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Research Paper

The association between Thrombin Antithrombin Complex and Maternal outcomes in women with Preeclampsia-Eclampsia at the University of Benin Teaching Hospital, Benin City, Nigeria

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ABSTRACT
***Background**: Preeclampsia and eclampsia are major contributors to maternal/perinatal morbidity and mortality globally. Haematologicderangements have been associated with adverse outcome in women with preeclampsia. However, this has not been adequately investigated in our environment.*
***Aim**: This study aimed at determining the association between thrombin antithrombin complex (TAT) and maternal outcomes in patients with preeclampsia-eclampsia*
***Methodology**: This is a hospital based cohort 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 ware estimated using an auto analyser (Sysmex Haematology Autoanalyser model KN21). Coagulation parameters (Prothrombin time (PT) and Activated partial thromboplastin time (APTT)) were estimated manually and TAT was estimated using the enzyme linked immunosorbent assay method. Data were analyzed using the statistical package for social sciences (SPSS) version 21.*
***Results**: 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). Preeclampsia patients had reduced mean platelet count compared to controls but it was not statistically significant (155.9±60.4x109/L vs 165.3±109/L; P= 0.295). The mean PT was significantly higher in the case group (14.3±2.8sec vs 13.2±0.8sec; p= 0.002). APTT was also increased in the case group but it did not reach statistical significance (34.2±6.4sec vs 31.2±2.4sec; p= <0.001).*
***Conclusion**: Preeclampsia-eclampsia is associated with elevated TAT levels but there were no significant associations with maternal outcomes.*

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I. INTRODUCTION

Preeclampsia has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality. It complicates 2-10% of all pregnanciesworldwide.[1] Although, maternal death due to preeclampsia is less common in developed countries, maternal morbidity is still high and is a major contributor to intensive care unit admissions during pregnancy.[2] The impact of the disease is felt more severely in developing countries as the World Health Organization (WHO) estimates the incidence of preeclampsia to be seven times higher in developing countries than in developed countries (0.4%).[1]

WHO also estimates the incidence of eclampsia in the developed countries of North America and Europe to be about 5–7 cases per 10,000 deliveries.[1]The incidence of eclampsia in developing nations varies widely, ranging from 1 case per 100 pregnancies to 1 case per 1700 pregnancies. Rates from African countries such as South Africa, Egypt, Tanzania, and Ethiopia vary from 1.8% to 7.1%.[1] In Nigeria, prevalence ranges between 2% to 16.7%and it is 5.6% in Benin City.[3]Nigeria has one of the highest maternal mortality in the world (545/100,000 live births), the worse in Africa.[4] Preeclampsia-eclampsia accounted for 36.9% of these deaths second to ante and postpartum haemorrhage.[5]

HDP refer to a group of conditions of vascular origin and systemic manifestations caused by a mixture of genetic and acquired factors, which occur during pregnancy.[6] According to the National High Blood Pressure Education Program Working Group, it includes chronic hypertension, Preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension and gestational hypertension.[7] This widely used classification takes into account the time of appearance of the condition in relation to the pregnancy. The outcome of pregnancy is different depending on the type of disorder concerned.

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 a 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.[7] Eclampsia is the convulsive phase of the disease, when seizures cannot be attributed to other cause.

Superimposed preeclampsia is characterized by (1) new onset proteinuria (≥300 mg/24 h) in a known hypertensive but no proteinuria before 20 weeks' gestation and (2) a sudden increase in proteinuria or blood pressure (BP), or a platelet count of less than 100,000/mm3, in a woman with hypertension.

Despite a vast literature on these disorders, the pathophysiology is poorly understood.[8] The abnormal invasion of 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.[9] With respect to developing preeclampsia, the following risk factors have been described: previous preeclampsia or hypertension in pregnancy, chronic kidney disease, diabetes (type 1 and 2) and autoimmune disorders.[10] Others include, first pregnancy, age>40 years, >10 year interval from last pregnancy, body mass index (BMI) >35kg/m^2, polycystic ovarian syndrome, family history of preeclampsia and multiple pregnancies are considered to be moderate risk factors.[10]

