The Association between Thrombin Antithrombin Complex and Foetal Outcomes in Women with Preeclampsia-Eclampsia at the University of Benin Teaching Hospital, Benin City, Nigeria

***Okuonghae ME,[1] Nwogoh B,[2] Chimeziem C[3]**

ABSTRACT

Preeclampsia and eclampsia are major contributors to perinatal morbidity and mortality globally. Haematologic derangements have been associated with adverse perinatal outcomes in women with preeclampsia. However, this has not been adequately investigated in our environment. This study aimed at determining the association between thrombin antithrombin complex (TAT) and foetal outcomes in patients with Preeclampsia-eclampsia. This is a hospital-based cross-sectional study conducted at the university of Benin teaching hospital, Benin City, Edo state. Seventy-two preeclampsia-eclampsia women and seventy controls participated in the study. Full blood count parameters were estimated using an auto analyser (Sysmex Haematology Autoanalyser model KN21). Thrombin antithrombin complex was estimated using the enzyme-linked immunosorbent assay method. Data were analyzed using the statistical package for social sciences (SPSS) version 21. The mean TAT concentration for women with preeclampsia-eclampsia was significantly higher than the control group (19.6 ± 3.2µg/L vs 15.7 ± 3.9µg/L; p = < 0.001). Newborns born of women with preeclampsia-eclampsia had low birth weight in comparison with controls (33.3% vs 4.3%; p = < 0.001). Babies born in the study group also had more neonatal intensive care unit (NICU) admissions and foetal death than in the normotensive group (45.8% and 33.3% vs 5.7% and 1.4% respectively). Preeclampsia-eclampsia is associated with elevated TAT levels in women with preeclampsia- eclampsia and there was a significant association with foetal low birth weight, admission into NICU and perinatal mortality.

Keywords: Foetal Outcomes (FO), Thrombin-antithrombin Complex (TAT), Preeclampsia-eclampsia (PE)

INTRODUCTION

Preeclampsia is a pregnancy-specific condition, with a serious impact on the health and quality of life of both mother and child.[1] It is a multisystemic progressive disorder, characterized by elevated blood pressure and proteinuria occurring after 20 weeks gestation.[1] When convulsions occur in addition to these signs, the condition is referred to as Eclampsia.

Preeclampsia has remained a significant public health threat in both developed and developing countries contributing significantly to perinatal morbidity and mortality.[2] It complicates 2-10% of all pregnancies worldwide and the prevalence in Nigeria ranges between 2% to 16%.[1] The prevalence in Benin City is 5.6%.[3] Approximately 12% to 25% of fetal growth restriction and small for gestational age infants as well as 15 to 20% of all preterm births are attributable to preeclampsia.[2] The impact of the disease is felt more in developing countries as the World Health Organization (WHO) estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4% of live births).[2]

WHO estimates the incidence of eclampsia in the developed countries of North America and Europe to be about 5-7 cases per 10,000 deliveries.[2] The incidence of eclampsia in developing nations varies widely, ranging from 1 case per 100 pregnancies to 1

Department of Haematology and Blood Transfusion,[1] Delta State University Teaching Hospital, Oghara. Nigeria.
Department of Haematology and Blood Transfusion,[2] University of Benin Teaching Hospital, Benin City, Nigeria.
Department of Haematology,[3] University of Calabar, Cross-River state, Nigeria.

