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Original Research Article

Clinical correlates of plasma antithrombin and protein C levels in patients with pre-eclampsia and eclampsia in Sokoto, Northwest Nigeria

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ABSTRACT

Background: Hypertensive disorders of pregnancy complicate 17% of pregnancies in Sokoto, Nigeria with pre-eclampsia and eclampsia accounting for 6% and 4.29% respectively. Pre-eclampsia and eclampsia stand out as major causes of poor pregnancy outcomes with eclampsia contributing 46% of adolescent maternal mortality in Sokoto. These disorders increase risk of venous thromboembolism, DIC, placental abruption, IUGR, premature delivery and recurrent pregnancy loss. The roles of antithrombin and protein C in disease severity and outcomes of pregnancies in pre-eclampsia/eclampsia are subject of recent researches albeit with conflicting findings. The aim of the study was to determine the plasma antithrombin and protein C levels of pre-eclampsia and eclampsia in Sokoto with a view to assessing any relationship with clinical severity and pregnancy outcomes.
Methods: Prospective comparative study involving 31 each of pregnant women with pre-eclampsia, eclampsia and normotensive pregnancy. Plasma antithrombin and protein C levels were determined via kinetic method using S4 Nortek semi-automated coagulometer. Data analysis was performed using SPSS version 21.0.
Results: The mean plasma antithrombin and protein C levels for eclampsia, pre-eclampsia and normotensive pregnancy were (61.17±9.13 and 60.00±5.76) vs (71.24±13.15 and 71.06±6.16) vs (85.54±8.77 and 89.64±7.61) respectively; p=0.0001. Severe pre-eclampsia when compared with mild pre-eclampsia had lower antithrombin (70.21±13.58 vs 73.74±12.43; p=0.507) and protein C (70.52±6.27 vs 72.40±6.00; p=0.451) levels respectively, though without statistical significance. Pre-eclampsia with low plasma antithrombin levels had increased risk of preterm delivery when age, gravidity and booking status were factored (OR, 1.2, 95% CI 0.035 to 0.348, p=0.017).
Conclusions: Lower plasma antithrombin and protein C levels were found with eclampsia and severe pre-eclampsia suggesting consumptive depletion of anticoagulants with disease progression. Women with pre-eclampsia and low plasma antithrombin levels were found to have increased odds of having preterm delivery when age, gravidity and booking status were considered.

Keywords: Antithrombin, Protein C, Pre-eclampsia, Eclampsia, Pregnancy, Sokoto

INTRODUCTION

Hypertensive disorders of pregnancy complicate about 10% of pregnancies worldwide and comprise of diseases such as pre-eclampsia, eclampsia, gestational hypertension and chronic hypertension.[1,2] Pre-eclampsia and eclampsia stand out among the hypertensive disorders of pregnancy for their impact on maternal and neonatal health

particularly in developing countries where there is dearth of optimal health care services.[3] In Sokoto Northwest Nigeria, 17% of pregnancies are complicated by hypertensive diseases of pregnancy with pre-eclampsia and eclampsia affecting 6% and 4.29% of pregnancies respectively.[4,5] Eclampsia alone contributes about 46% of adolescent maternal mortality in Sokoto.[6]

Pre-eclampsia is the occurrence of hypertension and proteinuria beyond 20 weeks of gestation while eclampsia is the occurrence of convulsions and or unexplained coma in association with pre-eclampsia.[3,7,8] These disorders are believed to result from defective placentae secondary to impaired trophoblastic invasion of the uterine spiral arteries; an event needed to provide the necessary vascular remodeling required for ensuring adequate perfusion at the utero-placental bed.[9] The abnormal placentae elaborate substances that mediate widespread arterial vasoconstriction, generalized inflammation, endothelial injury, activation of intravascular coagulation and deposition of microvascular thrombi in multiple organs.[9,10] These effects manifest as hypertension, proteinuria, acute renal failure, pulmonary oedema, hepatic dysfunction, headache and seizures or convulsions.[9-11]

Pre-eclampsia and eclampsia pose additional haemostatic challenge to pregnancy with resultant increased risk of complications such as venous thromboembolism, disseminated intravascular coagulopathy, placental abruption, intrauterine growth restriction, premature delivery and recurrent pregnancy loss.[12-16] The roles of naturally occurring anticoagulants such as antithrombin and protein C in the determination of disease severity or pregnancy outcomes of pre-eclampsia and eclampsia have become an interesting subject of research in recent times with conflicting findings.[17] While some works have established a link between plasma levels of these anticoagulants with worsening disease conditions and/or poor pregnancy outcomes, others couldn't.[14,15,17]

The aim of the study was to determine the plasma antithrombin and protein C levels of patients with pre-eclampsia and eclampsia in Sokoto Northwest Nigeria with a view to assessing any relationship with clinical severity and pregnancy outcomes.

