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Research Article

Plasma Levels of Fibrinogen and D-Dimer of Eclamptic Patients in Sokoto, Northwest Nigeria

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Abstract: Haemostatic abnormalities such as thrombocytopaenia, consumptive coagulopathy and exaggerated fibrinolysis complicate eclampsia and may lead to poor materno-fetal outcomes; underscoring the need for haemostatic surveillance in the management of this disorder. This study was aimed to determine plasma levels of fibrinogen and D-dimer in eclamptics and their value for predicting some poor materno-fetal outcomes. Two hundred women were recruited comprising of 100 eclamptics as study group and 50 each of pregnant non-eclamptics and non-pregnants as comparison groups. Plasma levels of fibrinogen and D-dimer were quantitatively determined via semi-automation and results compared among study participants. The predictive ability of fibrinogen and D-dimer levels for maternal death and fetal still birth were ascertained. The eclamptics had lower fibrinogen levels than the pregnant non-eclamptics (445.02±194.44 mg/dl vs. 530.80±158.44 mg/dl respectively; $p<0.05$). Highest D-dimer levels were observed with the eclamptics with a mean value of 56661.06±1991.18ng/ml compared to 1808.12±728.89ng/ml and 88.04±44.61ng/ml for pregnant non-eclamptic and non-pregnant groups respectively, $p<0.05$. Though plasma levels of fibrinogen and D-dimer of the eclamptics were deranged, but none was found to be predictive of maternal death or fetal still birth. Low plasma fibrinogen and elevated D-dimer levels were found with the eclamptics; reflecting consumptive coagulopathy and exaggerated fibrinolysis. This finding underscores the importance of haemostatic surveillance in the management of eclampsia.

Keywords: Plasma, Fibrinogen, D-dimer, Eclampsia, Pregnancy, Sokoto.

INTRODUCTION:

Eclampsia is a life-threatening complication affecting approximately 0.1% of pregnancies worldwide (Rodie VA, 2006). In Sokoto Northern Nigeria; eclampsia complicates 4.29% of pregnancies and contributes up to 53.9% of adolescent maternal mortality (Ekele BA *et al.*, 2007; Nwobodo EI *et al.*, 2012).

Eclampsia is characterized by widespread vasoconstriction, endothelial injury and activation of intravascular coagulation consequently posing additional haemostatic challenge during pregnancy (Cunningham FG. *et al.*, 2005). The resultant haemostatic perturbations may culminate into consumptive coagulopathy and exaggerated fibrinolysis; the occurrence of which have been associated with poorer materno-fetal outcomes (Rodie VA, 2006; Cunningham FG *et al.*, 2005; Matsouka CJ 2005).

This work was undertaken to determine the plasma levels of fibrinogen and D-dimer in eclamptic women and to ascertain the value of these parameters in predicting poor materno-fetal outcomes such as maternal death and fetal still birth.

EXPERIMENTAL SECTION:

This was a cross sectional study involving pregnant women receiving care at the department of Obstetrics and Gynaecology Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto Nigeria. Non-pregnant women were recruited from the female members of staff and students of UDUTH Sokoto. Approval was obtained from the Ethical and

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Research Committee of UDUTH Sokoto while informed consent was obtained from study participants.

A total of 200 women were recruited via convenient non-probability sampling technique and comprised of 100 eclamptics as study group and 50 each of pregnant non-eclamptics and non-pregnant women as comparison groups. For the comparison groups, women with hypertension, previously diagnosed bleeding disorders or recent use of drugs (Aspirin, Warfarin and Heparin) that affect haemostasis were excluded.

All participants had their blood samples taken for the determination of plasma levels of fibrinogen and D-dimer at the department of Haematology UDUTH, Sokoto.

Sample Collection and Preparation:

Four and half milliliters of free flowing venous blood were obtained from each participant and dispensed into a specimen bottle containing 0.5mls of 3.2% trisodium citrate which was gently but thoroughly mixed. This was then centrifuged at 2000g for 15mins to prepare platelet poor plasma and analysed within 1 hour of collection. However, samples that could not be analyzed within 1 hour of collection were stored in 2 aliquots (of 1ml each) at -20°C for a period not exceeding 1 week.

Determination of plasma levels of fibrinogen and D-dimer: Both plasma levels of fibrinogen and D-dimer tests were determined by semi-automation using HumaClot junior coagulometer and commercially available kits (Hemostat Fibrinogen and Hemostat D-dimer Human GmbH/Germany).

