**Altered Expression of Plasminogen Activator Inhibitor Type 1 in Placentas From Pregnant Women With Preeclampsia and/or Intrauterine Fetal Growth Retardation**

By A. Estellés, J. Gilabert, M. Keeton, Y. Eguchi, J. Aznar, S. Grancha, F. España, D.J. Loskutoff, and R.R. Schleef

Elevated plasma levels of type 1 plasminogen activator inhibitor (PAI-1) have been implicated in mediating the fibrin deposition and occlusive lesions that occur within the placental vasculature in preeclampsia (PE) and intrauterine growth retardation (IUGR). In this report we identify the cells within the normal-appearing villous tissue that are responsible for the local production of PAI-1 in women with PE and IUGR. Levels for another fibrinolytic inhibitor (ie, type 2 plasminogen activator inhibitor [PAI-2]) were determined for comparative purposes. Elevated levels of PAI-1 were detected in placenta extracts from PE/IUGR patients (121 ± 38 ng/mg, n = 8) when compared with the levels in placenta extracts from normal women (43 ± 17 ng/mg, n = 10) or women with IUGR but not PE (51 ± 22 ng/mg, n = 11).

Immunohistochemical analysis of paraffin sections showed an increased immunoreactivity for PAI-1 in the placental villous syncytiotrophoblasts from PE/IUGR women compared with the immunostaining of placental samples from the normal or IUGR group. In contrast, antigen levels and immunostaining for PAI-2 were reduced in the placentas harvested from not only the PE/IUGR women (209 ± 144 ng/mg) but also the IUGR group (169 ± 106 ng/mg) in comparison with the PAI-2 levels in normal placentas (535 ± 98 ng/mg). To document that the increased immunoreactivity for PAI-1 in PE/IUGR syncytiotrophoblasts was mediated by an increased production of PAI-1 within these cells, in situ hybridization analysis was performed. A strong positive signal for PAI-1 mRNA in villous syncytiotrophobasts from PE patients (n = 5) was obtained after 2 weeks of exposure to the NBT2 emulsion in comparison with the week signal for PAI-1 mRNA that required a 10-week exposure of the normal placenta sections (n = 10). Northern blotting for PAI-1 mRNA showed that both transcripts (ie, 3.2 and 2.3 kb) were elevated in samples of two PE patients in comparison with the PAI-1 mRNA transcripts present in a normal placenta and an IUGR placental sample. These results show increased PAI-1 and mRNA levels in placentas from PE patients and raise the possibility that localized elevated levels of PAI-1 may play a role in the initiation of placental damage, as well as in the thrombotic complications associated with this disease.

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**PREECLAMPSIA (PE)** is a multisystem disease of unknown etiology that is associated with increased perinatal/maternal morbidity and mortality.\(^1\) Fibrin deposition in the subendothelium of the kidney glomerulus and in the decidual segments of spiral arteries are observed in this disease.\(^2\) Occlusive lesions in placental vasculature and decidual spiral arteries, named atherosclerosis or atheromatous-like lesions, can also be found in pregnancy-induced hypertension associated with PE.\(^1\) Although PE is commonly associated with intrauterine fetal growth retardation (IUGR), small-for-gestation-age infants can also be observed without hypertensive disease, and the severity of fetal growth retardation is correlated with the degree of placental infarction and impaired placental nutrient transport.\(^1\) Physiologic changes in the coagulation and fibrinolytic systems\(^2,3,4\) are known to result in an increased susceptibility of pregnant women to thrombotic disorders and the formation of fibrin deposits, which can lead to a reduction in nutrient transport across the placenta.\(^4\)

Because the formation of plasmin and the degradation of fibrin clots appear to be precisely regulated by specific plasminogen activator inhibitors (PAIs), our group\(^5,6,10\) and others\(^1,5,13,14\) have been interested in correlating the levels of these molecules in blood obtained from normal pregnant women with those levels present in blood of patients with PE. More specifically, decreases in plasmatic fibrinolytic activity in PE patients have been reported to be caused by increased levels for type 1 PAI (PAI-1),\(^10,14\) and we have observed that the plasma levels of PAI-1 in PE are positively correlated with the severity of placental damage.\(^10\) This inhibitor inhibits both tissue-type plasminogen activator (t-PA) and urokinase-type PA (u-PA) by forming a 1:1 stoichiometric complex with them.\(^10,15,16\) Moreover, a number of experimental observations support the hypothesis that PAI-1 is the principal physiologic inhibitor of t-PA and a primary regulator of vascular fibrinolysis in vivo.\(^10,16\)

