. Adjustments were done for VWF Ag or ADAMTS13 levels and further for PE risk factors (pregestational body mass index >30 kg/m², nulliparity, multiple pregnancy, personal history of thrombosis, connective tissue disease, or antiphospholipid antibody syndrome). The relationship between the studied variables and PE characteristics (time-onset and severity) or complications (occurrence of fetal growth restriction <10th percentile [z-score = −1.28]) and preterm delivery before 37 WG) were determined using unconditional logistic regression analysis after dividing the levels into tertiles based on their distribution in the case group. All analyses were performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

**Results**

**Study Population**
Table 1 shows general demographic, obstetric, and medical characteristics of the study population. Patients and controls were matched on 3 criteria: maternal age (±2 years) (mean, 31 years), gestational age at enrollment (±2 weeks) (mean, 34 weeks), and ethnic origin (113 pairs were from Europe, 25 pairs were from the Maghreb, and 2 pairs had mixed
Weak correlations were also found between ADAMTS13 activity or Ag levels and VWF:Ag (Figure). We found weak correlations between blood group and ADAMTS13 levels: 71% (O blood group) versus 72% (non–O blood group). No relationship was found between blood group and ADAMTS13 levels: 71 ± 16 (O blood group) versus 72 ± 18% (non–O blood group).

**ADAMTS13 and PE**

Table 3 shows the comparison of ADAMTS13 (activity and Ag) and VWF:Ag levels between cases and controls. Our results show that individuals with the lowest levels of ADAMTS13 (activity ≤70% or Ag ≤592 ng/mL) had a significantly increased risk of PE, independent of VWF:Ag levels (OR1 of 4.4 [1.6 to 12.5] and 4.3 [1.5 to 12], respectively). Further adjustments for PE risk factors did not modify these results (OR3 of 4.2 [1.1 to 15] and 14.3 [1.7 to 123], respectively).

We also made further adjustments for Ag levels, P-sel, and TSP-1 levels (OR3) or IL-6 and CRP levels (OR4) in a subgroup (n = 109) because of missing data, with similar demographic characteristics (data not shown). The association of the lowest levels of ADAMTS13 with PE is also independent of O blood group, TSP-1, and P-sel (OR3 of 16...
Interestingly, adjustments for IL-6 and CRP suppressed the association with ADAMTS13 activity (OR4 of 2 [0.5 to 9.1]) while maintaining that with ADAMTS13 Ag (OR4 of 10.6 [1.2 to 92]). Adjustment for IL-6 or CRP alone did not suppress the association with ADAMTS13 activity.

Our results also show a significant association between VWF:Ag highest levels (>242 IU/mL) and PE, independent of ADAMTS13 activity and PE risk factors (OR2 of 55 [7–426]), IL-6, CRP, TSP-1, or P-sel levels (Table 3).

**PE Characteristics and Complications**

We then searched for an association between ADAMTS13 concentration and either the time-onset or the severity of PE (Table 4). Our results show that the lowest levels of ADAMTS13 activity (≤57%) were significantly associated with early-onset PE with an OR of 2.5 (1.1 to 5.8). Severe PE was associated with the highest levels of P-sel (>57 ng/mL) with an OR of 3.4 (1.2 to 9.7).

We also searched for an association with the occurrence of a fetal growth restriction or a preterm delivery. Our results show no association between ADAMTS13 (activity or Ag), VWF:Ag, P-sel, or TSP-1 levels and any of these complications (data not shown).

**Discussion**

In this case-control study including 140 pairs of pregnant women, we showed for the first time an independent association between ADAMTS13 plasma levels and PE. Decreased levels of ADAMTS13 activity (≤70%) or Ag (≤592 ng/mL) were significantly associated with PE after adjustment for VWF:Ag levels and for PE risk factors. By contrast, the activity/Ag ratio did not differ significantly between the 2 groups, thus indicating the quantitative nature of the defect. Our results are at variance with the study by Molvarec et al, who did not find any association between ADAMTS13 and PE. Several points may explain this discrepancy: first, the larger number of patients of our study (140 versus 67); second, the strict matching criteria between cases and controls in the current study; and third, an earlier gestational age at enrollment in our study (34 versus 38 weeks). Interestingly, decreased ADAMTS13 activity levels have been reported in hemolysis, elevated liver enzymes, and low platelet count syndrome, a severe complication of PE. In this specific study on hemolysis, elevated liver enzymes, and low platelet count syndrome, increased amounts of active VWF related to acute endothelial cell activation and decreased ADAMTS13 activity could be observed. Also, in agreement with our results, several other studies reported increased levels of VWF as a marker of endothelial dysfunction in PE.