*Corresponding author: emokuonghae@delsu.edu.ng
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case per 1700 pregnancies. The prevalence of eclampsia in Nigeria varies between 0.91-9.42% and in Benin City, it is 1.32%.[4]

Reports have shown that preeclampsia-eclampsia accounts for the death of 500,000 babies yearly.[5] Relative to other low-income sub-Saharan African nations, Nigeria also has a high infant mortality rate (67 deaths per 1000 live births).[5]

Preeclampsia is defined as the presence of a systolic blood pressure (SBP) greater than or equal to 140mmHg or a diastolic blood pressure (DBP) greater than or equal to 90mmHg or higher, on two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient, OR an SBP greater than or equal to 160mmHg or a DBP greater than or equal to 110mmHg or higher with proteinuria greater than or equal to 300mg/24-hour urine OR protein creatinine ratio greater than or equal to 0.3 OR dipstick result of 1+. In the absence of proteinuria, it may be characterized by thrombocytopenia (platelet count less than 100,000 cells/ml); Impaired liver function (elevated blood levels of transaminases to twice the normal concentration); New development of renal insufficiency (serum creatinine greater than 1.1mg/dl or a doubling of serum creatinine in the absence of other renal diseases); Pulmonary oedema and new onset cerebral or visual disturbances.[6] Eclampsia is the convulsive phase of the disease when seizures cannot be attributed to other causes.

Despite a vast literature on these disorders, the pathophysiology is poorly understood.[7] The abnormal invasion of the placenta and the release of placenta-derived adverse factors during the first trimester is thought to be the main cause of the extensive damage to the maternal endothelium. This elicits a systemic inflammatory response involving many systems and organs in late pregnancy.[8]

Foetal complications associated with preeclampsia include increased premature delivery, intrauterine growth restriction (IUGR), low birth weight, increased admissions into the neonatal intensive care unit (NICU) and death.[9]

To date, there is no effective treatment for preeclampsia apart from the prompt termination of pregnancy.[10] Therefore, a reliable predictor for preeclampsia would play an important role in early prevention and intervention.

The association between coagulation activation and morbidity associated with preeclampsia has not been fully explored especially in our environment. Hypercoagulative tendency is a physiologic feature, especially in late pregnancy, and it is more pronounced in preeclampsia compared to normotensive women: this has been attributed to increased thrombin generation in women with preeclampsia-eclampsia.[11] In preeclampsia, due to endothelial injury, the delicate hemostatic mechanism is triggered, which ultimately leads to coagulation failure.

Thrombin antithrombin (TAT) is a complex formed when thrombin is inactivated by its major inhibitor, antithrombin (AT). This process leads to the appearance of TAT in peripheral blood. Thus, measurement of plasma TAT concentration allows the detection of coagulation activation and because TAT has a half-life of only a few minutes, the levels reflect the actual extent of the intravascular activation of coagulation in vivo at the time of sample collection.[12] The level of TAT in the plasma of healthy men and women ranges from 1-5μg/L and this increases to about 10μg/L in pregnancy.[13]

This study aims to evaluate the association between TAT complex as a marker of coagulation activation and foetal outcome in women with preeclampsia-eclampsia.

METHODOLOGY

This was a cross-sectional study conducted at the Obstetric/Gynaecology and Haematology departments of the University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria. Foetal outcomes of new born in a study on the association of thrombin antithrombin complex with maternal outcome of women with preeclampsia-eclampsia were analyzed and related to maternal TAT levels. The primary study has been published.[14] Recruitment of participants, sample collection and measurement of study outcome were done at the Obstetric department while analyses of markers of coagulation activation and other laboratory parameters were done at the department of Haematology.

Study population

The study participants consisted of newborns of women diagnosed with preeclampsia-eclampsia. They were recruited consecutively from the antenatal clinic (ANC), obstetric emergency unit and labour ward of the Obstetrics and Gynaecology department till the sample size was achieved. Healthy pregnant women matched for gestational age (±2weeks difference in GA with the study group) were recruited as the control cohort.

Sample size estimation

Using the sample size estimation formula for the comparison of two means and assuming the power of 80% and 95% confidence interval, the sample size was calculated thus:[15]

Number of participants per group

$$= \frac{2\,(- /2 + -)^2\,(d_2\ d_1)^2}{(U_2 - U_1)^2}$$

Given that − /2 at 80% is 0.84 and − at 95% is 1.96, $2\,(- \ 2 + -)^2)^2 = 15.68$

D_1 = Standard deviation of TAT in control from previous study done by Schjetlein *et al.* [5.8µg/L][16]

d_2 = Standard deviation of TAT in HDP from the same study [16.0µg/L]

U_1 = Mean TAT in control [17.5µg/L]

U_2 = Mean TAT in HDP [22.3µg/L]

n = Minimum sample size

n (number of subjects per group)

$$= \frac{15.68 \times (10.2)^2}{(4.8)^2}$$

= 70.805 (approximately 71 per group).