In a study to determine the incidence of severe maternal morbidity in the United States of America, women with preeclampsia and eclampsia had a 3-to 25-fold increased risk of severe complications, such as abruptio placentae, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), postpartum haemorrhage, disseminated intravascular coagulopathy (DIC), pulmonary oedema, aspiration pneumonia, acute liver/renal failure and sepsis.[11] More than half of the women with preeclampsia and eclampsia had caesarean delivery in the same study. African American women not only had higher incidence of hypertensive disorders in pregnancy but also tended to have a greater risk for most severe complication.[11] In southeast Nigeria it was reported that 87.9% of women with preeclampsia died from one or more complications and 51.7% delivered via a caesarean section.[12] Women with preeclampsia also have an increased lifetime risk of cardiovascular disease.[13]

To date, there is no effective treatment for preeclampsia apart from the prompt termination of pregnancy.[2] 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 or thrombophilic tendency is a physiologic feature especially in late pregnancy, and it is more pronounced in.[14]In preeclampsia, due to endothelial injury, the delicate hemostatic mechanism is triggered, which ultimately leads to coagulation failure. Hypercoagulability in pregnancy can be assessed using several coagulation activation markers: fibrinogen, D-dimer, prothrombin fragments F (1+2), thrombin-antithrombin Complex (TAT), and/or Fibrin monomer complexes. TAT is a preferred index because its half-life is within a few minutes (about 3minutes) and therefore may be more relevant than fibrin degradation products.[19]

TAT is a complex formed when thrombin is inactivated by its major inhibitor, antithrombin (AT). This process leads to the appearance of Thrombin – Antithrombin complex (TAT) in peripheral blood. Thus, measurement of plasma TAT concentration allows the detection of coagulation activation. Because of its short half-life, it reflect the actual extent of the intravascular activation of coagulation in vivo as at the time of sample collection.[19] The level of TAT in plasma of healthy men and women ranges from 1-5µg/L.[19] This increases throughout pregnancy to over 10 µg /L in the third trimester and to over 20µg/L during Labour.[20] In

preeclampsia, higher values have evenbeen reported.[19]Apart from pregnancy, increased TAT levels have been found in deep venous thrombosis (DVT) and disseminated intravascular coagulopathy (DIC).[21] The association of plasma levels of TAT in preeclampsiapatients with pregnancy outcomes have not been explored in our environment.

The aim of this study is to evaluate the association between TAT complex as a marker of coagulation activation and maternal outcome in women with preeclampsia - eclampsia.

II. METHODOLOGY

Study design This was a comparative cohort study.

Study area: This study was conducted at the Obstetric/Gynaecology and Haematology departments of the University of Benin Teaching Hospital (UBTH). UBTH is a Federal Government owned tertiary institution with over 800-bed capacity, situated in Egor LGA, Benin City, Edo State, Nigeria. 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 participantsconsisted of women diagnosed of 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. Apparently healthy pregnant women matched for gestational age (±2weeks difference in GA with the study group) wererecruited as the control cohort.

Sample size estimation: Using the sample size estimation formula[23] for comparison of two means and assuming the power of 80% and 95% confidence interval, the sample size was calculated thus:

Number of participants per group $= \frac{2\ (\neq\alpha/2 + \neq\beta)^2\ (d_2 - d_1)^2}{(U_2 - U_1)^2}$

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

d_1 = Standard deviation of TAT in control from previous study done by Schjetlein et al. [5.8µg/L][24]

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 6hours 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 which include but are not limited to chronic hepatitis, diabetes and renal disease.
iii. Participants with a history of coagulopathy which includes but not limited to deep venous thrombosis and haemophilia A and B.
iv. Participants on any form of anticoagulant or antiplatelet medication.

Study definition

a. **Preeclampsia:** Preeclampsia was defined as SBP greater than or equal to 140 mmHg 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. **Mild Preeclampsia:** It is defined as SBP ranges between 140-160mmhg and DBP between 90-110mmhg with proteinuria and no clinical symptoms.

c. **Severe Preeclampsia:** It is defined as SBP above 160mmhg and DBP above 110mmhg with proteinuria and clinical features of preeclampsia.

d. **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 maternal outcomes. The outcomes of interest include:

- Development of disseminated intravascular coagulopathy (DIC): An acquired syndrome characterized by activation of coagulation pathways, resulting in the formation of intravascular thrombi and depletion of platelets and coagulation factors.