### Table 2. Descriptive Analysis for ADAMTS13, VWF, P-sel, TSP-1, IL-6, and CRP Plasma Levels in PE Cases and in Controls

<table>
<thead>
<tr>
<th>Laboratory Data</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean±SD (Median; Q1; Q3)</td>
</tr>
<tr>
<td>ADAMTS13 activity, %</td>
<td>140</td>
<td>66±17 (64; 53; 79)</td>
</tr>
<tr>
<td>ADAMTS13 Ag, ng/mL</td>
<td>139</td>
<td>559±183 (543; 418; 700)</td>
</tr>
<tr>
<td>VWF:Ag, IU/mL</td>
<td>139</td>
<td>0.125±0.032 (0.121; 0.104; 0.146)</td>
</tr>
<tr>
<td>WF-Ag, IU/mL</td>
<td>140</td>
<td>363±128 (350; 263; 449)</td>
</tr>
<tr>
<td>P-sel, ng/mL</td>
<td>139</td>
<td>52±29 (44; 32; 66)</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>138</td>
<td>4.97±8.57 (2.34; 0.96; 4.39)</td>
</tr>
<tr>
<td>CRP, ng/mL</td>
<td>130</td>
<td>10.7±13.1 (5.1; 1.9; 12.6)</td>
</tr>
<tr>
<td>Platelet count, Giga/L</td>
<td>140</td>
<td>197±80.7 (189; 141.5; 232.5)</td>
</tr>
</tbody>
</table>

*P* was determined by signed rank test. Q1 indicates lower quartile; Q3, upper quartile; ADAMTS13 activity/Ag, ADAMTS13 specific activity; NA, not available.

![Figure. Correlations between ADAMTS13 activity (A) or ADAMTS13 Ag (B) and VWF:Ag plasma levels. Shown is the Spearman rank coefficient of correlation (*r*); *P*<0.005 denotes statistical significance.](http://atvb.ahajournals.org/content/7/4/1706/F2.large.jpg)
Severe ADAMTS13 deficiency is associated with thrombocytopenic purpura, and its involvement in the pathogenesis of this thrombotic microangiopathy has been clearly established. Besides this extreme case, partial deficiencies of ADAMTS13 have been observed in other contexts. However, the clinical relevance of these partial deficiencies of ADAMTS13 has not been clearly elucidated in these various contexts so far. In physiological conditions, ADAMTS13 is dependent on age: it is decreased in neonates and in individuals over 65 years old. During normal pregnancy, ADAMTS13 mean levels decrease progressively to 23% at the third trimester. More precisely, ADAMTS13 activity begins to decrease at 12 to 16 WG, suggesting an increased sensitivity to thrombotic microangiopathy from the second trimester of pregnancy. In pathology, partial deficiencies of ADAMTS13 have been observed in diseases sharing an inflammatory state, including cardiovascular diseases (coronary heart disease, ischemic stroke, peripheral arterial disease), severe sepsis and septic shock, myocardial infarction, severe Plasmodium falciparum malaria, alcoholic hepatitis, and antiphospholipid syndrome. In these studies, correlation between ADAMTS13 and VWF levels are pronounced, weak, or more usually absent, especially when there is an adjustment for age. In our study, this correlation was weak ($r = -0.17$

### Table 3. Odds Ratios for Risk of PE, for ADAMTS13 (Activity, Ag), and for VWF:Ag

<table>
<thead>
<tr>
<th>ADAMTS13 activity (%)</th>
<th>OR (95% CI)</th>
<th>OR1 (95% CI)</th>
<th>OR2 (95% CI)</th>
<th>OR3 (95% CI)</th>
<th>OR4 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>1.1 (0.4 to 2.9)</td>
<td>0.8 (0.6 to 2.3)</td>
<td>0.8 (0.6 to 2.3)</td>
<td>0.8 (0.6 to 2.3)</td>
<td>0.8 (0.6 to 2.3)</td>
</tr>
<tr>
<td>70 to 80</td>
<td>3.5 (2.1 to 5.9)</td>
<td>3.1 (1.9 to 5.1)</td>
<td>3.1 (1.9 to 5.1)</td>
<td>3.1 (1.9 to 5.1)</td>
<td>3.1 (1.9 to 5.1)</td>
</tr>
<tr>
<td>≤70</td>
<td>0.5 (0.3 to 0.9)</td>
<td>0.5 (0.3 to 0.9)</td>
<td>0.5 (0.3 to 0.9)</td>
<td>0.5 (0.3 to 0.9)</td>
<td>0.5 (0.3 to 0.9)</td>
</tr>
</tbody>
</table>