METHODS

Study design

This was a prospective comparative study which involved use of interviewer-administered questionnaire, physical examination and laboratory tests. Case folders of study participants were later on retrieved after delivery and the pregnancy outcomes were extracted and recorded.

Study area

This study was conducted at the antenatal clinics, pre-eclamptic and eclamptic duty rooms, labour rooms and lying-in wards of the departments of obstetrics and gynaecology of two tertiary hospitals in Sokoto Northwest Nigeria namely, Usmanu Danfodiyo University Teaching Hospital and Specialist Hospital Sokoto.

Study population

These comprised of pregnant women diagnosed of pre-eclampsia or eclampsia as cases, while healthy normotensive pregnant women served as control group.

Duration of study

This study was conducted between October 2019 and September 2020

Ethical considerations

Approval to conduct this study was obtained from the Health and Ethics Research committees of the two study centres while written informed consent was obtained from study participants or their proxy (in case of unconscious patients with eclampsia).

Selection of study participants

Patients with eclampsia admitted at the study centres during the study period were consecutively enrolled based on the inclusion and exclusion criteria below. Thereafter, gestational age matched patients with pre-eclampsia and normotensive pregnancies were similarly enrolled based on the inclusion and exclusion criteria below.

Inclusion criteria

Pregnant women with eclampsia before commencement of magnesium sulphate therapy. Pregnant women with pre-eclampsia and matched for gestational age with the enrolled eclampsia patients. Pregnant women with normotensive pregnancies and matched for gestational age with the enrolled eclampsia patients.

Exclusion criteria

Pregnant women with previous history and/or family history of non-pregnancy related seizure disorders, haemostatic disorders or haemoglobinopathies. Presence of gestational trophoblastic diseases, pre-existing diabetes mellitus, cardiovascular or renal disorders. Recent usage of drugs that could interfere with coagulation such as aspirin, warfarin and magnesium sulphate.

Definition of clinical variables

Pregnancy

A positive plasma and or urine pregnancy test and was corroborated by presence of intrauterine fetus via obstetric USS.

Pre-eclampsia

Pregnancy at gestational age of ≥20 weeks with blood pressure ≥140/90 mmHg on ≥2 occasions at least 6 hours apart with proteinuria of ≥1+ on 2 random urine samples 6 hours apart.[3,7]

Mild pre-eclampsia

Pregnancy at gestational age of ≥20 weeks with systolic blood pressure 140-159 mmHg and diastolic blood pressure 90-109 mmHg on ≥2 occasions at least 6 hours apart with proteinuria of ≥1+ on 2 random urine samples 6 hours apart.[3]

Severe pre-eclampsia

Pregnancy at gestational age of ≥20 weeks with severe hypertension; systolic blood pressure ≥160 mmHg and or diastolic blood pressure ≥110 mmHg.[3]

Eclampsia

Occurrence of convulsions and/or unexplained coma during pregnancy or postpartum in patients with features of pre-eclampsia.[3,7,8]

Sample size determination

Sample size was determined using the G*Power Statistical Power Analysis Program for the Social, Behavioural and Biomedical Sciences Version 3.[17] The following parameters were utilized in a priori analysis based on one-way ANOVA-

Input

Effect size f=0.3773233; α error probability=0.05; power (1-β error probability)=0.90; number of groups=3.

Output

Total sample size=93; actual power=0.9035412.