Sampling technique

Consecutive sampling technique was used for this study.

Inclusion criteria

i. Pregnant women with blood pressure ≥ 160/110mmhg or ≥140/90mmhg 6 hours apart.
ii. Proteinuria 1+ and above.
iii. Women diagnosed with eclampsia

Exclusion criteria

i. Patients with chronic hypertension in pregnancy and gestational hypertension.
ii. Participants with comorbidities include but are not limited to chronic hepatitis, diabetes and renal disease.
iii. Participants with a history of coagulopathy which includes but is not limited to deep venous thrombosis and haemophilia A and B.
iv. Participants are on any form of anticoagulant or antiplatelet medication.

Study definition

a. Preeclampsia: Preeclampsia was defined as SBP greater than or equal to 140mmHg or a DBP greater than or equal to 90mmHg taken at least 4 hours apart after 20 weeks of gestation measured 6 h apart associated with

proteinuria (> 300mg/ 24h OR ≥ 1+) in a previously normotensive patient.

b. Eclampsia: Eclampsia was defined as the occurrence of convulsions and/or coma unrelated to other cerebral conditions in women with signs and symptoms of preeclampsia.

Outcome measures

The primary outcome measure includes TAT levels and foetal outcomes. The outcomes of interest include:

- Fetal maturity
- Low birth weight: An infant born weighing 2.5kg or less
- Neonatal sepsis (NNS): Neonatal sepsis refers to an infection involving the bloodstream in newborn infants less than 28 days old.
- Respiratory distress syndrome (RDS)
- Hypoxic ischaemic encephalopathy (HIE)
- Admission into the Neonatal intensive care unit (NICU)
- Survival (Alive/dead)

Study instrument

After obtaining consent, a study proforma was used to collect the demographic parameters of the study participants, history of current pregnancy, previous pregnancy history, medical, social and family histories. Thereafter, blood samples were collected for the assessment of TAT.

Specimen collection and analysis

4.5 millilitres (mls) of venous blood was drawn aseptically from the antecubital vein of each subject with minimal stasis and dispensed into a sample bottle containing 0.5mls of 0.109M sodium citrate (3.2%). This was to obtain blood: citrate ratio of 9:1. The sample was mixed by gentle inversion to ensure adequate mixing of the anticoagulant with the blood. The sample was transported in an ice pack to maintain viability from point of collection to the laboratory within two minutes. The sample was centrifuged at room temperature at a speed of 2000 gravities (g) for 10mins to obtain platelet-poor plasma. The specimen was immediately frozen at -80^0C and analysed about six weeks later. All specimens were labelled with personally generated identification numbers and recorded in the datasheet.

Study duration: The study was carried out overten months.

Test procedures

Determination of TAT: The plasma level of TAT was evaluated using ELISA quantitation assay (Elabscience assay kit).

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Data analysis

Data was analysed using SPSS version 23. Continuous variables were tested for normality. Normally distributed variables were summarized as mean, standard deviation and ranges while skewed variables were summarized as median and interquartile ranges. The student t-test was used to compare differences in the mean between groups while the Mann-Whitney U test was used to compare differences in the median.

Categorical variables including foetal outcomes were summarized as percentages. Chi-square (or Fischer's exact test as appropriate) was used to compare categorical outcome variables. Multivariate regression analysis was used to test for the association between TAT and foetal outcome. Statistical significance was set at less than 0.05 ($p < 0.05$).

