Fibrinolytic proteins of normal pregnancy and pre-eclamptic patients in North West Nigeria

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Abstract

Background: The hypercoagulability of pregnancy is exaggerated in pre-eclamptic state because of endothelial activation with resultant production of some endothelial derived proteins that are said to be inhibitors of fibrinolysis. This study compares these proteins like tPA, PAI-1 and D-dimers in normal pregnant women and the pre-eclamptic women.

Methodology: This was a comparative cross-sectional study. Eighty-five pre-eclamptic women were recruited as subjects and eighty five age, trimester and parity matched normotensive pregnant women as controls. Levels of PT, aPTT, tPA, PAI-1, D-dimer protein were determined in blood samples of subjects and controls. Urinalysis was performed with dipstick method on their urine samples. Data generated was analysed using the IBM®SPSS 20.0 (2011) soft ware packages and the level of significance was a p-value <0.05.

Results: The mean age of the respondents was 29.9±5.2 years. The median(25^{th}-75^{th} percentile) values of D-dimer, tPA, and PAI-1 of subjects were 730 (305.000-1560.000ng/ml), 0.11 (0.065-0,300ng/ml) and 3.65 (2.970-4,400ng/ml) respectively which were significantly higher than the corresponding values in the controls of 520 (24.000-1030.000ng/ml), 0.05 (0.040-0.090ng/ml and 2.650 (2.125-3.400ng/ml) respectively, p<0.05 each.

Conclusion: The abnormal levels of PAI-1,D-dimer and tPA imply that they contribute to the exaggerated hypercoagulabilty state in pre-eclampsia thus, measuring their levels can help in the management of the condition.

Keywords: Fibrinolysis, pregnancy ,pre-eclampsia.

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Introduction

Normal haemostasis is a complex network of interactions with positive and negative feedback loops which integrate at least five major components namely the blood vessels, the platelets both in number and functions, the coagulation factors and their co-factors, coagulation factor inhibitors and the fibrinolytic pathway.[1]

Activation of the coagulation factors, the blood vessels and platelets results in the formation of a firm, definitive and stable haemostatic plug while the removal of the product of coagulation, namely fibrin from the circulation is the function of the fibrinolytic system. This makes fibrinolysis a normal response to vascular injury similar to coagulation.[1]

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Pregnancy, a physiological condition however is associated with a profound change in both coagulation as well as the fibrinolytic systems.[2,3] These changes are such that coagulation is enhanced by the virtue of increased synthesis of all the coagulation factors most especially fibrinogen, factors VIII, IX, X and a significant reduction in the fibrinolytic pathway due to increased synthesis of plasminogen activator inhibitors type 1 and 2, all these making pregnancy a hypercoagulable state.

The purpose of these changes is to minimize bleeding during and after placental separation at parturition.[4] The changes in the coagulation and fibrinolytic system is even more pronounced in pregnancy induced hypertension and in eclampsia.

Pre-eclamptic toxaemia (PET) is a disease of pregnancy occurring after twenty weeks gestation, and characterized by blood pressure of 140/90mmHg or above-on two occasions about 4-6 hours apart with a preceding normal blood pressure. The increase in blood pressure is associated with significant proteinuria (300mg in 24 hours). These features all resolve completely by the sixth postpartum week.[5] Pre-eclampsia is a pregnancy-specific syndrome of decreased organ perfusion due to vasospasm and endothelial activation.[6]

Roberts and colleagues proposed that alterations in endothelial cell function by activating agents, produced by the placenta, initiates the clinical syndromes of pre-eclampsia.[7] Also, unknown factor(s), likely from the placenta are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium.[8] Therefore, endothelial cell injury or activation is believed to play a central role in pre-eclampsia and may underlie the haemostatic changes observed in this syndrome.[9] Factors like, tPA, fibronectin, PAI-1 are endothelial derived and may be markers of endothelial activation in pre-eclampsia.[10,11]

The localized elevated concentration of placental PAI-1 and PAI-2 protein and mRNA observed in PET patient would be expected to foster the deposition of fibrin and thus play a role in the complications associated with the disease for example, fibrin deposition in placental and other organs causing infarction.[12]

Therefore pre-eclampsia is characterized by a maternal hypercoagulable state,intravascular coagulation, microthrombosis in several organs and impairment of the uteroplacental circulation. Also, the evidence of this was suggested by Tanjung,who described PET as a state of enhanced thrombin generation with alteration in the coagulation pathway.[13,14]

Based upon this background, this study determined and compared the PCV, platelet count, Prothrombin time (PT), activated partial thromboplastin time (aPTT), tPA, PAI-1,D-dimer, of pre-eclamptic subjects and normotensive non-proteinuric pregnant women and to find out if there would be significant differences in their values.