A total sample size of 93 was obtained and thus 31 each for pre-eclampsia, eclampsia and normotensive pregnant women were recruited for the study. These were proportionately enrolled from the two study centres based on the monthly average number of cases attended to at the centres.[16,17,19]

Laboratory tests

Plasma antithrombin and protein C levels were determined on all participants' venous blood by kinetic method using the S4 Nortek® semi-automated coagulometer. Berichrom® antithrombin and Berichrom® protein C reagents with BATCH/LOT numbers (10) 49939 and (10) 49700 respectively (SIEMENS healthcare diagnostics products GmbH, 35041 Marburg/Germany) were utilized. Manufacturers' guidelines were strictly adhered for the analysis.[20, 21]

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp, Armonk, NY, USA). Shapiro-Wilk test was used to determine normality of data distribution. Quantitative data were summarized as mean±standard deviations and compared using Independent samples t test or Anova as appropriate. Qualitative data were summarized using percentages and proportions. Pearson tests were used for correlations analysis while associations between categorical variables were explored using Chi square. Binary logistic and multinomial regression analyses were conducted to determine value of plasma antithrombin and protein C levels in predicting pregnancy outcomes. Level of significance was set at $p<0.05$.

RESULTS

A total of 93 pregnant women were enrolled in the study and grouped into three groups each comprising of 31 study participants. The first two groups were women with eclampsia and pre-eclampsia as study groups while normotensive pregnant women made up the control group. The eclampsia group had the youngest maternal age with mean±SD age of 20.61±3.92 years when compared with 30.52±6.73 and 27.32±4.99 years for the pre-eclampsia and normotensive groups respectively; F test 27.759, $p<0.001$.

Hausa was the predominant tribe across all study participants. All patients with eclampsia were housewives 31 (100%) with majority 23 (74.2%) coming from the rural areas and without formal education 27 (87.1%). Additional sociodemographic features of the study participants are in Table 1.

There was no statistically significant difference across the study participants with respect to estimated gestational ages $p>0.05$. Significantly lower mean parity and gravidity were encountered for the eclampsia group when compared to both the pre-eclampsia and normotensive groups. Higher mean values for both systolic and diastolic blood pressures were recorded for eclampsia group when compared to pre-eclampsia and normotensive groups. Though there was no statistically significant difference in the recorded fetal birth weight across study participants but mean Apgar scores were lowest with the eclampsia group (Table 2).

Up to 30 (96.8%) of the eclampsia weren't booked for antenatal care. Twenty (64.5%) of patients with eclampsia had intrapartum eclampsia while 22 (71.0%) of patients with pre-eclampsia had severe form of pre-eclampsia. Though equal number of pre-eclampsia and eclampsia patients had preterm delivery but more obstetric

interventions were recorded with the latter. Similarly, poorer pregnancy complications and outcomes were encountered within the eclampsia group. The lone maternal death recorded was within the eclampsia group (Table 3).

The eclampsia group had statistically significant lower mean plasma antithrombin and protein C levels when compared with the pre-eclampsia and normotensive pregnant groups $p<0.05$ (Table 4).

Though lower mean values for both plasma antithrombin and protein C were found with severe pre-eclampsia when compared to mild pre-eclampsia, this didn't attain statistical significance $p>0.05$ (Table 5). For both the eclampsia and pre-eclampsia groups, no significant correlation was noted between their plasma antithrombin and protein C levels. However, for the normotensive group, a moderately positive and significant correlation was recorded between plasma antithrombin and protein C levels (Table 6).

Both Table 7 and 8 depict the relationship between plasma antithrombin and protein C levels with pregnancy outcomes among study participants. A significant relationship was found only between plasma antithrombin levels and time of delivery among the pre-eclampsia group (Table 8).

As a follow-up to this, Table 9 depicts two logistic regression models developed to ascertain the ability of plasma antithrombin levels in predicting preterm delivery within the pre-eclampsia group.

Comparison of the performance metrics for the two logistic regression models developed for the predictive ability of plasma antithrombin level among the pre-eclampsia group is shown in Table 10.

Table 1: Sociodemographic characteristics of study participants.

Characteristics	Classification	Participants					
		Pre-eclampsia (N=31)		Eclampsia (N=31)		Normotensive (N=31)	
		N	%	N	%	N	%
Tribe	Hausa	23	74.2	31	100	23	74.2
	Yoruba	2	6.5	0	0	4	12.9
	Igbo	3	9.7	0	0	3	9.7
	Others	3	9.7	0	0	1	3.2
Place of residence	Urban	28	90.3	8	25.8	26	83.9
	Rural	3	9.7	23	74.2	5	16.1
Occupation	Housewife	24	77.4	31	100	19	61.3
	Civil servant	2	6.5	2	6.5	9	29.0
	Trader	4	12.9	4	12.9	0	0
	Student	1	3.2	1	3.2	3	9.7
Educational status	Primary	6	19.4	3	9.7	8	25.8
	Secondary	14	45.2	1	3.2	1	3.2
	Tertiary	6	19.4	0	0	6	19.4
	No formal education	5	16.1	27	87.1	16	51.6

Table 2: Obstetrics characteristics and pregnancy outcomes of study participants.