Recent data from a number of laboratories indicate that the regulation of plasminogen activation may occur as a localized event in the vascular system.\(^19,20\) For example, two groups have recently shown elevated PAI-1 expression in several defined areas within atherosclerotic human arteries.\(^21,22\) Thus, altered PAI-1 levels may play a prominent role in regulating the activation of plasminogen and the hemostatic balance within the placenta. Unfortunately, information is only available on the immunohistochemical distribution of PAIs in placenta obtained from normal pregnancies.\(^23,24\) In these studies, the villous syncytiotrophoblasts stained intensely using antibodies to PAI-2,\(^23,24\) whereas a weak reactivity was detected in the cells using antibodies to PAI-1.\(^24\) Therefore, the current study was initiated to analyze the local expression and distribution of this molecule in pregnant women suffering with PE/IUGR.

*From Centro Investigacion and Centro Maternal, Hospital La Fe, Valencia, Spain; and Department of Vascular Biology, The Scripps Research Institute, La Jolla, CA.*

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Address reprint requests to R.R. Schleef, PhD, The Scripps Research Institute, Department of Vascular Biology (VB-3), 10666 North Torrey Pines Rd, La Jolla, CA 92037.

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**MATERIALS AND METHODS**

**Clinical groups.** Patients and normal pregnant women entered into this study were from the Maternity Center of Hospital La Fe during 1991 and 1992. Informed consent was obtained from the women before blood sampling and collection of placenta. Birth weight was determined after cutting of the umbilical cord within 2 cm of newborn insertion about 15 minutes after delivery. The placental weight was determined after removal of blood clots from the decidual surface, trimming of the membrane, and cutting of the umbilical cord within 2 cm of its insertion.

The control group (group A) consisted of 10 healthy normotensive women in the third trimester of pregnancy (range 33 to 40 weeks of pregnancy) whose newborns had a weight in the 10th percentile of appropriate birth weight for gestational age (range: 2,800 to 4,500 g) and a neonatal ponderal index >2.20. No complications were observed during pregnancy and labor. The women did not receive any type of medication except a vitamin complex.

The pure severe preeclamptic group (group B) included eight patients with no previous history of hypertension in whom severe PE developed during the third trimester of pregnancy (range: 32 to 40 weeks of pregnancy). Severe PE was diagnosed in these women when blood pressure was >160/110 mm Hg at bed rest on at least two occasions 6 hours apart. In these patients, proteinuria was >1 g/L in at least two random specimens collected 6 hours apart. All of these PE patients had pregnancies complicated with IUGR.

The IUGR group without PE (group C) included 11 pregnant women in the third trimester of pregnancy (range: 32 to 40 weeks of pregnancy) who were diagnosed as having suspected IUGR when serial ultrasonographic measurements of biparietal diameter and femur length were >2 SD below the mean for gestational age two consecutive times in a month. After delivery, diagnosis of IUGR was confirmed when newborn weight (range: 700 to 2,400 g) was below the 10th percentile of appropriate birth weight for gestational age and neonatal ponderal index was <2.20 (range: 1.95 to 2.19). This IUGR group shows fetal growth retardation type II or asymmetrical IUGR. Although asymmetrical IUGR are often caused by maternal diseases, our IUGR cases without PE are of unknown etiology and only two mothers whose pregnancies were complicated with IUGR without PE were smokers.