- Abruptio placentae (premature separation of the placenta from the uterus)
- Acute kidney injury (AKI): An abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function).
- Developing HELLP syndrome (Haemolysis, elevated liver enzymes and low platelets)
- Premature rupture of membrane: Premature rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labour.
- Postpartum haemorrhage: blood loss of 500 ml or more within 24 hours after birth.
- Preterm delivery:Any delivery after fetal viability but before 37 completed weeks of pregnancy.
- Maternal survival

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 blood count, clotting profile and assessment of TAT. Participants were sampled at recruitment and during labour.

Specimen collection and analysis

Eight milliliters (mls) of venous blood was drawn aseptically from the antecubital vein of each subject with minimal stasis.Four and a half (4.5mls) of whole blood for TAT and coagulation test (Prothrombin time and activated partial thromboplastin time) were dispensed into a sample bottle containing 0.5mls of 0.109M sodium citrate (3.2%). This was to obtain a blood: citrate ratio of 9:1. The sample was mixed by gentle inversion at least six times 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 plasma was carefully removed to prevent cell lysis with a plastic pipette into a plane bottle. The specimen was divided into aliquots; one aliquot for Prothrombin and activated Thromboplastin time assays and the other aliquot for TAT assay. The PT and APTT assays were analyzed immediately. Reagents used for coagulation screening were quality controlled before analyses. The specimen for TAT was immediately frozen at -80^0C and analysed about six weeks later.

The remaining volume of whole blood was dispensed into a commercially prepared ethylene di-amine tetra-acetic acid (EDTA) bottle for basic haematological parameters (full blood count). The sample was mixed gently but thoroughly to prevent cell lysis and ensure anticoagulation and analysed immediately. All specimens were labelled with personally generated identification numbers and recorded in the datasheet.

Study duration: The study was carried out over a period of ten months.

Test procedures

1. Basic Haematological Parameters: Full blood count which includes haematocrit, haemoglobin concentration, total white cell count and platelet counts will be obtained from the EDTA sample using automated blood cell counter (Sysmex Haematology Autoanalyser).
2. Coagulation tests: Prothrombin time and activated partial thromboplastin time test was carried out for both control and study group. This was doneusing Helena biosciences kit. (PT Lot No.21483896, APTTLot No. 21724948)
3. Determination of TAT: The plasma level of TAT was evaluated using ELISA quantitation assay (Elabscience assay kit).

Data analysis: Data was analysed using Statistical Package for the social sciences (SPSS) version 23. Continuous variables (maternal age, gestation age, PT, APTT and TAT) 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 maternal 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 pregnancy outcome. Statistical significance was set at less than 0.05 ($p < 0.05$).

Ethical consideration: The study wasapproved by the Hospital's Ethical Review Committee (Insert no.). Participants gave informed consent prior to recruitment.

III. RESULTS

Demographics of the study population

A total of 142 subjects were recruited for the study comprising of 71 women with Preeclampsia-eclampsia and 71 apparently 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 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 of twenty-three participants (31.9%) in the study group and fifty-seven women (81.4%) of 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 emergency Caesarean 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).

Maternal Outcomes:

Primary postpartum haemorrhage (PPH) was the predominant obstetric complication in the study, occurring in seven participants (9.7%) of the case group population and two women (2.9%) in the control group. This was immediately followed by disseminated intravascular coagulopathy (DIC) and antepartum haemorrhage (APH) which occurred in the Case group only, affecting five women (6.9%) each. (Table 2)

Premature rupture of membrane (PROM), HELLP syndrome and sepsis affected three women each (2.1%) in the Case group only. Two women (2.9%) each in the case group had intensive care unit (ICU) admission and ophthalmic complications. Only one patient (0.7%) had pregnancy complicated by acute kidney injury and psychosis each.There was no significant difference in the maternal outcomes between women with preeclampsia-eclampsia and their normotensive counterparts apart from the surgical interventions in delivery.

The study recorded four maternal deaths (5.6%) in the case group while no death was recorded in the control. All deaths occurred within sixteen days of delivery. The difference in the proportion of maternal death between the two study groups did not reach statistical significance (p = 0.119).

Haematological Parameters

Tables 3 show the distribution of haematological parameters of the study and control population. The mean haemoglobin level in patients with preeclampsia-eclampsia was significantly lower than those of the Control (11.2±1.7g/dl vs. 12.0±0.9g/dl, p = 0.002). Similarly, they had a significantly lower mean packed cell volume (32.8±4.8% vs. 35.4±2.3%; p = <0.001).