Characteristics	Participants (mean±SD)			Anova		Post hoc test (Games-Howell)	
	Pre-eclampsia (P) N=31	Eclampsia (E) N=31	Normotensive (N) N=31	F test	P value	Comparison of groups' means	P value
Gestational age (weeks)	36.98±4.36	37.14±1.79	37.73±1.23	13.36	0.140	-	
Parity	2.61±2.47	0.35±1.47	1.39±2.19	9.10	0.000	P vs E	0.000
						P vs N	0.106
						E vs N	0.084
Gravidity	3.94±2.71	1.35±1.47	2.45±2.29	10.57	0.000	P vs E	0.000
						P vs N	0.060
						E vs N	0.074
Systolic BP (mmHg)	162.26±19.20	168.39±24.51	118.26±11.92	62.79	0.000	P vs E	0.519
						P vs N	0.000
						E vs N	0.000
Diastolic BP	106.13±10.86	107.42±13.66	76.45±9.59	72.02	0.000	P vs E	0.911

Continued.

Characteristics	Participants (mean±SD)			Anova		Post hoc test (Games-Howell)	
	Pre-eclampsia (P) N=31	Eclampsia (E) N=31	Normotens-ive (N) N=31	F test	P value	Comparison of groups' means	P value
(mmHg)						P vs N	0.000
						E vs N	0.000
Fetal birth weight (kg)	3.00±0.45	2.74±0.58	2.94±0.50	1.676	0.194	-	-
Apgar score$_1$	6.11±1.40	4.95±1.61	7.52±0.96	24.38	0.000	P vs E	0.035
						P vs N	0.000
						E vs N	0.000
Apgar score$_5$	7.86±1.08	7.30±1.98	8.81±0.75	9.28	0.000	P vs E	0.496
						P vs N	0.001
						E vs N	0.009

Table 3: Obstetrics characteristics and pregnancy outcomes of study participants.

Characteristics	Classification	Participants					
		Pre-eclampsia (N=31)		Eclampsia (N=31)		Normotensive (N=31)	
		N	%	N	%	N	%
Antenatal booking	Booked	23	74.2	1	3.2	31	100
	Un-booked	8	25.8	30	96.8	0	0
Severity of pre-eclampsia	Mild	9	29.0	-	-	-	-
	Severe	22	71.0	-	-	-	-
Type of eclampsia	Antepartum	-	-	11		-	-
	Intrapartum	-	-	20		-	-
	Postpartum	-	-	0		-	-
Type of delivery	Pre-term	7	22.6	7	22.6	0	0
	Term	24	77.4	24	77.4	31	100
Mode of delivery	SVD*	18	58.1	8	25.8	19	61.3
	Assisted VD**	3	9.7	14	45.2	3	9.7
	Caesarean section	10	32.3	8	25.8	9	29.0
	Undelivered	0	0	1	3.2	0	0
Maternal bleeding	Nil	26	83.9	2	6.45	31	100
	Antepartum bleeding	4	12.9	6	19.4	-	-
	Intrapartum bleeding	0	0	21	67.7	-	-
	Postpartum bleeding	1	3.2	1	3.2	-	-
Maternal mortality	Died	0	0	1	3.2	0	0
	Survived	31	100	30	96.8	31	100
Outcome of birth	Live birth	28	90.3	20	64.5	31	100
	Fresh still birth	3	9.7	8	25.8	0	0
	Macerated still birth	0	0	2	6.45	0	0

Note: *SVD=spontaneous vaginal delivery; **VD=vaginal delivery.

Table 4: Comparison of plasma antithrombin and protein C levels among study participants.

Characteristics	Participants (mean±SD)			Anova		Post hoc test (Games-Howell)	
	Pre-eclampsia (P) N=31	Eclampsia (E) N=31	Normotens-ive (N) N=31	F test	P value	Comparison of groups' means	P value
Antithrombin (%)	71.24±13.15	61.17±9.13	85.54±8.77	41.85	0.000	P vs E	0.003
						P vs N	0.000
						E vs N	0.000

Continued.