**Blood sampling.** Pregnant women suffering with severe PE (group B) or IUGR without PE (group C) were hospitalized 1 to 3 days before delivery to monitor their pregnancy. A blood sample was obtained from these patients at that time. The women included in the control group had provided a blood sample for clinical analyses during a routine examination that occurred 1 to 3 days before delivery at Hospital La Fe. Blood was obtained by venipuncture of the cubital vein and anticoagulated with 3.8% sodium citrate (9:1, vol:vol, blood:anticoagulant). Citrated blood was centrifuged at 1,500g for 15 minutes at 4°C. Platelet-poor plasma was collected and stored at −80°C until analyzed.

**Tissue collection and protein extraction from placenta.** Placental samples for this study were obtained immediately after delivery. Villous trophoblast tissue was removed from the placenta with care and rinsed in phosphate-buffered saline (PBS) to remove blood. Pieces of placental villous trophoblast tissue were processed as follows: (1) for protein extraction, specimens from normal-appearing villous tissue were further dissected into smaller pieces (≤1 mm²), washed extensively in cold PBS to remove residue blood, and flash frozen in liquid nitrogen; (2) for RNA extraction, specimens from normal-appearing villous tissue were flash frozen in liquid nitrogen; and (3) for immunohistochemistry and in situ hybridization, sections either selected randomly or selected from subject infarction areas were fixed overnight at 4°C and embedded in paraffin blocks. The placental infarct area was defined after microscopic examination of stained hematoxylin/eosin sections as previously described.

Proteins were extracted from the frozen placenta sections by incubating 1 g of a sample in 10 mL of 0.1 mol/L Tris-HCl, pH 7.5, 2 mol/L potassium thiocyanate (KSCN) at 4°C. The cellular debris was removed by centrifugation (10,000g, 30 minutes) and the supernatant was dialyzed against cold PBS. All steps during the extraction of the placenta were performed at 4°C to minimize degradation of PAIs. Total protein in the samples was determined by using the bicinchoninic acid (BCA) protein assay (Pierce, Rockford, IL).

**Assay for PAI-1 and PAI-2 antigen.** PAI-1 antigen in plasma and placental samples was quantified using a two-site immunoonasay according to procedures described previously. PAI-2 antigen in samples was quantified by a commercially available enzyme-linked immunosorbant assay (Tint Elize PAI-2; American Diagnostica, Greenwich, CT).

**Immunohistochemistry.** Immunohistochemical staining was performed using a three-step avidin-biotin-peroxidase method as described in detail previously. Briefly, fixed and paraffin-embedded placental tissue blocks were cut into 3- to 5-μm sections using a microtome, placed onto slides coated with polylysine, and air dried. The sections were deparaffinized in xylene, cleared in 95% ethanol, incubated (22°C, 10 minutes) in 3% hydrogen peroxide in methanol, and rehydrated through a graded ethanol. After washing with Tris-buffered saline (TBS; 0.05 mol/L Tris-HCl/0.15 mol/L NaCl, pH 7.4), the sections were treated with an increasing concentration of Triton X-100 (0.1% to 1%) in TBS for permeabilization. To unmask PAI immunoreactivity, the sections were incubated (37°C, 5 minutes) with 0.23% (wt/vol) pepsin (2,830 U/hg; Worthington Biochemical Corp, Freehold, NJ) in 0.1 N HCl. Tissue sections were subse- quently blocked with normal serum to prevent nonspecific binding by incubation (1 hour, 22°C) with either 1% normal goat serum in TBS for PAI-1 antigen or 1% normal rabbit serum for PAI-2. Then the sections were incubated with either 10 μg/mL of affinity-purified rab- bit antihuman PAI-1 or either 10 μg/mL of affinity-purified goat antihuman PAI-2 (American Diagnostica) or 5 μg/mL of preimmune goat IgG (American Diagnostica). After washing with 1% Triton-TBS (3 × 3 minutes), the appropriate secondary antibody (i.e., biotinylated goat antirabbit IgG or biotinylated rabbit antigen IgG; Jackson Immunoresearch Laboratories, Inc, West Grove, PA; 1:100 dilution) was added (22°C, 15 minutes). The tissue sections were washed again with 1% Triton-TBS (3 × 3 minutes), incubated (22°C, 10 minutes) with the streptavidin-peroxidase conjugate (Jackson Immunoresearch Laboratories), washed with 1% Triton-TBS (3 × 3 minutes), and incubated (22°C, 15 minutes) with the chromogen amni- ethylcarbazole/hydrogen peroxide mixture (Jackson Immunoresearch Laboratories) that results in a reddish-brown deposit indicative of positive immunoreactivity. Finally, the sections were counterstained with Mayer’s hematoxylin for 3 minutes at room temperature, rinsed well with tap water, and mounted in GVA-mount (Zymed, San Francisco, CA).