- Fibrinogen levels were determined using the Clauss method which entailed the use of excess thrombin to clot diluted plasma. Initially, 1:5, 1:10 and 1:20 dilutions of reference plasma were made in Imidazole buffered saline. Hundred microliters of each dilution were prewarmed in a cuvette for 5minutes, then 50µl of thrombin were added and the time taken to clot formation was recorded. The mean clotting time and the corresponding fibrinogen concentrations of these dilutions were entered into the coagulometer and stored as calibration points. Thereafter, 100µl of 1:10 dilution of each participant's plasma was prewarmed and 50µl of thrombin added to form clot. The corresponding fibrinogen concentrations of participants' plasma were automatically generated by the coagulometer via extrapolation from the in-built calibration curve.
- D-dimer levels were determined using immuno-turbidimetric method which entailed the use of D-dimer latex reagent (coated with D-dimer specific antibodies) that agglutinates upon exposure to D-dimer contained in plasma. The resultant agglutination leads to increased light scattering which is proportional to the amount of D-dimer in the plasma. Initially, 25µl of calibrator reagent (CR1) and 100µl of reaction buffer were mixed in a cuvette and incubated for 10minutes. Fifty microliters of D-dimer latex reagent were then added and mixed until the resultant change in optical density (ΔOD) was displayed by the coagulometer. The same procedure was repeated with a second calibrator reagent (CR2). Both the ΔOD and concentrations of CR1 and CR2 were entered into the coagulometer and stored as calibration points. Thereafter, 25µl of each participant's plasma and 100µl of reaction buffer were mixed in a cuvette and incubated for 10minutes. Fifty microliters of D-dimer latex reagent were then added and mixed to generate a ΔOD. The corresponding D-dimer concentrations of participants' plasma were automatically generated by the coagulometer via extrapolation from the in-built calibration curve.

Results of the plasma fibrinogen and D-dimer were entered into Statistical Programme (SPSS 20, Statistical Package for Social Sciences IBM Corp. Released 2011 version 20 Armonk, NY) for analysis. Using ANOVA, the values for plasma fibrinogen and D-dimer were compared between eclamptics, pregnant non-eclamptic and non-pregnant groups. Binary logistic regression analysis was employed to determine the value of plasma fibrinogen and D-dimer in predicting maternal death and fetal still birth. Statistical significance was set at $p<0.05$.

RESULTS:

The mean ages of the eclamptics and non-pregnant women were 20.65±4.68 years and 20.24±4.58 years respectively with no statistically significant difference, $p> 0.05$. However, the mean age of the eclamptics was lower than that of the pregnant women (26.32±6.30 years), $p <0.05$. The mean gestational ages of the eclamptics and pregnant non-eclamptics were 35.80±2.15 weeks and 35.26±1.56 weeks respectively with no statistically significant difference, $p> 0.05$. Antepartum, Intrapartum and Postpartum types of eclampsia were recorded in 21%, 59% and 20% of the eclamptics respectively.

The highest mean value of D-dimer levels was recorded with the eclamptics while the least was with the non-pregnant. The mean fibrinogen level of the eclamptics was found to be lower than that of the pregnant non-eclamptic, though not as low as that recorded with the non-pregnant as further highlighted in Table I.

Table I: Fibrinogen and D-dimer levels of study participants

Variable	Group of Participants (N=200)			Anova		Post hoc test (Games-Howell)	
	Eclamptics n=100 Mean±SD*	Pregnant non-eclamptics n=50 Mean±SD*	Non-pregnant n=50 Mean±SD*	F-test	P-value	Comparison of groups' Means	P-value
Fibrinogen (mg/dl)	445.02±194.44	530.80±158.44	176.78±76.96	66.425	0.000	E† vs. PNE‡ E† vs. NP§ PNE‡ vs. NP§	0.013 0.000 0.000
D-dimer (ng/ml)	5661.06±1991.18	1808.12±728.89	88.04±44.61	278.710	0.000	E† vs. PNE‡ E† vs. NP§ PNE‡ vs. NP§	0.000 0.000 0.000

Reference values are: Fibrinogen 180-360mg/dl, D-dimer <200ng/ml, *p* is significant at <0.05, *Standard deviation, †Eclamptics, ‡Pregnant non-eclamptics, §Non-pregnant

No statistically significant difference was observed with fibrinogen and D-dimer levels when the type of eclampsia is taken into consideration (Table II).