Methodology

The study was carried out at the Obstetrics emergency ward and antenatal clinic of Obstetrics & Gynaecology department, and the department of Haematology and Blood transfusion, all of the University of Ilorin Teaching Hospital (UITH), Ilorin between November 2012 and February 2013, about three months..

It was a comparative cross-sectional non-intervention based study that included 85 subjects with pre-eclampsia aged 18-42 years who were yet to be delivered of their-pregnancies. Also, age, parity and trimester matched normotensive non-proteinuric pregnant women were recruited as controls. Sample size was calculated using the formular that compares Two Group Means[15]; $n=1 + 2c(s/d)2$, where n= minimal sample size, c= 10.5(a constant) if $\alpha= 0.05$ and $1-\beta=0.9$, s= Standard deviation(SD) of D-dimer in pre-eclampsia from the literature, d= difference in SD of D-dimer in pre-eclamptic and SD of D-dimer in normotensive pregnant women, where SD of D-dimer in pre-eclampsia from the literature[16] = 1.07μg/ml and SD of D-dimer in normotensive pregnant women[16] = 0.51 μg/ml and d=1.07- 0.51=0.56 μg/ml. Therefore, the calculated sample size was 77. After correcting for an anticipated attrition rate of 10%, the sample size was 85.

Pre-eclampsia was diagnosed according to the criteria of the National Blood Pressure Education Program Working Group as blood pressure of 140/90mmHg and confirmed proteinuria (0.3g/L/24h) with or without previous evidence of an underlying hypertensive

disorder.[17] Confirmed pregnant women beyond 20 weeks gestation who were normotensive and had no proteinuria were recruited as controls.

However, pregnant women with arterial or venous thrombosis, post-operative and trauma cases, pregnant women with significant medical disorders such as, diabetes mellitus,chronic renal failure, or on any form of anticoagulant therapy and those who declined consent were excluded from the study.

Ethical clearance was obtained from the Ethics and Research Committee of the University of Ilorin Teaching Hospital. Written informed consent was obtained from the patients after explaining the aim of the study and the procedure involved. A study pro-forma was used to obtain information on socio-demographic parameters and obstetric history.

Eight and half millilitres (ml) of venous blood was taken by standard sterile procedure from each subjects included in this study. Four and half ml out of the whole blood was put plastic tubes containing half ml sodium citrate(3.8%), and four ml was dispensed into a bottle containing ethylene diamine tetra acetic acid(EDTA). Both bottles were gently mixed to allow proper mixture of the blood sample with the anticoagulant.

The sample in the citrate bottle was centrifuged for 20 mins at 3500g to obtain a platelet-poor supernatant, and the supernatant plasma stored at -800C until assayed. The blood in the EDTA bottle was used for the estimation of packed cell volume (PCV), platelet count within two hours of collection. The same method of blood collection and storage was done for the controls. Also, a urine sample from each patient and contol subject was obtained in a universal plain bottle and analyzed-immediately by urinalysis.

The following tests were carried out on the blood sample: PCV, Platelet count,Prothrombin time, Activated partial thromboplastin time (aPTT), D-dimer assay,Tissue plasminogen activator, Plasminogen activator inhibitor-type 1.

The platelet count and PCV was performed on all samples using the sysmex KX21® (Sysmex Corporation, Kobe, Japan) automated cell counter.

Prothrombin Time was determined using commercially prepared reagents based on the one stage test of Owren.

Activated Partial Thromboplastin Time was determined using commercially prepared reagents based on the method of Proctor and Rapaport. Tissue plasminogen activator was assay using a AssayMax Human tPA ELISA kit(Product of Saint Charles, Missouri, USA). Plasminogen activator inhibitor type-1 (PAI-1) was determined using AssayMax Human PAI-1 ELISA kit (Product of Saint Charles, Missouri, USA). Assessment of D-DIMER ASSAY was by TECHNOZYM D-dimer ELISA kit (Product of Technozyme, Austria) .

Data analysis was done using the IBM® SPSS version 20.0 (IBM corporation,Virgina, USA) 2011 for windows software package. After the generation of frequency tables and simple proportions, Student's t-tests and Mann-Whitney U tests were used to identify significant differences for normally distributed continuous variable and the skewed data respectively. Fisher's exact test were used for testing the significance of associations from cells with small numbers (<5) as appropriate.