The mean total white blood cell count was significantly higher in the Case group than in the controls (9.5±4.2 x 10^9/L vs 7.4±1.6 x 10^9/L, p =< 0.001). The white blood cell ranged between 3.4 -27.4 x 10^9/L in the case group and 3.4-10.7 x 10^9/L in the control. The mean granulocyte count was significantly higher in women with preeclampsia-eclampsia (6.7 ± 3.8 x 10^9/L vs 4.7 ± 1.4 x 10^9/L, p= <0.001).

The Case group had a mean platelet count of 155.9±60.4 x 10^9 cells/L with a range of 48.0-405 x 10^9 cells/L while the control group had a mean platelet count of 165.0 ± 45.6 x 10^9 cells/L and a range of 51.0-289.0 x 10^9 cells/L.The difference in mean platelet count was not statistically significant (p = 0.295). Eight women (11.1%) in the case group had platelet count below 100x10^9 cells/Lversus three (4.3%) in the control (p = 0.208).

The mean prothrombin time (PT)for the subject group was 14.3± 2.8seconds with a range of 12-27 seconds while that of the control group had a mean prothrombin time of 13.2± 0.8seconds with a range of 13.4 -14.1 seconds. The difference in the mean prothrombin time between the two groups was significantly significant (p= 0.002). Fourteen (19.4%) women in the case group had prolonged PT while three women (3.0%) in the control group had prolonged prothrombin time. There was significant difference in the proportion of women with prolong PT between both groups (p = 0.005). (Table 4)

The mean activated partial thromboplastin time (APTT) for women in the case group was significantly higher than in the case group (34.2± 6.4 seconds vs. 31.2± 2.4 seconds, p= <0.001).Ten women (13.9%) in the Case group had prolonged APTT as against non in the control. The difference was significantly significant (p=0.001).

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).

Distribution of Haematological parameters based on Severity of Preeclampsia

Thirteen (18.1%) women had mild preeclampsia and fifty-nine (81.9%) women had severe preeclampsia. There were no significant differences in the platelet counts, PT and APTT of women with mild and severe preeclamp-

sia. However, TAT concentration was significantly higher in women with severe preeclampsia than those with mild disease (20.1±2.4µg/L vs 15.3±2.6µg/L; p=<0.001). (Table 5)

Correlation between TAT complex, maternal age, BMI and haematologic parameters

There was no significant statistical correlation between TAT complex with maternal age and BMI in this study (r = 0.082, p=0.495 and r = 0.066, p=0.959 respectively) and the controls (r =0.081, p=0.506 and r=0.203, p=0.092).The correlation coefficient between TAT complex, haemoglobin concentration and total WBC were not statistically significant (r = 0.076, p = 0.523 and r=0.230, p=0.052 respectively) in women with preeclampsia-eclampsia. However, platelet count had a significant negative correlation with TAT concentration (r = -0.406, p<0.001) (Figure II). TAT had a positive correlation with prothrombin time (r = 0.300, p=0.010) in the study group, however there was no significant correlation with APTT (r= 0.201, p= 0.091). The relation between TAT complex with haemoglobin concentration, WBC and platelets were all not statistically significant in the normotensive group. (Table 6)

Logistic regression of TAT, Preeclampsia and maternal outcome

There was a significant association between elevated TAT complex and preeclampsia-eclampsia after adjusting for maternal age. Preeclampsia was significantly associated with increased odds of elevated TAT (OR 5.293, 95% confident interval (CI) = 2.222 – 12.605, p <0.001).There were no significant association between elevated TAT and the following maternal outcomes: occurrence of sepsis, APH, PPH, DIC and HELLP syndrome. The correlation between TAT and these maternal complications were statistically insignificant (p=0.999, 0.999, 0.999, 0.999 and 1.000 respectively). (Table 7)

IV. DISCUSSION

The study findings include significantly elevated mean TAT level in women with preeclampsia-eclampsia in comparison to the controls. This was consistent with the study by *Reinthaller et al* who noted higher levels of TAT in women with hypertensive disorders of pregnancy (HDP) when compared with those with uncomplicated pregnancy.[19] Similarly, *Schjetlein et al* and *Dreyfus et al* in different and relatively larger studies reported significantly elevated TAT levels in women with preeclampsia.[24-25]

However, the mean TAT values obtained from the index study was 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 of the study population. Variations in haemostatic parameters with geographical and ethnic variations have been reported in literature. 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.