**In situ hybridization.** A PAI-1 cDNA fragment containing nucleo- tides 1 to 1085 in pGEM-32 was used for the preparation of anti- sense and sense riboprobes by in vitro transcription in the presence of 35S-UTP (specific activity, 1,200 Ci/mmol; Amersham, Arlington Heights, IL) using SP6 RNA polymerase or T7 RNA polymerase, respectively. The DNA template was removed by digestion using RQ1 DNase for 15 minutes at 37°C and the riboprobes purified by phenol extraction and ethanol precipitation, and the probes were used at a specific activity of 2 × 108 cpmpg of riboprobe. After in situ hybridization of the 35S-labeled antisense probe with the tissue sections, the slides were coated with Kodak NTB2 emulsion (Eastman Kodak, Rochester, NY) and exposed in the dark at 4°C for 2 to 12 weeks. Slides were developed for 2 minutes in Kodak D19 developer, fixed, washed, and counterstained with hematoxylin/eosin that stains nuclei blue. Parallel sections were analyzed using a sense...
Overall clinical data

Age (yrs)

Mean ± SD

28 ± 7

Range

21-37

Gestational age at sampling (wks)

Mean ± SD

37 ± 3

Range

32-40

Birth weight (g)

Mean ± SD

1,622 ± 625

Range

700-2,400

Placental weight (g)

Mean ± SD

348 ± 105

Range

180-500

PAIs in PPP

PAI-1 in PPP (ng/mL)

Mean ± SD

69 ± 21

Range

40-105

PAI-2 (ng/mL)

Mean ± SD

94 ± 45

Range

42-184

PAIs in placental extracts

PAI-1 (ng/mg)

Mean ± SD

51 ± 22

Range

22-96

PAI-2 (ng/mg)

Mean ± SD

168 ± 106

Range

30-333

Abbreviation: NS, not significant.

RESULTS

 Plasma and placental PAI levels in the clinical groups. Table 1 summarizes several pertinent features of the clinical population analyzed in this study. For example, no differences were observed between the three clinical groups in relation to their gestational age and the age of the women. Immunologic quantitation of PAI-1 showed a significant correlation (r = .68, P < .001) between the levels for this inhibitor in the plasma and the levels in the placental extracts obtained from the women classified into these three groups (Fig 1A). Thus, the higher PAI-1 levels previously detected in the plasma of PE/IUGR patients5,14 correlated with higher levels of PAI-1 antigen in the placenta of these patients (group B: 121 ± 38 ng/mg) when compared with the levels for this inhibitor present in extracts of placentas obtained from normal (43 ± 17 ng/mg) and pregnancies complicated solely with IUGR (51 ± 22 ng/mg) (Table 1). In light of the reduced newborn birth weight of both PE/IUGR patients (group B) and the patients with IUGR (group C), the elevated placenta PAI-1 levels of only group B resulted in a clustering of the individual data points into three distinct populations when the newborn birth weight was compared with the PAI-1 levels in either the plasma (Fig 1B) or in the placenta (Fig 1C).