Results

The mean age of respondents was 29.9±5.2, majority 72(84.7%) were 19-35years and only 2(2.4%) were aged ≤18 years while 11(12.9%) were aged >35years.Most of the respondents were married and had tertiary level of education. Also, 36(42.4%) of the respondents were primigravida while 28(32.9%) and 21(24.7%) weremultigravida and granmultip respectively as shown in Table I.

Table I: Socio-demographic and reproductive characteristics of respondents

Variable	Subjects n(%)	Control n(%)
Age group(Years)		
≤18	2(2.4)	2(2.4)
19-35	72(84.7)	72(84.7)
>35	11(12.9)	11(12.9)
		p
X^2=0.0 p-value=1.000		
Range	18-42	18-40
Mean ±SD	29.9±5.2	29.9±5.2
Marital status		
Single	2(2.4)	-
Married	83(97.6)	85(100.0)
P value=0.497		
Level of Education		
No formal education	1(1.1)	-
Primary	1(1.1)	7(8.2)
Secondary	33(38.8)	27(31.8)
Tertiary	50(58.8)	51(60.0)
X^2=6.1; p-value=0.106		
Religion		
Islam	60(70.6)	58(68.2)
Christianity	25(29.4)	27(31.8)
X^2=0.217; p-value=0.641		
Occupation		
Civil servant	24(28.2)	33(38.8)
Trading	34(40.0)	30(35.3)
House-wife	20(23.6)	22(25.9)
Student	7(8.2)	-
X^2=6.1; p-value=0.106		
X^2=8,766; p-value=0.033		
Gestational age(Weeks)		
20-26	17(20.0)	17(20.0)
27-39	68(80.0)	68(80.0)
Parity		
Primigravida	36(42.4)	36(42.4)
Multigravida	28(32.9)	28(32.9)
Granmultip	21(24.7)	21(24.7)
X^2=0.0; p-value=1.000		

Table II shows the median (25th-75th percentile values of D-dimer, tPA, and PAI-1 of subjects as730 (305.000-1560.000ng/ml), 0.11 (0.065-0.300ng/ml)and 3.65 (2.970-4.400ng/ml) respectively which were significantly higher than the corresponding values in the controls of 520 (240.000-1030.000ng/ml), 0.05 (0.040-0.090ng/ml), and 2.65 (2.125-3.425ng/ml) respectively,$p<0.05$ each. However, PT, aPTT and platelet count were not significantly different between pre-eclamptics and controls.

Table II: Haematological and Haemostatic Parameters among pre-eclamptics and controls

Variables	Subjects n=85	Controls n=85	t / Mann Whitney U test	p-value
PT (sec) Mean (SD)	13.90 (1.00)	14.10	0.985	0.328
aPTT (sec) Mean (SD)	35.40 (4.80)	34.40 (1.90)	1.569	0.121
D-dimer (ng/ml)				
Median	730.00	520.00	*2138.500	**0.003**
25^{th}-75^{th} percentile	305.00-1560.00	240.00-1030.00		
tdtpaPA (ng/ml)				
tPA(Median)	0.11	0.05	*1198.000	**0.001**
tPA(25^{th}-75^{th}percentile)	0.065-0.30	0.040-0.09		
PAI-1 (ng/ml)				
PAI-1(Median)	3.65	2.65	*1609.000	**0.001**
PAI-1(25^{th}-75^{th}percentile)	2.98-4.40	2.13-3.40		
Platelet count (X109/L)				
Plateletx 10^9(Median)	161.00	175.00	*2722.500	0.457
Plateletx10^9(25^{th}-75^{th}percentile)	115.00-225.00	160.00-190.00		
PCV(%))				
Mean (SD)	35.40 (4.60)	33.00 (3.40)	3.559	**0.001**

*= Mann Whitney U test

Discussion

In this study pre-eclampsia was commoner in women between 19-35 years .This is not in keeping with previous reports in which pre-eclampsia was commoner in women who were less than 18 years and women older than 35 years of age. It is however similar to the findings reported by Osunkalu and others.[18] The difference in age of occurrence of pre-eclampsia may be due to the higher level of education of the respondents in this study.