This study noted an increase in the concentration of TAT with disease severity. This is similar to reports by *Dreyfus et al and Schjetlein et al*in their respective studies. They noted that women with severe preeclampsia had higher values of TAT than those with mild preeclampsia.The difference in TAT concentration between the two groups implies that there is increased coagulation activation in severe preeclampsia.

The pathophysiology behind elevated TAT in hypertensive disorders of pregnancy 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 suitable marker of coagulation activation in hypertensive disorders of pregnancy.

Similar to reports by*Reinthaller et al*, there was no significant difference in the concentration of TAT between the second and third trimester in the case group. This suggests that the sudden increase in TAT concentration may coincide with the onset of preeclampsia, hence early detection of high TAT value may be suggestive of the disease. However, unlike the findings by *Reinthaller*, this study also noted a significant increase in TAT concentration between the second and third trimester in normotensive women. Notably, the values were still lesser than those in the preeclampsia group.

The mean platelet count in patients with preeclampsia was found not to differ significantly from those of the control group. However, the incidence of thrombocytopenia was higher in women with preeclampsia but did not reach statistical significance. Also the mean platelet count in women with severe preeclampsia was lower than those with the mild disease but the difference was not statistically significant. These were in contrast to findings from a number of Studies that reported significant association of hypertensive disorders of pregnancy and thrombocytopeniaand significant reduction in platelet counts in patients with severe disease.[24, 26]*Galton et al* and *Schjetlein et al* had reported that severity of thrombocytopenia correlated with the severity of preeclampsia.[24,27]This disparity may be due to the difference in reference range of gestational thrombocytopenia between Caucasians and blacks.[28]

Nevertheless, some studies have reported similar rate of thrombocytopenia as found in the index study. *Perry et al* reported that only 15% of women with preeclampsiahad low platelet count which was relatively close to the incidence rate of 11.1% found in this study.[29]

A weak negative correlation was found between platelet count and TAT levels in the index study. Increased platelet activation, consumption and enhanced thrombin generation associated with increased TAT levels may have accounted for this relationship.

The mean Prothrombin time was found to be significantly increased in women with preeclampsia. Similarly, the incidence ofprolonged PT was also significantly higher in the preeclampsia group. This study agree withfindings by *Lakshmi et al, FitzGerald et al and Hajier et al* who in their different studies noted prolonged PT in women with HDP.[16, 30, 31] However, this was in contrast to findings in Tanzania by *Mtali et al,* who reported lack of any statistically significant difference in mean PT between women with preeclampsia and control.[17]The disparity in mean PT could be because *Mtali et al* in his study included women with gestational hypertension which a milder form of HDP. Also the proportion of women with complicated disease (disseminated intravascular coagulation, HELLP syndrome) may also contribute to differences in the mean PT and proportion of women with consumptive coagulopathy. In the index study, relatively few proportion of women developed complications. Quality of care and degree of intervention to control the disease may contribute to proportion of women who ultimately develop coagulopathy. The hospital has a well-established obstetric team with proactive management measures for women with obstetric complications and may thus impact of clinical course of the disease.

Although, the mean PT was higher in severe than mild preeclampsia but there was no statistical significance. This is contrary to the reports by*Lefkou et al, Hajier et al and Lakshmi et al* who all reported significant difference in the mean PT in severe preeclampsia in comparison to women with mild preeclampsia.[16, 30, 32]

A weak positive correlation between PT and TAT complex concentration was observed in women with preeclampsia in this study, inferring that prolonged PT was associated with increasing TAT concentrations. This may be due by enhanced endothelial activation and exaggerated hypercoagulable state initiated in women with preeclampsia.

The mean activated partial thromboplastin time (APTT) was significantly increased in women with preeclampsia compared to control. Similarly, the incidence of prolongation of APTT was significantly higher in the patient group.*Hajier et al* in their study among Sudanese women with HDP, reported similar mean APTT and incidence rate amongst the study group (13% vs. 14.7%).[30]

Unlike the findings by *Lefkou et al* and *Hajier et al* who both reported increasing APTT with severity of disease, there was no significant increase in mean APTT between the women with mild and severe preeclampsia. Similar to PT, APTT had a weak positive correlation with TAT in the index study but this was not statistically significant. This also implies enhanced coagulation activation.

