Original Article

Early Pregnancy Plasminogen Activator Inhibitor-1 Levels in Nigerian Women and its Relationship with Preeclampsia

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Abstract

Aim: This study compared early plasma levels of plasminogen activator inhibitor-1 (PAI-1) in normal pregnancy and preeclampsia and determined its relationship with disease severity. **Subjects and Methods:** This was a prospective cohort study of 195 normotensive, aproteinuric pregnant women without prior history of gestational hypertension. The women were attending the Antenatal Clinic at The Lagos University Teaching Hospital and were within 24 weeks gestation at recruitment. The outcome measures were PAI-1, systolic blood pressure (SBP), diastolic blood pressure (DBP), and significant proteinuria. The endpoint of the study was the development of preeclampsia. The diagnosis of preeclampsia was made by the attending Obstetrician. The data were analyzed using the IBM SPSS statistical software. Statistical significance was set at $P < 0.05$. **Results:** First trimester PAI-1 levels were significantly higher in the women who later developed preeclampsia compared to those who had a normal pregnancy ($P < 0.0001$). In these group of women who later developed preeclampsia, PAI-1 had an inverse relationship with gestational age ($r = 0.878$) whereas in normal pregnancy, PAI-1 and gestational age had a direct relationship ($r = 0.017$). Second trimester systolic and DBP values were also significantly higher in the women who later developed preeclampsia compared to normal pregnancy, $P = 0.007$ and 0.004, respectively. There was, however, no correlation between PAI-1 values and SBP, DBP and proteinuria in the women who developed preeclampsia. **Conclusion:** Plasma levels of PAI-1 are increased early in pregnancies complicated by preeclampsia, but the lack of correlation of this marker with disease severity may limit its clinical utility.

Keywords: *Disease severity, plasminogen activator inhibitor-1, preeclampsia, pregnancy*

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Introduction

Maternal adaptations in pregnancy which contribute to reduced risk of hemorrhage and well-being of mother and fetus, include changes in the expression of the coagulation and fibrinolytic proteins.[1] Increased fibrinogen and some coagulation factors of the intrinsic and extrinsic coagulation pathways have been documented in pregnancy, tilting the balance toward a procoagulant state.[1,2]

Changes also occur in the fibrinolytic system in pregnancy.[3] Normal pregnancy has been associated with an increase in plasma levels of the plasminogen activators (PAs)-tissue PA (t-PA) and urokinase-type PA (u-PA) as well as in the PA inhibitors type 1 (PAI-1) and type 2 (PAI-2).[3] The greater increase in the PAI-1 levels, however, surpasses that of t-PA and a tendency toward a procoagulation state is maintained in pregnancy.[4]

PAs, t-PA and u-PA, are serine proteases which convert the inactive plasminogen to the active protease plasmin.

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Plasmin is the primary enzyme responsible for removing fibrin clots and preventing thrombosis.[5] The activity of the PAs is regulated by specific PAI-1 and 2.[5] During pregnancy, PAI-1 is a primary inhibitor of t-PA, a key protein involved in fibrin degradation.[5,6]

Although dramatic changes occur in the coagulation and fibrinolytic systems in normal pregnancy, a delicate homeostatic balance is maintained which facilitates blastocyst implantation and prevents excessive clotting or hemorrhage.[7] In certain disorders of pregnancy such as preeclampsia, there is a more pronounced exacerbation of the procoagulable state, distorting the delicate balance and threatening maternal and fetal well-being.[8]

Preeclampsia is a multisystem disorder peculiar to pregnancy. It is characterized by hypertension and proteinuria and by a variable affectation of many organ/systems including the liver, renal, hemostatic, and central nervous systems.[9] Despite complicating about 5–10% of pregnancies[10] and contributing significantly to maternal and perinatal morbidity and mortality,[11] the exact pathophysiologic mechanisms leading to the disorder remains poorly understood.[9] Placental ischemia caused by defective trophoblastic invasion in early pregnancy has been implicated in the pathogenesis of preeclampsia.[9] Bioactive factors released by the ischemic placenta cause widespread endothelial damage responsible for the manifestations of the disorder.[9]

Many studies have reported increased plasma levels of PAI-1 in preeclampsia.[8,12,13] It is not clear, however, whether the increased levels is indicative of a causative role in preeclampsia or is as a result of the endothelial damage that occurs in preeclampsia.[14,15] There is also is a potential role for PAI-1 in the early prediction of preeclampsia.[16,17] Studies of polymorphisms in genes encoding the PAI-1 protein and their relationship with preeclampsia are also areas of current research interest.[18,19]

There is a paucity of data from Nigeria on PAI-1 and its relationship with normal pregnancy and pregnancy complicated by preeclampsia. This study compared early pregnancy plasma levels of PAI-1 in normal pregnancy and preeclampsia and determined its relationship with disease severity.