Characteristics	Participants (mean±SD)			Anova		Post hoc test (Games-Howell)	
	Pre-eclampsia (P) N=31	Eclampsia (E) N=31	Normotensive (N) N=31	F test	P value	Comparison of groups' means	P value
Protein C (%)	71.06±6.16	60.00±5.76	89.64±7.61	161.82	0.000	P vs E	0.000
						P vs N	0.000
						E vs N	0.000

Note: Reference values- antithrombin 75-125%; protein C- 70-140%.[20,21]

Table 5: Comparison of plasma antithrombin and protein C levels among participants with mild and severe pre-eclampsia.

Parameters	Participants (mean±SD)		T test	P value
	Mild pre-eclampsia N=9	Severe pre-eclampsia N=22		
Antithrombin (%)	73.74±12.43	70.21±13.58	0.672	0.507
Protein C (%)	72.40±6.00	70.52±6.27	0.765	0.451

Table 6: Relationships between plasma antithrombin and protein C among study participants.

Protein C (%)			Pre-eclampsia (N=31)	Eclampsia (N=31)	Normotensive pregnant (N=31)
Antithrombin (%)	Pre-eclampsia	Pearson's r	0.151	-	-
		P value	0.418	-	-
	Eclampsia	Pearson's r	-	0.095	-
		P value	-	0.613	-
	Normotensive pregnancy	Pearson's r	-	-	0.599
		P value	-	-	<0.001

Table 7: Relationship between plasma levels of antithrombin and protein C with neonatal pregnancy outcome.

Parameters	Category of outcome		Group of study participants					
			Pre-eclampsia N=31		Eclampsia N=31		Normotensive N=31	
			Statistics	P value	Statistics	P value	Statistics	P value
Plasma antithrom-bin levels	Birth outcome	Live birth	0.017*	0.983	0.234*	0.206	All had live birth	
		FSB						
		MSB						
	Apgar score	1 min	-0.010**	0.966	-0.047**	0.813	0.155**	0.406
		5 min	-0.087**	0.716	-0.125**	0.526	0.113**	0.546
Plasma protein C levels	Birth outcome	Live birth	0.758*	0.535	0.155*	0.404	All had live birth	
		FSB						
		MSB						
	Apgar score	1 min	-0.065**	0.785	0.002**	0.993	0.266**	0.148
		5 min	-0.025**	0.916	-0.025**	0.899	0.297**	0.105
	Birth weight		-0.023**	0.922	-0.124**	0.530	-0.437**	0.140

Note: FSB= Fresh still birth; MSB= Macerated still birth; *Anova; ** t test.

Table 8: Relationship between plasma levels of antithrombin and protein C with maternal pregnancy outcome.

Parameters	Category of outcome		Group of study participants					
			Pre-eclampsia N=31		Eclampsia N=31		Normotensive N=31	
			Statistics	P value	Statistics	P value	Statistics	P value
Plasma antithrom-bin levels	Time of delivery	Pre-term	2.571*	0.016	0.233*	0.818	All term delivery	
		Term						
	Mode of delivery	SVD	0.205**	0.816	0.205**	0.816	0.126**	0.884
		AVD						
		CS						
	Bleeding	APH	1.58**	0.664	0.558**	0.647	Nil bleeding	

Continued.

Parameters	Category of outcome		Group of study participants					
			Pre-eclampsia N=31		Eclampsia N=31		Normotensive N=31	
			Statistics	P value	Statistics	P value	Statistics	P value
		IPH						
		PPH						
	Survival	Died	No death		Only 1 death		No death	
		Survived						
Plasma protein C levels	Time of delivery	Pre-term	0.502*	0.620	0.343*	0.734	All term delivery	
		Term						
	Mode of delivery	SVD	0.176**	0.840	0.163**	0.850	0.733***	0.516
		AVD						
		CS						
	Bleeding	APH	3.89**	0.273	1.89**	0.156	Nil bleeding	
		IPH						
		PPH						
	Survival	Died	No death		Only 1 death		No death	
		Survived						

Note: SVD= Spontaneous vaginal delivery, AVD= Assisted vaginal delivery, APH=Antepartum haemorrhage, IPH=Intrapartum haemorrhage, PPH=Postpartum haemorrhage, * t test, **Anova.