Ethical consideration

The study was approved by the Hospital's ethical review committee (Protocol number: ADM/E22/A/VOL. VII/1483052). Participants gave informed consent before recruitment.

RESULTS

Demographics of the study population

A total of 142 subjects were recruited for the study comprising 71 women with preeclampsia-eclampsia and 71 normal pregnant women. However, one of the controls developed preeclampsia and was thus transferred to the case group. In all, 72 subjects in the preeclampsia-eclampsia group and 70 patients in the controls were analyzed.

The mean age of the study and control group were 31.3 ± 5.3 years and 28.9 ± 5.9 years respectively. The difference in their mean age was statistically significant (p = 0.010). The mean gestational age at sampling was 34.2 ± 4.4 weeks with a range of 20.6-40.0 weeks and 34.3 ± 5.4 weeks with a range of 13.0-41.3 weeks for case and control groups respectively. The difference in their mean gestational age was not statistically significant (p = 0.872).

Forty-five (31.7%) of the women recruited in the study were nulliparous. This was relatively evenly distributed between both groups; 24(33.8%) study group and 21(32.8%) normotensive participants. No participant in the study group was grand multiparous but one (0.7%) in the control group. The majority, 96(67.6%). of the participants were multiparous.(Table 1)

Mode of delivery

Eighty women (56.3%) had vaginal deliveries comprising twenty-three participants (31.9%) in the study group and fifty-seven women (81.4%) in the control group. Sixty-two women (43.7%) had Caesarean section: 49(68.1%) of the women in the study population and 13(18.6%) of the control group. The difference in the number of Caesarean sections was statistically significant (p = 0.001). Fifty- three women (85.5%) had emergencyCaesarean section (EMCS) and the study group comprised the bulk of the population [forty-five (91.8%)]. Nine women (14.5%) had elective caesarean sections (ELCS).

Foetal Outcomes

The mean birth weight of newborns in the case group was significantly lower than that of the control group (2.4kg ± 0.8 vs 3.3kg ± 0.5, p = < 0.001). NICU admission was the commonest foetal complication recorded in the study, having 33 babies (45.8%) in the study group and 4 babies (5.7%) in the control group. This was immediately followed bylow birth weight (LBW) and foetal deaths (IUFD/SB/NND) each affecting 24 babies (24%) in the study group and 3 babies (4.3%) and 1(1.4%) newborns respectively. The difference in the proportion of newborns with LBW and foetal deaths between both groups was statistically significant (p = < 0.001).

In addition, 12 newborns (16.7%) developed neonatal sepsis (NNS) in the case group as against just 2 babies (2.9%) in the control. The difference in the proportion of NNS between the two study groups reached statistical significance (p = 0.009).

9 babies (12.5%) were affected by respiratory distress syndrome (RDS)/ hypoxic ischaemic encephalopathy in women with preeclampsia versus 2 babies (2.9%) in the normotensive group. However, there was no statistical difference between the case group and the control (p = 0.056).

The mean concentration of thrombin antithrombin (TAT) complex was significantly higher in the case group compared to controls (19.6 ± 3.2µg/L vs. 15.7 ± 3.9µg/L; p = <0.001). Nineteen (26.4%) women in the Case group had elevated TAT complex as against one (1.4%) normotensive woman (p <0.001). (Figure I).

Logistic Regression of TAT and Fetal Outcome

TAT levels were associated with reduced birth weight but this did not reach statistical significance (OR = 0.516, 95% CI = 0.146-1.819, p = 0.303). HIE and NNS were

associated with increased odds of elevated TAT level, however, this did not reach statistical significance (OR-2.096, 95% CI-0.219-20.027; p = 0.521 and OR 2.286, 95% CI 0.415-12.582, p = 0.342 respectively). Similarly, elevated TAT was associated with high odds of NICU admissions but also not statistically significant (OR = 2.678, 95% CI = -0.723-9.919, p = 0.140).

Elevated TAT was associated with increased odds of foetal deaths (IUFD/NND/SB) and it was statistically significant (OR = 5.532, 95% CI = 1.131-27.068, p = 0.035).