Subjects and Methods

This was a prospective cohort study of 195 normotensive, aproteinuric pregnant women without prior history of gestational hypertension. The women were attending the Antenatal Clinic at The Lagos University Teaching Hospital and were within 24 weeks gestation at recruitment. Pregnant women with multiple gestation and sickle cell disorder were excluded from the study. The outcome measures were PAI-1, systolic blood pressure (SBP), diastolic blood pressure (DBP) and significant proteinuria. The endpoint of the study was the development of preeclampsia. Pregnant women were diagnosed with preeclampsia if they developed hypertension with SBP ≥140 mmHg and/or DBP ≥90 mmHg and ≥2+ of proteinuria.[20] The blood pressure was determined using the Accoson's Mercury Sphygmomanometer (cuff size 15 cm × 43 cm). The subjects were seated and rested for 5 min before measurement. The SBP was taken at the first Korotkoff sound and diastolic at the fifth Korotkoff sound.[20]

Preeclampsia was defined as the on set, after 20 weeks gestation of proteinuria (≥300 mg/24 h or ≥100 mg/L, equivalent to ≥2+ on dipstix urinaysis) on at least two random urine samples at least 4–6 h apart but not more than 7 days apart, and SBP ≥140 mmHg or a DBP ≥90 mmHg measured using an appropriate sized cuff repeatable at least 4–6 h apart but not more than 7 days apart and a remission of these symptoms by 6 weeks postpartum.[20]

Approval for the study was obtained from the hospital's Ethics Committee and consenting subjects signed an informed consent form. At recruitment, initial blood pressure measurements were recorded and blood was collected for PAI-1 assay.

Information on the index pregnancy and past obstetrics history were obtained using a structured questionnaire. Pregnancy was dated from the last menstrual period and confirmed by clinical examination and ultrasonography scanning. The women were then followed up with blood pressure measurements and urinalysis at antenatal visit till the development of preeclampsia.

PAI-1 levels in plasma were determined from citrated plasma using an ELISA technique[21] on Acurex Plate Read (Acurex Diagnostics, Ohio, USA, 419-872-4775).

The data were analyzed using the IBM Statistical Software for Social Sciences (SPSS, Inc., Chicago, IL) version 20.0. ANOVA, Mann–Whitney *U*-test and Spearman's correlation were employed for the analysis. Statistical significance was set at $P < 0.05$.

Results

One hundred and ninety-five pregnant women participated in this study. Twelve women (6.2%) developed preeclampsia, seven (3.6%) developed pregnancy-induced hypertension (PIH), and 176 women (90.2%) had a normal pregnancy. Table 1 shows the demographic and clinical characteristics of the study cohort.

The categorical variables (age group and parity) are presented as numbers and percentages and the Chi-squared test was used for the statistical analysis. The continuous variables (age, body mass index [BMI], gestational age, SBP, DBP) are presented as mean ± SD and ANOVA were used for statistical analysis for comparing the three groups of data; preeclampsia, PIH, and control. *Post-hoc* analysis identified the groups contributing to observed differences as designated using the superscripts.[a,b]

At recruitment, all the women had similar maternal age, gestational age, BMI and parity. Despite being normotensive and aproteinuric at recruitment, early blood pressure values were significantly higher in the women who later developed preeclampsia.

Thirty-four women (17.44%) out of the 195 women who participated in the study were recruited in the first trimester of pregnancy, and 161 (82.56%) were in the second trimesters. Four (33.33%) of the 12 women who later developed preeclampsia were in their first trimester of pregnancy at recruitment, and eight (66.66%) were in their second trimesters. Of the women who later had normal pregnancies, 28 (15.9%) were in their first trimester, and 148 (84.1%) were in their second trimester at the time of recruitment.

For the women who developed preeclampsia, the first-trimester median value for PAI-1 was 5.29 ng/ml and the range was from 4.79 ng/ml to 6.78 ng/ml. In these same group of women, their second trimester PAI-1 values had a median of 1.38 ng/ml and a range of 0.328 ng/ml to 2.71 ng/ml.

In the women who had normal pregnancy, the first-trimester median value for PAI-1 was 1.30 ng/ml and the range was from 0.425 ng/ml to 4.38 ng/ml. In these women, their second trimester PAI-1 values had a median of 1.73 ng/ml and a range of 0.102 ng/ml to 9.10 ng/ml. The mean gestational age for the diagnosis of preeclampsia was 38.2 ± 2.36 weeks with a range of 35–41 weeks. Three of the four women with high first trimester PAI-1 values developed severe preeclampsia whereas the others developed a mild form of the disease.