Table II: Fibrinogen and D-dimer levels of eclamptics based on type of eclampsia

Variable	Type of Eclampsia (N=100)			Anova		Post hoc test (Games-Howell)	
	Antepartum n=21 Mean± SD*	Intrapartum n=59 Mean± SD*	Postpartum n=20 Mean± SD*	F-test	P-value	Comparison of groups' Means	P-value
Fibrinogen (mg/dl)	450.43±191.10	447.46±195.02	432.15±205.52	0.055	0.957	†AP vs. ‡IP †AP vs. §PP ‡IP vs. §PP	0.998 0.953 0.954
D-dimer (ng/ml)	4615.00±1269.93	5913.90±1960.85	6013.55±2384.38	3.903	0.077	†AP vs. ‡IP †AP vs. §PP ‡IP vs. §PP	0.073 0.068 0.984

Reference values are: Fibrinogen 180-360mg/dl, D-dimer <200ng/ml, P is significant at <0.05, *Standard deviation, †Antepartum, ‡Intrapartum, §Postpartum

Plasma levels of fibrinogen and D-dimer for the eclamptic showed a negative correlation while a positive correlation was noted in respect of these analytes and gestational ages. (Figures 1-3).

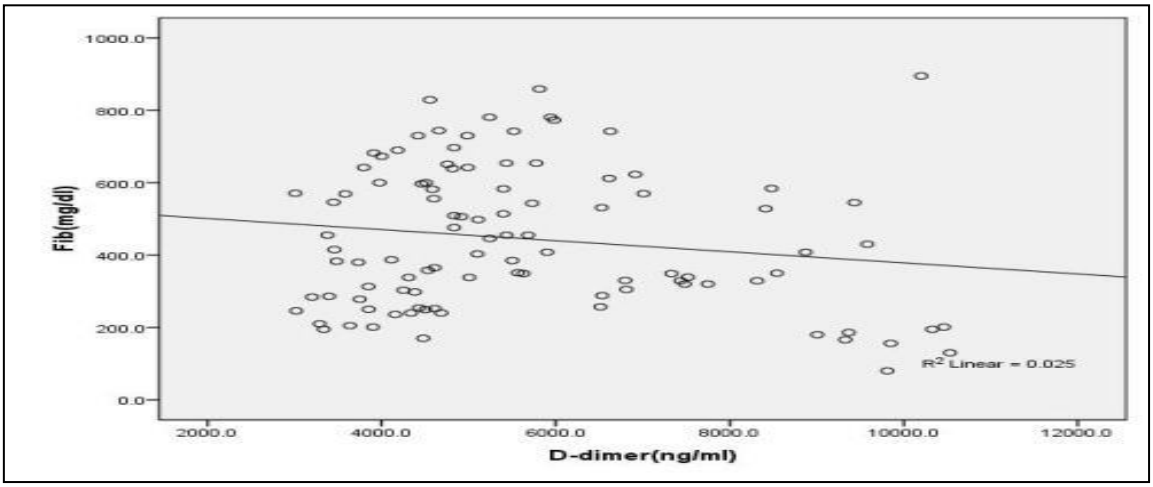

Figure 1: Scatter plot of Fibrinogen and D-dimer levels of the eclamptics depicting a negative correlation

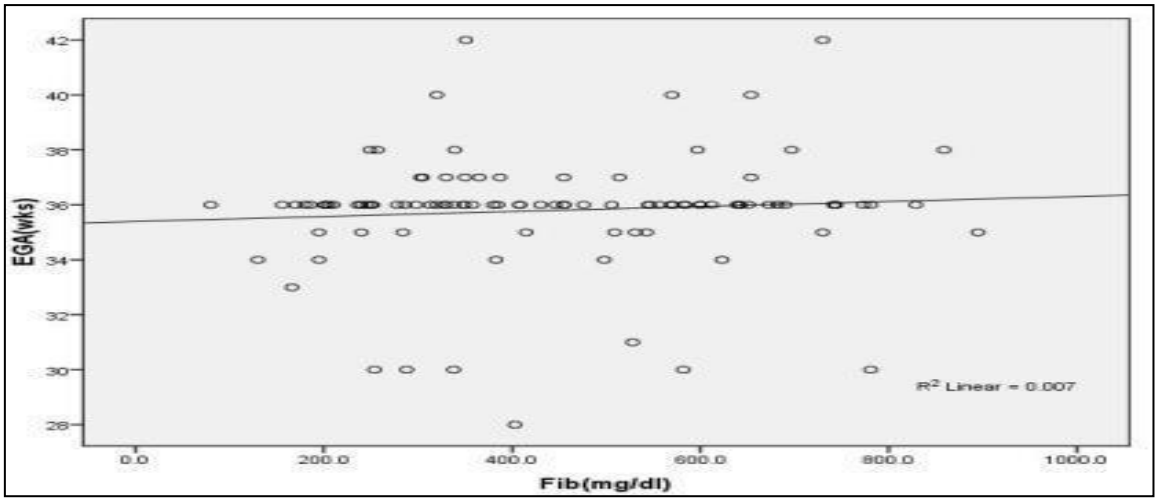

Figure 2: Scatter plot of Estimated Gestational Age (EGA) and Fibrinogen (Fib) levels of the eclamptics depicting a positive correlation