Table 1. Statistical Comparison of Data Obtained From the Three Clinical Groups

<table>
<thead>
<tr>
<th>Overall clinical data</th>
<th>Normal Preg Group A</th>
<th>Severe PE With IUGR Group B</th>
<th>IUGR Without PE Group C</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>n = 10</td>
<td>n = 8</td>
<td>n = 11</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28 ± 7</td>
<td>28 ± 5</td>
<td>NS</td>
<td></td>
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<tr>
<td>Range</td>
<td>21-37</td>
<td>21-37</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gestational age at sampling (wks)</td>
<td>Mean ± SD</td>
<td>37 ± 3</td>
<td>32-40</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>Mean ± SD</td>
<td>1,622 ± 625</td>
<td>348 ± 105</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>Mean ± SD</td>
<td>348 ± 105</td>
<td>180-500</td>
<td></td>
</tr>
<tr>
<td>PAI-1 in PPP</td>
<td>Mean ± SD</td>
<td>69 ± 21</td>
<td>40-105</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Range</td>
<td>40-105</td>
<td>42-184</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>PAI-2 (ng/mL)</td>
<td>Mean ± SD</td>
<td>94 ± 45</td>
<td>42-184</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Range</td>
<td>42-184</td>
<td>42-184</td>
<td>NS</td>
<td></td>
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<tr>
<td>Range</td>
<td>30-333</td>
<td>30-333</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
In addition to alterations in the plasma levels of PAI-1 in PE, reduced levels of PAI-2 in plasma of women whose pregnancies were complicated with IUGR have been reported. An analysis for PAI-2 antigen in the various samples showed a significant correlation between the levels of PAI-2 in plasma and the levels for this inhibitor in placental extract (plasma vs placental PAI-2: $r = .63$; Fig 1D). Furthermore, significant positive correlations were observed in all the clinical groups between newborn weight and either plasma PAI-2 concentration ($r = .75$; Fig 1E) or placental PAI-2 concentration ($r = .74$, Fig 1F). Thus, the individuals who delivered small-for-gestational-age infants were found to have significantly reduced placenta PAI-2 levels (group B: $209 \pm 144$ ng/mg, $P < .001$; group C: $169 \pm 106$ ng/mg, $P < .0001$) than present in normal placentas ($535 \pm 98$ ng/mg) (Table 1).

**Immunohistochemical localization of PAI-1 and PAI-2 in placental tissues.** Immunohistochemical staining for PAI-1 and PAI-2 was initially used to investigate the distribution of these inhibitors within the placentas of these three groups. As described by Feinberg et al, weak PAI-1 immunoreactivity was observed in the syncytiotrophoblast cells from the normal placentas studied (Fig 2A shows a representative syncytiotrophoblast area from a normal placenta). No PAI-1 signal was observed in the endothelial cells (ECs) of these cells could be identified.
Fig 2.
in parallel sections by positive stained using an antibody to von Willebrand factor (data not shown). Weak PAI-1 immunoreactivity was also observed in the syncytiotrophoblasts of the 11 placentas from the UGR group (Fig 2B), whereas prominent PAI-1 immunostaining was observed in numerous villous syncytiotrophoblast cells from the eight PE placentas (Fig 2C shows a representative syncytiotrophoblast area from one of the eight PE patients). Moreover, extensive infarction areas (infarcts involved >20% of total villous tissue) were observed in five of the eight PE patients studied. An increase in PAI-1 mRNA was observed in two placentas from severe PE patients (Fig 3, lanes 1 and 4) in comparison with the PAI-1 mRNA level in the placenta from a normal pregnancy (Fig 3, lane 3) and from an IUGR pregnancy (Fig 3, lane 2).

**DISCUSSION**

The plasminogen activation system appears to be regulated in the human female during ovulation, blastocyst implantation, and pregnancy. Two distinct fast-acting inhibitors of PAs have been identified, and both immunologic and molecular probes are available for analyzing the cellular expression of these two inhibitors. Immunologic analyses have shown that both PAI-1 and PAI-2 are present in normal human placental tissue and that plasma levels for both inhibitors continuously increase during the course of pregnancy. A number of published reports have raised the possibility that abnormal production of these inhibitors during pregnancy may not only be correlated with but may contribute to certain obstetric pathologies.