Table 1: Demographic characteristics of the study population

	Case n(%) = 72	Control n(%) =70	Total n(%) = 142	Stats	P- value
Age group(years)					
<25	8(11.1)	15(21.4)	23(16.2)		
25-29	19(26.4)	25(35.7)	44(31.0)	Fishers	0.196
30-34	25(34.7)	18(25.7)	43(30.3)		
35-39	14(19.4)	9(12.9)	23(16.2)		
≥40	6(8.3)	3(4.3)	9(6.3)		
Marital status					
Single	1(1.4)	4(5.7)	5(3.5)	Fishers	0.206
Married	71(98.6)	66(94.3)	137(96.5)		
Education					
Primary	10(13.9)	11(15.7)	21(14.8)		
Secondary	30(41.7)	27(38.6)	57(40.1)	0.177	0.195
Tertiary	32(44.4)	32(45.7)	64(45.1)		
Gravidity					
1	10(14.1)	10(14.1)	20(14.1)		
2- 5	57(80.3)	53(74.6)	110(77.5)	Fishers	0.553
>5	4(5.6)	8(11.3)	12 (8.5)		
Parity					
0	24(33.8)	21(32.8)	45(31.7)		
1- 5	47(66.2)	49(69.0)	96(67.6)	Fishers	0.719
>5	0(0.0)	1(1.4)	1(0.7)		

Table 2: Foetal Complications and Birth Weight

Outcome	Case Group n(%) = 72	Controls n(%) = 70	Total n(%) = 142	Stats	P value
Foetal Complications					
IUFD/SB/NND	24(33.3)	1(1.4)	25(17.6)	Fishers	<0.001
LBW	24(33.3)	3(4.3)	27(19.0)	Fishers	<0.001
NNS	12(16.7)	2(2.9)	14(9.9)	Fishers	0.009
HIE/RDS	9(12.5)	2(2.9)	11(7.7)	Fishers	0.056
NICU	33(45.8)	4(5.7)	37(26.1)	Fishers	<0.001
Birth weight(Kg)					
Mean ± SD	2.4 ± 0.8	3.3 ± 0.5		-7.721	<0.001
Range	0.8-4.0	2.3-4.1			

IUFD: Intra-uterine foetal death SB; Stillbirth, NND; Neonatal death, LBW: Low birth weight, NNS: Neonatal sepsis, HIE: Hypoxic ischaemic encephalopathy, RDS; Respiratory distress syndrome, NICU; Neonatal intensive care unit.

Table 3: TAT levels in women with preeclampsia-eclampsia versus controls

	Case Group n(%) = 72	Controls n(%) = 70	Total n(%) = 142	Stats	P value
TAT					
Normal	53(73.6)	69(98.6)	122(85.9)	Fishers	<0.001
Elevated	19(26.4.)	1(1.40)	20(14.10)		

TAT: Thrombin antithrombin complex

Table 4: Logistic Regression of TAT and Foetal Outcome

	B	S.E	P	OR	95% CI
LBW	-0.662	0.643	0.303	0.516	0.146-1.819
HIE	0.740	1.152	0.521	2.096	0.219-20.027
NNS	0.827	0.870	0.342	2.286	0.415-12.582
NICU	0.985	0.668	0.140	2.678	0.723-9.919
IUFD/NND/SB	1.711	0.810	0.035	5.532	1.131-27.068

LBW: Low birth weight, HIE: Hypoxic ischaemic encephalopathy, NNS: Neonatal sepsis, NICU: Neonatal intensive care unit, IUFD: Intrauterine foetal death, NND: Neonatal death, SB: Stillbirth

DISCUSSION

The study findings include significantly elevated mean TAT levels in women with preeclampsia-eclampsia in comparison to the controls. This was consistent with the studies by Reinthaller *et al*, Schjetlein *et al.* and Dreyfus *et al.*[12,16,17]