The finding of the current study in which pre-eclampsia was commoner among primiparous women is supported by an earlier report,[19] and may be due to the absence of effective immunization against placental antigen by a previous pregnancy among primigravidas.[20]

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are tests of extrinsic and intrinsic pathway respectively. Ordinarily, one would expect that the hypercoagulable state in pregnancy would give shortened PT and aPTT.In this study, values of PT and APTT were not shortened and were similar in subjects

and controls. This finding among normotensive non proteinuric controls is similar to the findings of Jeremiah,[21] but in contrast to some studies in this environment,[22,23,24] where the values of PT and aPTT obtained were in support of an hypercoagulable state.Jeremiah's results on normal pregnant women(subjects)were similar to the results of the normal pregnant women(control) in this study ,although he did not study pre-eclamptics and there was paucity of data on the level of these proteins among pre-eclamptics in this environment.The hypercoagulability has been attributed to increase in level of coagulation factors caused by pregnancy maintaining hormones particularly oestrogen and progesterone which are able to stimulate hepatocytes to produce more coagulation factors.[25] However, nutritional deficiency due to loss of appetite in early pregnancy may counter balance the increase to give apparently normal PT and aPTT values as was found in this study. Also, PT and aPTT were not different in both pre-eclamptics and normotensive pregnant women in this study. This is similar to what was found by Jahromi et al[26] and Mehmet[27] but in contrast to the finding of Awodu.[28] The apparently normal PT and aPTT results among pre-eclamptics in these studies may be due to the result of the balance between the hypercoagulability of normal pregnancy and the production of coagulation inhibitors which increases in pre-eclampsia.[27,29] However, Awodu speculated that the prolonged PT in their pre-eclamptics might be due to quantitative or qualitative abnormalities of factors in the extrinsic pathway of coagulation, while the prolonged aPTT in another study by Awodu might be caused by anti-phospholipid antibodies or lupus anticoagulant.[30]

It is known that the pathogenesis of pre-eclampsia is associated with endothelial cell(EC) dysfunction. This tends to increase the expression of endothelial- derived fibrinolytic proteins, its inhibitor and products in pre-eclamptic subjects more than in normotensive pregnant women. This is supported by the finding in the present study in which plasma levels of endothelially derived tPA and PAI-1 were significantly higher in subjects than controls.

Similar to this, are studies of several researchers.[31], but in contrast to the study of Declerck who reported that PAI-1 level of several pre-eclamptic patients were not different from those obtained in normal pregnancy.[34] The disparity of Declerck study may be attributed to the time of specimen collection.

D-dimer is increased in normal pregnancy because of compensated state of low grade intravascular coagulation; Moreover, this increase shows that, inspite of the marked impairment in fibrinolytic potential, the fibrinolytic system remains functionally active. In this study, values among pre-eclamptics were significantly higher than the controls indicating an increased intravascular coagulation and activation of fibrinolysis among pre-eclamptics.

This is similar to the findings of several researchers,[21,35,36,37] Physiological anaemia occurs in pregnancy because of an increase in blood volume that outweighs the increase in red cell mass, thus, giving anaemia. In this study, the PCV of the pre-eclamptic subjects were higher than the normotensive non-proteinuric group, this is similar to thestudy of Awodu,[28] where PCV was also higher among pre-eclamptics than the controls. The increased PCV may be due to the additional effect of haemoconcentration in pre-eclampsia. The haemoconcentration could be as a result of decrease oncotic pressure which can create a filtration imbalance, further displacing intravascular fluid. Also, endothelial damage can lead to pathologic capillary leakage of fluid further causing the haemoconcentration.

Gestational thrombocytopaenia occurs as a result of haemodilution, increased consumption with reduced life span and increased aggregation of platelets by increased levels of thromboxane A2 at placental circulation.[38,39] Also,pre-eclampsia is also one of the causes of thrombocytopaenia in pregnancy and it is as a result of uncontrolled intravascular platelets activation and fibrin deposition.[40] Surprisingly, Platelet count was not different among subjects and controls in the index study, this is in contrast to a study by Sayin et al.[41] The insignificant difference in platelet count is due to the relative increase in thrombopoetin level in pre-eclampsia.2016

Conclusion

It has been identified that the haemostatic system is actively involved in pre- eclampsia and endothelial derived fibrinolytic proteins are higher in them than in normal pregnancy. Thus, measuring these proteins could improve obstetrics care.

However, there were some limitations to this study, this includes the fact that non-pregnant women were not investigated in this study. Therefore, comparism of measured parameters between pregnant and non-pregnant women could not be done. Thus, the significance of the findings in normal pregnancy could not be substantiated. Also, the fact that the present study was an hospital based has limited its generalizability. Furthermore, most of the subjects presented as emergencies and the baseline blood pressure and body weight couldn't be documented.

Conflict of interest

There was no conflict of interest as this research was self sponsored.

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Contribution

All authors contributed to the study protocol, data collection and the corresponding author did the final draft of the paper.

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