Table 2 shows the first trimester and second trimester PAI-1 levels of study participants who later developed preeclampsia and those who had normal pregnancy.

Table 3 shows the correlation of PAI-1 with markers of disease severity in preeclampsia.

Figure 1 shows an inverse relationship between PAI-1 levels and gestational age in the women who developed preeclampsia.

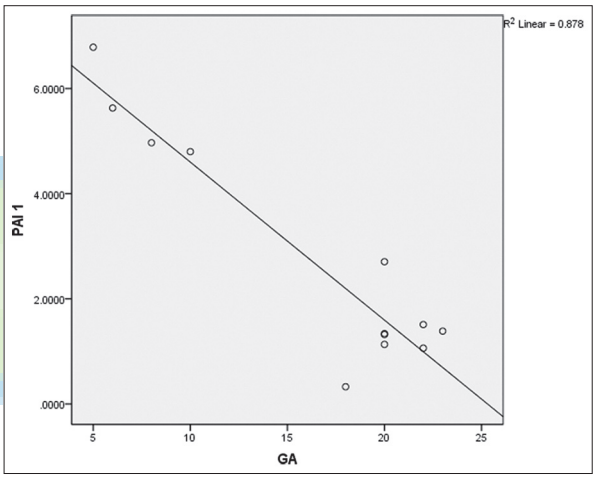

Figure 1: The relationship between plasminogen activator inhibitor-1 values and gestational age in women with preeclampsia

Table 1: Demographic and clinical characteristics of the study cohort at recruitment

Characteristics	All participants (*n*=195) (%)	Preeclampsia (*n*=12) (%)	Pregnancy induced hypertension (*n*=7) (%)	Normal pregnancy (*n*=176) (%)	*P*
Age (years)					
20-30	105 (53.85)	4 (33.33)	3 (42.86)	90 (51.13)	0.079
31-40	86 (44.10)	8 (66.66)	4 (57.14)	79 (44.89)	
>40	4 (2.05)	0 (0.00)	0 (0.00)	7 (3.98)	
Mean age	30.62±4.58	33.00±4.83	32.57±4.99	30.38±4.51	0.082
BMI (kg/m^2)	27.02±4.97	29.17±4.2	25.43±5.65	26.94±4.97	0.223
Gestational age (weeks)	17.49±4.35	18.25±4.69	19.71±1.97	17.35±4.39	0.306
SBP (mmHg)	108.76±8.33	114.83±8.96[a]	113.57±12.48	108.15±7.91[b]	0.007*
DBP (mmHg)	67.77±7.14	74.17±9.96[a]	69.29±10.96	67.27±6.56[b]	0.004*
Parity					
Nullipara	87 (44.61)	5 (41.66)	2 (28.57)	80 (45.45)	0.286
Primipara	54 (27.69)	1 (8.33)	3 (42.85)	50 (28.40)	
Multipara	54 (27.69)	6 (50.00)	2 (28.57	46 (26.13)	

*Statistically significant; [a,b]The groups contributing to the observed differences using *post hoc* analysis. BMI=Body mass index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure

Table 2: First trimester and second trimester plasminogen activator inhibitor- 1 levels of study participants who developed preeclampsia and those who had normal pregnancy

Trimester	Preeclampsia (*n*=12)	Normal pregnancy (*n*=176)	*P*
First trimester	5.62±1.31 (*n*=4)	1.54±0.95 (*n*=28)	<0.0001*
Second trimester	1.51±0.62 (*n*=8)	2.20±1.65 (*n*=148)	0.17

*Statistically significant. PAI-1=Plasminogen activator inhibitor-1

Table 3: Correlation of plasminogen activator inhibitor-1 with clinical parameters in pregnancy

Clinical parameters	Spearman's correlation coefficient	*P*
SBP	−0.047	0.525
DBP	0.062	0.400
Proteinuria	0.049	0.648

There was no significant correlation of PAI-1 with blood pressure and proteinuria. PAI-1=Plasminogen activator inhibitor-1; SBP=Systolic blood pressure; DBP=Diastolic blood pressure