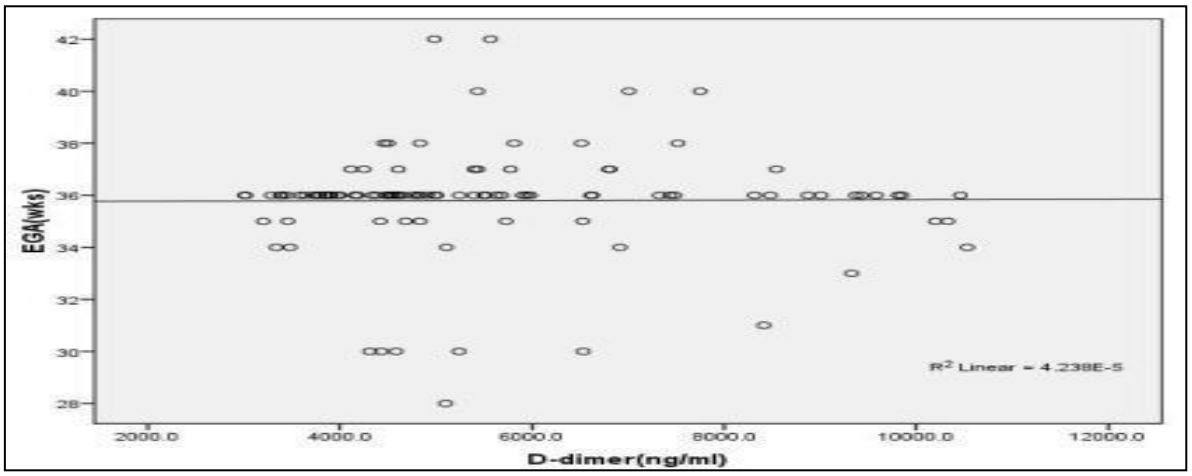

Figure 3: Scatter plot of Estimated Gestational Age (EGA) and D-dimer levels of the eclamptics depicting a positive correlation

Though levels of fibrinogen and D-dimer for the eclamptics were found to be deranged, but the result of logistic regression (Table III) showed that they were not found to be predictive of poor maternofetal outcomes such as maternal death and fetal still birth.

Table III: Plasma levels of fibrinogen and D-dimer as predictors of materno-fetal outcome among the eclamptics

Maternal/ Fetal outcome	Haemostatic variable	Sig	Odds Ratio (aOR)	95% Confidence Interval	
				Lower bound	Upper bound
Maternal death (n=12)	Fibrinogen (mg/dl)	0.555	1.002	0.995	1.009
	D-dimer (ng/ml)	0.858	1.000	1.000	1.001
Fetal still birth (n=25)	Fibrinogen (mg/dl)	0.221	1.002	0.999	1.004
	D-dimer (ng/ml)	0.057	1.001	1.000	1.001

The reference category for maternal outcome was survival while that for fetal outcome was live birth. Reference values are: Fibrinogen 180-360mg/dl, D-dimer <200ng/ml, P is significant at <0.05

DISCUSSION:

Pregnancy is characterized by increased production of coagulation factors, thrombocytopaenia, decrease in quantity or activities of coagulation inhibitors and suppression of plasma fibrinolytic activity (Cunningham FG et-a,l 2005; Matsouka CJ 2005). These haemostatic perturbations convert pregnancy into a hypercoagulable state which is a crucial step towards ensuring haemostasis at the placental site and prevention of severe bleeding during pregnancy, delivery and puerperium (Cunningham FG *et al.*, 2005; Matsouka CJ 2005). Our study found

elevated levels of fibrinogen and D-dimer with the pregnant woman who is in keeping with the enhanced synthesis of fibrinogen and increased production of FDPs reported in normal pregnancy (Prisco D *et al.*, 2005; Holmes VA *et al.*, 2005; Benner B 2004).