### Table 4. OR for PE Time of Onset and Severity, ADAMTS13 (Activity and Ag), VWF:Ag, and P-sel

<table>
<thead>
<tr>
<th>ADAMTS13 activity (%)</th>
<th>Early PE (n=64)</th>
<th>Late PE (n=76)</th>
<th>Severe PE (n=66)</th>
<th>NS PE (n=74)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;75</td>
<td>23.4 (15)</td>
<td>40.8 (31)</td>
<td>30.3 (20)</td>
<td>35.1 (26)</td>
<td>1</td>
</tr>
<tr>
<td>57 to 75</td>
<td>34.4 (22)</td>
<td>30.3 (23)</td>
<td>2.0 (0.8 to 4.6)</td>
<td>33.3 (22)</td>
<td>1.2 (0.5 to 2.8)</td>
</tr>
<tr>
<td>≤57</td>
<td>42.2 (27)</td>
<td>28.9 (22)</td>
<td>2.5 (1.1 to 5.8)</td>
<td>36.4 (24)</td>
<td>1.2 (0.6 to 2.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADAMTS13 Ag (ng/mL)</th>
<th>Early PE (n=64)</th>
<th>Late PE (n=76)</th>
<th>Severe PE (n=66)</th>
<th>NS PE (n=74)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;635</td>
<td>28.1 (18)</td>
<td>38.2 (29)</td>
<td>37.9 (25)</td>
<td>29.7 (22)</td>
<td>1</td>
</tr>
<tr>
<td>457 to 635</td>
<td>31.2 (20)</td>
<td>34.2 (26)</td>
<td>2.1 (0.9 to 4.8)</td>
<td>33.3 (22)</td>
<td>0.6 (0.3 to 1.4)</td>
</tr>
<tr>
<td>457</td>
<td>40.6 (26)</td>
<td>26.3 (20)</td>
<td>2.1 (0.9 to 4.8)</td>
<td>33.3 (22)</td>
<td>0.8 (0.4 to 1.8)</td>
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<table>
<thead>
<tr>
<th>VWF:Ag (IU/mL)</th>
<th>Early PE (n=64)</th>
<th>Late PE (n=76)</th>
<th>Severe PE (n=66)</th>
<th>NS PE (n=74)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤283</td>
<td>32.8 (21)</td>
<td>34.2 (26)</td>
<td>31.8 (21)</td>
<td>35.1 (26)</td>
<td>1</td>
</tr>
<tr>
<td>283 to 401</td>
<td>35.9 (23)</td>
<td>32.9 (25)</td>
<td>1.1 (0.5 to 2.5)</td>
<td>33.3 (22)</td>
<td>1.0 (0.5 to 2.3)</td>
</tr>
<tr>
<td>&gt;401</td>
<td>31.2 (20)</td>
<td>32.9 (25)</td>
<td>0.9 (0.4 to 2.2)</td>
<td>34.8 (23)</td>
<td>1.3 (0.6 to 2.9)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>P-sel (ng/mL)</th>
<th>Early PE (n=64)</th>
<th>Late PE (n=76)</th>
<th>Severe PE (n=66)</th>
<th>NS PE (n=74)</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>≤36</td>
<td>34.4 (22)</td>
<td>34.2 (26)</td>
<td>25.7 (17)</td>
<td>41.9 (31)</td>
<td>1</td>
</tr>
<tr>
<td>36 to 57</td>
<td>21.9 (14)</td>
<td>39.5 (30)</td>
<td>7.0 (0.2 to 1.3)</td>
<td>27.3 (18)</td>
<td>1.3 (0.5 to 2.9)</td>
</tr>
<tr>
<td>&gt;57</td>
<td>43.7 (28)</td>
<td>25.0 (19)</td>
<td>1.7 (0.8 to 3.9)</td>
<td>47.0 (31)</td>
<td>3.5 (1.5 to 8.2)</td>
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Analyses are by thirds (case population tertiles). In cases and controls, values are percentage (No.) of subjects. NS indicates nonsevere.
and −0.14, for ADAMTS13 activity and Ag, respectively), suggesting that the consumption of ADAMTS13 by its increased substrate VWF may only partially explain ADAMTS13 decrease in PE. Recent findings linking ADAMTS13 to inflammation suggest the involvement of other mechanisms to explain ADAMTS13 partial deficiencies. Inflammatory cytokines, including tumor necrosis factor-α, IL-6, or IL-8, which are increased in PE, have been shown to inhibit ADAMTS13 synthesis or activity in endothelial cells. In the present study, we confirmed a 4-fold IL-6 increase in cases versus controls; this was associated with an increase in CRP level concentration. Although an increase in IL-6 and CRP had no impact on the association of PE with ADAMTS13 Ag, the statistical adjustment on these parameters abolished its association with ADAMTS13 activity. This result is in agreement with similar ADAMTS13-specific activity (activity/Ag ratio) that we observed between PE and control groups and suggests a quantitative decrease of the protein in PE. Nevertheless, the decrease of ADAMTS13 activity in PE appears to be at least partially dependent on IL-6 and CRP levels, as suggested by the results of multivariate analysis. Feys et al reported similar results when comparing groups of patients with inflammatory bowel disease displaying high or low CRP levels (10 mg/L threshold): both ADAMTS13 activity (P=0.11) and Ag (P=0.03) were lower in patients with high CRP levels, although only Ag levels reached statistical significance. Alternatively, ADAMTS13 proteolysis by plasmatic proteases such as thrombin or by proteases released by granulocytes may also be involved.