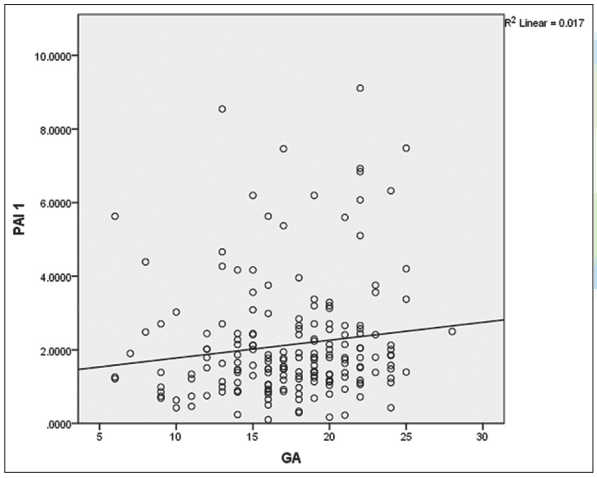

Figure 2: The relationship between plasminogen activator inhibitor-1 values and gestational age in women with normal pregnancy

Figure 2 shows a direct relationship between PAI-1 levels and gestational age in the women who had normal pregnancy.

Discussion

This study reports a statistically significant increase in the first-trimester plasma levels of PAI-1 in women who later developed preeclampsia compared to women who had normal pregnancy but found no difference in the second-trimester values of PAI-1 between the two groups of pregnant women. Reith *et al*.[13] and Gao *et al*.[14] also reported increased plasma levels of PAI-1 in preeclampsia compared to normal pregnancy. PAI-1 has antifibrinolytic activity through inhibition of tissue PA, thus opposing fibrinolysis[22] and promoting a procoagulant state in pregnancy, reducing hemorrhage and promoting clot stability.[1] The increased levels of PAI-1 in preeclampsia may play a role in the initiation of placental damage.[7] An ischemic placenta has been reported to be central to the pathology and pathogenesis of preeclampsia, releasing various bioactive factors that mediate widespread endothelial damage culminating in the maternal syndrome of preeclampsia.[9] Elevated levels of PAI-1 would result in fibrin deposition and occlusive lesions leading to thrombosis of the intervillous or spiral arteries and hence placental ischemia.[7] Authors such as Gow *et al*.[23] and Ho *et al*.[17] found no difference in the PAI-1 levels in women with preeclampsia compared to controls. This could be because these studies did not classify the women into different trimesters or because they had a large proportion of women in the second trimester of pregnancy, in keeping with this study which found similar second-trimester values of PAI-1 in both groups of women who later developed preeclampsia and those who had normal pregnancy. Another reason for finding similar PAI-1 levels in both groups of women may also be because some authors[24] have reported increased PAI-1 levels in early onset, but not late-onset preeclampsia, and some other studies[17,23] have not subclassified preeclampsia into early and late onset disease. This study found an inverse relationship between PAI-1 and gestational age in pregnancies complicated by preeclampsia but found a direct relationship between PAI-1 and gestational age in normal pregnancy.[14] In the pregnancies complicated by preeclampsia, high PAI-1 levels in the first trimester decreased to second- trimester levels comparable to that in normal pregnancy.[23] The hemodynamic changes in pregnancy may explain these observations. Normal pregnancy is characterized by increased blood volume and sodium and water retention leading to volume expansion[25] creating a dilutional effect. Renal plasma blood flow and glomerular filtration rate increase by 75% and 50%, respectively, leading to increased renal clearance.[25] These changes which begin early in pregnancy and peak in the second trimester[26] are exaggerated before the onset of clinical disease in pregnancies complicated by preeclampsia.[27]

The increased PAI-1 level early preeclampsia has been investigated, and a role has been suggested for PAI-1 as an early marker for the prediction of preeclampsia.[13,16]

This study reports a significant increase in the second trimester systolic and DBP values in women who later developed preeclampsia compared to controls before the development of clinically overt hypertension. The increased PAI-1 levels in the first trimester may have set off the cascade of events gradually initiating the

symptomatology of the disorder.[7] The precise role of PAI-1 in the pathogenesis of preeclampsia is however not entirely clear. Genetic studies of polymorphism in the 4G/5G promoter region of the PAI-1 gene which leads to increased gene expression and its association with preeclampsia have yielded conflicting results.[18,19] This study found no correlation between early PAI-1 levels with markers of disease severity such as the systolic and DBP values and proteinuria. This poor correlation with disease severity also reported by other studies,[19,28] downplays a causative role for PAI-1 in preeclampsia. PAI-1is a protein produced by endothelial cells, some studies have reported PAI-1 to be a marker of endothelial damage.[12,29] A longitudinal study will be required to determine whether the changes in PAI-1 levels observed in pregnancies complicated by preeclampsia is a cause or a reflection of the endothelial damage associated with the disorder.

Conclusion

Plasma levels of PAI-1 increased early in pregnancies complicated by preeclampsia but did not correlate with markers of disease severity. This may limit its role as a marker of preeclampsia.

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Conflicts of interest

There are no conflicts of interest.

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