Maternal complications (PROM, sepsis, APH, HELLP syndrome, DIC, PPH, ophthalmic, AKI, puerperal psychosis and ICU admissions) occurred more in women with preeclampsia than in controls, though these did not reach statistical significance. This finding is in contrast to reports from numerous authors who reported significant association.[33-36]*Adu-Bonsaffoh et al* and *Wolde et al* both reported significant increase in ICU admissions and incidence of DIC in preeclampsia patients in Ghana and South Africa respectively.[36] Also, *Yücesoy et al* reported same amongst the Caucasian population.[37]However, similar to this study, *Saadat et al* reported a higher incidence of AKI and PPH in women in preeclampsia but as in this study not statistically significant.[38] The relatively small sample size may have partly accounted for this disparity and also timely and expert intervention by the obstetricians may have attributed to this finding. The study did not find any association between TAT levels and maternal complications.

Although, maternal mortality was higher in women with preeclampsia but the difference in proportion was not statistically significant. A number of studies have reported significantly increased maternal deaths in association with preeclampsia but similar to the index study, *Obi et al* reported that there was no significant difference.[39] The lack of statistical significance observed in this study may be attributed to improved and proactive care rendered in the index facility. The high skilled expertise and established protocol to reduce maternal death may have contributed to the relatively lower maternal death. Also the relatively small sample size may contribute to the observed differences in findings. There was no association between TAT complex concentration and maternal mortality.

The index study noted a significant increase in caesarean sections(CS) in the case group with majority of the women (91.8%) having emergency caesarean sections (EMCS). *Obi et al, Olusanya et al and Saadat et al* all reported similar findings.[38-40]This may be attributed to the management principle.

The study had some strength. This is among the pioneer studies on the association of TAT on maternal and perinatal outcome in women with preeclampsia-eclampsia in this region. It could be used as a pilot study in developing the reference range of TAT in blacks as values for Caucasians may not be directly extrapolated to our region.

Despite attempting to establish maternal and 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 center. A multicenter study would have helped to improve external validity of the study.

.In conclusion the study has demonstrated increased morbidity in women with preeclampsia-eclampsia, and their foetus. TAT levels have also been shown to be significantly in increased in the study group compared to normal pregnancy and increasing with disease severity. The mean PT and APTT were increased in the study group in comparison with controls. TAT correlated with maternal platelets, PT and APTT.

TABLES AND FIGURES

Table 1: Demographic characteristics of 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: Maternal Outcome and Mode of Delivery

OUTCOME	Case Group n(%) = 72	Controls n(%) = 70	Total n(%) = 142	Stats	P value
Obstetric Complications					
PROM	3 (4.2)	0(0.0)	3 (2.1)	Fishers	0.245
Sepsis	3 (4.2)	0 (0.0)	3 (2.1)	Fishers	0.245
APH	5 (6.9)	0 (0.0)	5 (3.5)	Fishers	0.058
HELLP	3 (4.2)	0 (0.0)	3 (2.1)	Fishers	0.245
DIC	5 (6.9)	0 (0.0)	5 (3.5)	Fishers	0.058
PPH	7 (9.7)	2 (2.9)	11 (7.7)	Fishers	0.166
ICU admissions	2 (2.8)	0 (0.0)	2 (1.4)	Fishers	0.497
Ophthalmic	2 (2.8)	0 (0.0)	2 (1.4)	Fishers	0.497
AKI	1 (1.4)	0 (0.0)	1 (0.7)	Fishers	1.000
Psychosis	1 (1.4)	0 (0.0)	1 (0.7)	Fishers	1.000
Mode of delivery					
Vaginal	23 (31.9)	57(81.4)	80 (56.3)		
CS	49 (68.1)	13 (18.6)	62(43.7)	24.132	0.001
EMCS	45 (91.8)	8 (61.5)	53 (85.5)		
ELCS	4(8.2)	5 (38.5)	9 (14.5)		
Maternal mortality	4 (5.6)	0 (0.0)	4 (2.8)	Fishers	0.120

PROM: Premature rupture of membrane, APH: Antepartum haemorrhage, HELLP: Haemolysis, Elevated liver enzymes, Low platelets, DIC: Disseminated intravascular coagulopathy, PPH: Postpartum haemorrhage, ICU: Intensive care unit, AKI: Acute kidney injury, EMCS: Emergency caesarean section, ELCS: Elective caesarean section.