In addition, as PE patients have a significant proteinuria, decreased ADAMTS13 could also have been a consequence of elimination in the urine. To evaluate the possible involvement of this mechanism, we prospectively collected urine from 11 pregnant women displaying proteinuria (including women with PE and miscellaneous other causes of proteinuria) ranging from 0.21 to 1.92 g/L (mean, 0.67±0.62 g/L). ADAMTS13 Ag was measured in all samples and was undetectable in all cases. Finally, although not measured in our study, similar total protein concentrations in subjects with PE and normal pregnant controls have been reported, which also argues against a role of increased vascular permeability in ADAMTS13 decrease.

We also found a significant association between ADAMTS13 activity levels (<57%) and early-onset PE (before 34 WG), whereas severe PE was associated with increased levels of P-sel >57 ng/mL, probably because of a more pronounced endothelial lesion or platelet activation. This could indicate that ADAMTS13 is decreased early in PE, but this finding does not indicate the severity of the decrease. Interestingly, decreased serum levels of ADAM12, another member of ADAM family, have been reported in PE. In addition, multiple ADAMTS subtypes have been detected, albeit many at low levels, in total RNA lysates prepared from human term placenta or uterine tissues, suggesting that these metalloproteinases may play important roles in implantation and placentalization. A spliced form (2.4 kb of mRNA) of ADAMTS13 has also been identified in placenta, but the expression of the protein in the placenta or any specific cell in placenta has not been explored yet. In our study, placentas from patients or controls were not available, and further study could not be performed.

This study is the first to suggest a link between ADAMTS13 deficiency and PE. We observed an association between decreased ADAMTS13 plasma levels and PE. Our results show that this decrease is quantitative, occurs early, and might be at least partially dependent on inflammation. Decreased ADAMTS13 activity is likely to participate in the increase of circulating VWF levels in PE. Both these proteins constitute a particularly interesting couple because hemodynamics of placental microcirculation offer ideal conditions to both activate VWF and make it very sensitive to any ADAMTS13 defect. A prospective study should be conducted, including placenta analysis to confirm our results.

Acknowledgments

We thank M. Lamotte for expert technical assistance. We also thank the staff and participants of the ECLAXIR study and the Centre de Ressources Biologiques Colombes for their important contributions.

Sources of Funding

This work was supported by Grant CRC 08 078 (Contrat d’Initiation à la Recherche Clinique 2008) from Assistance Publique–Hôpitaux de Paris.

Disclosures

None.

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Arterioscler Thromb Vasc Biol. 2011;31:1703-1709; originally published online April 21, 2011;
doi: 10.1161/ATVBAHA.111.223610
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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