Table 9: Logistic regression models for plasma antithrombin levels predicting maternal preterm delivery among women with the pre-eclampsia.

Model predictors	Deviance	X2	P	Nagelkerke's R2	Standardized estimate	OR	95% CI	P value
1-Plasma antithrombin alone	H0-33.118 H1-26.905	6.213	0.013	0.277	1.247	1.099	0.009 0.181	0.013
2- Plasma antithrombin, patients' age, gravidity, booking status and severity of pre-eclampsia	H0-32.6 H1-19.3	13.301	0.004	0.537	2.513	1.211	0.035 0.348	0.017

Note: Outcome: pre-term coded 1.

Table 10: Performance metrics of the two models of plasma antithrombin levels predicting maternal preterm delivery among women with pre-eclampsia.

Model	AUC	Sensitivity	Specificity	Precision
1	0.792	0.286	0.917	0.500
2	0.911	0.571	0.917	0.667

DISCUSSION

Pre-eclampsia and eclampsia are hypertensive disorders of pregnancy that stand out as major causes of materno-fetal morbidity and mortality.[3] They emanate from defective placentation and pose additional haemostatic challenge to pregnancy due to widespread endothelial injury, circulating thromboplastins, intravascular deposition of fibrin, consumptive coagulopathy and increased fibrinolysis.[9] Socio-economic, genetic, co-morbidity factors and thrombophilia have been reported to contribute to their severity and outcome.[9,14,15,22,23] Thus this study seeks to identify the roles of the naturally occurring anticoagulants; antithrombin and protein C, in the determination of the severity or pregnancy outcomes of pre-eclampsia and eclampsia. Our finding of women with eclampsia mostly of young maternal age of ≤20 years supports the observation that eclampsia is a disease of early exposure to fetal tissue and is in agreement with the works of Ekwempu and Yakasai in Northwest Nigeria.[24,25] However, sclerotic lesions leading to placental ischaemia with advancing age may pose additional risk of eclampsia occurring at later maternal age as reported by other workers.[26] Most of our study participants were Hausa being the predominant tribe in Sokoto and agree with an earlier work in Sokoto.[6] The finding of all women with eclampsia in this study as housewives is similar to the work of Jimoh in Nigeria and is in agreement with the observed low average age at marriage in Hausa communities.[27,28] Majority of the women with eclampsia were rural dwellers with high level of illiteracy and poor antenatal care. These findings are similar to other findings in Nigeria and beyond; and are largely attributable to poor economic empowerment, cultural attitude towards seeking

formal education, poor health seeking behaviour and dearth of health facilities in rural arears where most of women with eclampsia reside.[29,30,31]

The finding of majority of the women with eclampsia being nulliparous supports earlier observations by some researchers and probably is due to the first maternal exposure to chorionic villi, which is fetal in origin.[22,32,33] Majority of women with pre-eclampsia in this study had severe pre-eclampsia; a finding consistent with other studies and may be due to the fact that pre-eclampsia is classified into mild or severe only without an intermediate category and the progression from mild to severe can be rapid and unexpected and thus majority are likely to present with severe form.[3,14,34] Majority of women with eclampsia in this study had intrapartum eclampsia which is similar to the earlier findings of Ekwempu in Zaria and Ekele in Sokoto both in Northwest Nigeria.[5,24] Our finding may reflect poor health seeking attitude of women with eclampsia or long distance from the health care facilities which can all delay hospital presentation. In contrast, higher occurrence of antepartum eclampsia has been reported in more developed countries where maternal health care is more readily available and accessible.[8,35]

In order to avert poor pregnancy outcomes, prompt obstetrics interventions are usually required for management of eclampsia and pre-eclampsia and this largely explains the higher rate of obstetric interventions recorded for these disorders. Additionally, poor antenatal care, delay in accessing healthcare and the predominance of intrapartum eclampsia and severe pre-eclampsia could have contributed to the attendant poorer pregnancy outcomes when compared with the normotensive pregnant group. These findings are similar to those of Ekwempu in Zaria and Nwobodo in Sokoto Nigeria.[24,36]