**Detection of PAI-1 mRNA in placental samples.** The elevated PAI-1 concentration and immunostaining of the PE samples may have occurred as a result of an altered deposition of this inhibitor in the placenta or because of altered PAI-1 production within placenta. To define the levels of PAI-1 mRNA in the placental tissue, we have used in situ hybridization. Analysis of paraffin sections of a placenta obtained from a healthy normotensive woman using ³⁵S-labeled antisense riboprobes for PAI-1 did not show any positive signal after 2 weeks of exposure, and only a weak signal was observed after 10 weeks exposure to the NTB2 emulsion (Fig 2, Q and F, respectively, n = 10). In contrast, a strong positive signal for PAI-1 mRNA in villous syncytiotrophoblast from PE patients was observed after 2 weeks of exposure (Fig 2L, n = 5). A strong positive signal for PAI-1 mRNA was also observed in infarction areas (Fig 2R, n = 5). When a sense probe was used as a control in these experiments, no specific signal was detected in placentas after 12 weeks of exposure.

To confirm that the level of PAI-1 mRNA in the placental tissue was elevated in PE patients, total RNA was extracted from placentas of pregnant women from each of the three groups and PAI-1 mRNA was analyzed by Northern blotting. An increase in PAI-1 mRNA was observed in two placentas from severe PE patients (Fig 3, lanes 1 and 4) in comparison with the PAI-1 mRNA level in the placenta from a normal pregnancy (Fig 3, lane 3) and from an IUGR pregnancy (Fig 3, lane 2).
To determine the distribution of these inhibitors within the placentas of the different clinical groups, immunohistochemical analysis for PAI-1 and PAI-2 were used. Prominent PAI-1 immunoreactivity was detected within the infarction areas and in numerous syncytiotrophoblast cells from PE/IUGR placentas in comparison with the weak immunoreactivity observed in placentas from the IUGR group (Fig 2) or reported for placentas from normal pregnant women.24 In contrast, a decrease in PAI-2 immunoreactivity was detected in syncytiotrophoblasts from all IUGR placentas (Fig 2) in comparison with the prominent PAI-2 staining reported for normal placentas.23,24 In situ hybridization analysis was subsequently used to document that the increased cellular staining for PAI-1 antigen correlated with an increased PAI-1 mRNA content. A strong positive hybridization signal was obtained in villous syncytiotrophoblasts and in infarction areas from placentas of PE/IUGR patients after 2 weeks of exposure (Fig 2). In comparison, a positive signal for PAI-1 mRNA in normal placentas required a 10-week length of exposure to the photographic emulsion. Because cultured trophoblasts have been reported to contain both the 2.3- and 3.2-kb mRNA transcripts for PAI-1,25 we examined placenta samples from a representative of all three groups by Northern analysis for these two PAI-1 mRNA species. Our data indicate that both transcripts of PAI-1 mRNA are increased in two placentas from severe PE/IUGR patients in comparison with placenta tissue from a normal pregnancy and from an IUGR pregnancy (Fig 3).

Although data presented in this study document that the expression of PAI-1 is elevated in PE/IUGR placenta, little information is available on the factors that regulate the production of PAI-1 within either normal or PE/IUGR placentas. Recent data indicate that a wide variety of compounds (eg, cytokines, growth factors, etc) are capable of affecting the expression of PAI-1.15,26 The observation that normal human27 and rat28 placentas are capable of producing several different cytokines, hormones, and growth factors raises the possibility that changes in the levels of one or more of these molecules may modulate the expression of PAI-1 in patients suffering with PE and/or IUGR. For example, the reduced uteroplacental blood flow often prominent in pregnancies complicated with PE and/or IUGR45 could increase the local concentration of a particular cytokine or growth factor. Moreover, the changes in the placental vasculature and deciduous spiral arteries, commonly observed in PE patients, often result in hypovascularity of the villi, placental infarction, and ischaemia.43-47 This latter condition is known to affect vascular PAI-1 production.48 In light of the high second-order rate constant of PAI-1 (Ki = 10-7 [mol/L]1 s-1) against single-chain t-PA (ie, the predominant form of t-PA in the vascular system) in comparison with the low second-order rate constant of PAI-2 (Ki = 9 × 10-10 [mol/L]1 s-1) against this form of the enzyme,49 the localized elevated placenta PAI-1 levels observed in PE/IUGR patients would be expected to rapidly neutralize single-chain t-PA and thus play a role in the thrombotic complications associated with this disease. Elucidation of the mechanisms that regulate the altered production of PAIs in a patient’s placenta should shed light on the processes that underlie these pathologic conditions.

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