However, the mean TAT values obtained from the index study were higher than those of Reinthaller *et al.* in a Caucasian population but relatively lower than those of Schjetlein *et al.* and Dreyfus *et al.* The differences in mean values obtained may be attributed to ethnic differences in the study population. Variations in haemostatic parameters with geographical and ethnic variations have been reported in the literature.[18] Another factor that may contribute to the observed differences in mean was disease severity. The study by Reinthaller *et al.* included mainly women with gestational hypertension which is a less severe form of hypertensive disorder of pregnancy while those of Schjetlein *et al.* included mainly women with preeclampsia which was the case in the index study.

The pathophysiology behind elevated TAT in HDP may be attributed to the chronic activation of the endothelium and the intravascular coagulation system. This results in the formation of thrombin which in turn is inactivated by a complex formed with its major inhibitor, antithrombin (AT). This process leads to the appearance of TAT in peripheral blood. Therefore measurement of plasma TAT complex concentrations is a suitable marker of coagulation activation in HDP.

The perinatal outcomes of foetus/newborns of women with preeclampsia were found to be significantly worse compared to those of women with normal uncomplicated pregnancies. The mean birth weight of neonates born of women with preeclampsia was significantly reduced compared to the controls. This was consistent with the findings of Schjetlein *et al*, Obi *et al.* and Reinthaller *et al.* who reported a statistical difference in birth weight between the two groups in their separate studies.[12,16,19] Also the mean birth weight observed in these studies was somewhat consistent with findings in this study.

Low birth weight (LBW) was found to be associated with preeclampsia in the index study and it was statistically significant. This was consistent with reports by Onyiriuka *et al.* in Benin City, Yilgwan *et al.*

in Jos, and Obi *et al.* in Abakalaki.[3,19,20] The LBW could be a consequence of intravascular coagulation leading to increased fibrin deposition, placental vessels thrombosis and culminating in foetal hypoperfusion. There is also a relatively higher incidence of preterm delivery in women with preeclampsia and this may contribute to the relatively LBW observed in newborns. Birth weight was observed to have a negative correlation with TAT; however, the logistic regression model showed that there was no significant association between LBW and TAT.

The newborns of women with preeclampsia had a higher incidence of neonatal sepsis and the differences in proportion were statistically significant. This was similar to the report by Onyiriuka *et al*.[3]

There was significantly increased rate of neonatal intensive care unit (NICU) admissions for babies born to women with preeclampsia. Though not statistically significant, a higher odd of NICU admissions was associated with TAT levels in the study. This is consistent with the reports by Yilgwan *et al*.[20] It is biologically plausible and not unexpected as generally shown in the index study and other studies, that foetal complication is increased in women with preeclampsia. It is implied that they will require more intensive care admissions.

Perinatal deaths including intrauterine deaths (IUFD), stillbirths (SB) and neonatal deaths (NND) were higher in pregnancies complicated with Preeclampsia and this was statistically significant. This is consistent with findings from various investigators.[21-23]The cause of increased perinatal mortality is multifactorial. It could be attributed to uteroplacental insufficiency associated with preeclampsia. The study also noted significantly increased odds of perinatal deaths in mothers with elevated levels of TAT complex.

In conclusion, the study has demonstrated increased morbidity and mortality of foetus in women with preeclampsia-eclampsia. TAT levels have also been shown to be significantly increased in the study group compared to normal pregnancy.

Study limitation

Despite attempting to establish foetal outcomes in women with preeclampsia-eclampsia, results from the study may have been different if a larger sample size was exploited. Hence the study was limited by its sample size. Also, the participants were drawn from a single centre. A multicenter study would have helped to improve external validity of the study.

Recommendation

Thrombin antithrombin complex could be institutionalized as a marker of coagulation activation, especially in high-risk patients. A larger study may help to establish an association between TAT and foetal outcome and also improve external validity of the study.

Conflict of interest: There was no conflict of interest.

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