From the foregoing, our findings have highlighted on the documented risk factors for the development of pre-eclampsia/eclampsia such as young maternal age, nulliparity, high level of illiteracy and poor or delayed access to maternal health care.[3,5,8,37] Other documented risk factors for the development of eclampsia include; chronic hypertension, cardiac disease, obesity and severe anaemia.[38] Pregnancy is a hypercoagulable state that ensures haemostasis at the placental bed to prevent severe bleeding during labour and delivery; but this may lead to depletion of naturally occurring anticoagulants in the setting of additional haemostatic challenge such as pre-eclampsia and eclampsia.[13,16,17,34,39,40] There are varying findings regarding the plasma levels of antithrombin and protein C during pregnancy. Similar to our finding, James et al, reported decline of these anticoagulants while others found normal levels in pregnancy.[16,39,41] Imoru and Buseri reported low protein C but normal antithrombin activities among healthy pregnant women in Kano Nigeria.[42] In contrasts to our finding of reduced levels of antithrombin and protein C in pre-eclampsia and eclampsia, both studies by Okoye and Yalinkaya in Nigeria and Turkey respectively did not find any significant difference in the plasma levels of these anticoagulants between pre-eclampsia and normal pregnancy.[15,43] Osmanagaoglu and Heilman found pre-eclampsia having lower levels of antithrombin only and not protein C when compared to normal pregnancy.[44,45] However, some studies have reported only protein C levels and not antithrombin to be significantly lower with pre-eclampsia when compared to normal pregnancy.[23,46] In what could be a reflection of increased consumptive depletion with worsening disease, we found lower levels of antithrombin and protein C with severe pre-eclampsia when compared to mild pre-eclampsia; a finding similar to other studies.[17,34]

With severe deficiency of naturally occurring anticoagulants or thrombophilia, utero-placental thrombosis may ensue and lead to intrauterine growth restriction and placental abruption.[14,15,47] In line with this, we found more unfavourable maternal outcomes such as preterm delivery, bleeding and death; and poorer neonatal outcomes such as still births, lower fetal birth weight and lower Apgar scores with the pre-eclampsia and eclampsia groups. Yalinkaya et al recorded lower Apgar scores and birth weights for neonates of mothers with pre-eclampsia and eclampsia when compared with normotensive pregnancies.[15]

In a large Italian case-control study, Mello et al, found thrombophilia including deficiency of antithrombin and protein C to be risk factors for the development of materno-fetal complications such as acute renal failure, DIC, placental abruption, low placental weight, fetal growth restriction, low birth weight, and perinatal mortality.[14] Similarly, Heilman et al had reported higher prevalence of preterm delivery and low birth weight with severe pre-eclampsia.[45] In contrast, Yenidede et al in Turkey didn't find any significant difference in pregnancy outcome between pre-eclampsia with lower levels of antithrombin and protein C and normal pregnancies; and based on their findings, they opined that there is no need for thrombophilia screening in pre-eclampsia.[48]

We found low plasma levels of antithrombin in pre-eclampsia to be significantly associated with preterm delivery suggesting that pro-thrombotic states predispose to pre-term delivery. This is in keeping with the findings by Mello and colleagues that women with severe pre-eclampsia and thrombophilia (deficiency of antithrombin, protein C, protein S, factor V Leiden, antiphospholipid syndrome, hyperhomocystenaemia) were about six and three times more likely to have preterm delivery and fetal weight restriction respectively.[14]

These findings further drive home the point that deficiency of antithrombin and protein C contribute to poor materno-fetal outcomes in the setting of pre-eclampsia and eclampsia.[14] However, data from this study also suggest that antithrombin level alone is a poor predictor of pre-term delivery in pre-eclampsia unless additional factors such as age, gravidity and booking status are taken into consideration.

These findings are expected as various factors contribute in determining clinical outcomes. This notion is further buttressed by the proportion of variance that the statistical model could explain. The unexplained deficit may be for factors not evaluated in this study such as time to intervention, quality of care provided, other thrombophilia and genetic variation in study participants among others.

CONCLUSION

This study has shown that pre-eclampsia and eclampsia pose additional haemostatic challenge to pregnancy as pregnant women with these disorders recorded significantly lower plasma levels of both antithrombin and protein C levels when compared to women with normal pregnancy. In the same vein, we observed lower plasma antithrombin and protein C levels with severe pre-eclampsia than with mild pre-eclampsia; reflecting increased consumptive depletion of these naturally occurring anticoagulants with worsening disease. Our study also found that low plasma antithrombin levels, when patient's age, gravidity and antenatal booking status were taken into consideration, was predictive of preterm delivery among pregnant women with pre-eclampsia.

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