With the occurrence of additional haemostatic challenge such as eclampsia, normal pregnancy could be transformed into a state of high grade consumptive coagulopathy and enhanced fibrinolysis which may become more manifest with disease progression (Lopez-Liara M *et al.*, 1976; Roberts JM *et al.*, 1976). Eclampsia is the occurrence of convulsions and or unexplained coma in association with pre-eclampsia (Rodie VA, 2006; Sibai BM 2005). It results from abnormal placentation that leads to restricted placental blood flow and ischaemia (Rodie VA, 2006; Sibai BM 2005). The resultant ischaemic placenta elaborates substances that lead to widespread arterial vasoconstriction, endothelial injury, activation of intravascular coagulation and deposition of microvascular thrombi in multiple organs (Rodie VA, 2006; Sibai BM 2005; Perry KG *et al.*, 1992).

Eclampsia usually occurs after 20 weeks of gestation among young mothers as found in this study and corroborated by the works of Yakasai and Ekwempu who found the mean ages of eclamptics to be 20.60 and 18.12 years respectively (Yakasai IA *et al.*, 2011; Ekwempu CC, 1982). Earlier workers had identified young maternal age to be a risk factor for the development of eclampsia.[15] Eclampsia could be antepartum, intrapartum or postpartum when it occurs before, during or after labour respectively (Rodie VA, 2006; Sibai BM 2005). Our finding of predominantly intrapartum eclampsia may not be unconnected with late hospital presentation by pregnant women in our locality; where eclamptics access alternative interventions and may not present to hospital until when labour has set in and without progression to delivery. Earlier studies had made similar observations of late or delayed hospital presentation leading to higher occurrence of intrapartum eclampsia (Sibai BM 2005; Perry KG *et al.*, 1992; Nwobodo EI *et al.*, 2011).

The eclamptics in our study had lower fibrinogen but higher D-dimer levels than the normal pregnant group; a finding consistent with earlier works (Pritchard *et al.*, 1976; Dube *et al.*, 1975; Tacoosian *et al.*, 2007; Zhon *et al.*, 1997). Our findings of high D-dimer in the setting of low fibrinogen levels depict activation of both coagulation and fibrinolytic systems in keeping with a consumptive coagulopathy observed by numerous other workers (Rodie VA, 2006; Roberts JM *et al.*, 1976; Sibai BM 2005; Perry KG *et al.*, 1992). In contrast to our study, Jahromi (Jahromi *et al.*, 2009) did not find a statistically significant difference between the mean fibrinogen levels of the eclamptics and pregnant women while Adediran (Adediran *et al.*, 1999) recorded elevated levels of fibrinogen with the eclamptics.

Our observation that these haemostatic derangements seem not to be affected by the type of eclampsia but rather worsen with advancing gestational age is in agreement with the works of Mjahed *et al.*, 1998 who in addition found significant effect of advancing maternal age on haemostasis in eclampsia. The rate of development of eclampsia is regarded as the most important determinant of haemostatic perturbation of the disease; thus underscoring the need for early identification of pregnant women at risk of developing eclampsia for prompt intervention (Roberts JM *et al.*, 1976; Perry KG *et al.*, 1992; Jahromi *et al.*, 2009).

The occurrence of haemostatic complications and their association with unfavourable materno-fetal outcomes in eclampsia have been demonstrated by several earlier workers (Sibai BM 2005; Okegbenin SA *et al.*, 2010; Oladokun A *et al.*, 2000; Odum CU, 1991). For instance, in a study involving 845 eclamptics, DIC contributed up to 10.9% of maternal complications in Nigeria (Odum CU, 1991). These observations led to the search for a variable that could possibly predict the development of such haemostatic complications for timely intervention (Leduc L *et al.*, 1992; Laskin S *et al.*, 2011; Dadelszen P *et al.*, 2011). Some workers have identified thrombocytopaenia to be predictive of materno-fetal morbidity and mortality as it was significantly associated fetal distress, intrauterine growth restriction (IUGR), maternal cerebral haemorrhage and both maternal and fetal deaths (Leduc L *et al.*, 1992; Laskin S *et al.*, 2011; Dadelszen P *et al.*, 2011). Although our study recorded deranged levels of fibrinogen and D-dimer with the eclamptics but such derangement was not found to be predictive of poor maternofetal outcomes such as maternal death and fetal still birth.

CONCLUSION:

This study has shown that haemostatic derangements such as low plasma fibrinogen and elevated D-dimer levels do complicate eclampsia; reflecting a state of consumptive coagulopathy and exaggerated fibrinolysis associated with the disorder. This finding underscores the importance of haemostatic surveillance in the management of eclampsia.

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Conflict of interest: Nil

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