Table 3: Age, BMI, HaematologicParameters of the Study Population

	Case Group n = 72		Controls n = 70		Stats	P value
	Mean ± SD	**Range**	**Mean ± SD**	**Range**		
Age (years)	31.3 ± 5.3	20.0 – 43.0	28.9 ± 5.9	18.0 – 43.0	3.669	0.010
BMI (Kg/m^2)	27.6 ± 4.2	16.4 – 37.1	26.5 ± 2.8	16.4 – 37.1	1.830	0.060
GA@ sampling (weeks)	34.2 ± 4.4	20.6 – 40.0	34.3 ± 5.4	13.0 – 41.0	-0.420	0.872
PCV (%)	32.8 ± 4.8	13.7 – 14.5	35.4 ± 2.3	14.0 – 41.0	-4.059	<0.001
Hb(g/dl)	11.2 ± 1.7	4.6 – 14.5	12.0 ± 0.9	4.6 – 14.5	-3.063	0.002
WBC($x10^9/L$)	9.5 ± 4.2	3.4 – 27.4	7.4 ± 1.6	3.4 – 27.4	3.715	<0.001
LYM ($x10^9/L$)	2.5 ± 2.5	1.0 – 7.5	2.2 ± 0.6	2.0 – 2.6	0.571	0.253
GRA ($x10^9/L$)	6.7 ± 3.8	1.6 – 21.6	4.7 ± 1.4	5.2 – 6.2	3.547	<0.001
PLT($x10^9/L$)	155.9 ± 60.4	48.0 – 409.0	165.3 ± 45.5	151.6 – 169.4	-0.736	0.295
PT(seconds)	14.3 ± 2.8	12.0 – 27.0	13.2 ±0.8	13.4 – 14.1	2.186	0.002
APTT(seconds)	34.2 ± 6.4	28.0 – 58.0	31.2 ± 2.4	31.9 – 33.5	3.463	<0.001
TAT(µg/L)	19.6 ± 3.2	9.4 – 27.7	15.7 ± 3.9	17.0 – 18.4	6.383	<0.001

BMI: Body mass index, GA: Gestational age, PCV; Packed cell volume, Hb: Haemoglobin concentration, WBC: White blood count, LYM: Lymphocytes, GRA: Granulocyte, PLT: Platelet count, PT: Prothrombin time, APTT: Activated partial thromboplastin time, TAT: Thrombin antithrombin complex

Table 4: Comparison of Platelet count, PT, APTTand TAT levels between the Case and Controlgroup

	Case Group n(%) = 72	Controls n(%) = 70	Total n(%) = 142	Stats	P value
Platelet					
<100 x 10^9cells/L	8 (11.1)	3 (4.3)	11 (7.7)	Fishers	0.208
100 x 10^9cells/L	64 (88.9)	67 (95.7)	131 (92.3)		
PT					
Normal	58 (80.6)	67 (95.7)	125 (88.0)		
Prolonged	14 (19.4)	3 (4.3)	17 (12.0)	Fishers	0.005
APTT					
Normal	62 (86.1)	70(100.0)	132 (93..0)	Fishers	0.001
Prolonged	10 (13.9)	0 (0.0)	10 (7.0)		
TAT					
Normal	53 (73.6)	69 (98.6)	122 (85.9)	Fishers	<0.001
Elevated	19(26.4.)	1 (1.40)	20 (14.10)		

PT: Prothrombin time, APTT: Activated partial thromboplastin time, TAT: Thrombin antithrombin complex

Table 5: Haematological Parameters based on severity of Preeclampsia

	Mild Mean±SD	Severe Mean±SD	T test	P value
Platelet count($x10^9/L$)	172.3 ± 94.2	152.2±50.6	1.090	0.279
PT(seconds)	13.7 ± 1.9	14.5 ± 2.9	-0.911	0.365
APTT(seconds)	34.0 ± 5.3	34.2 ± 6.7	-0.120	0.905
TAT(µg/L)	15.3 ± 2.6	20.1 ± 2.4	- 7.186	< 0.001

PT: Prothrombin time, APTT: Activated partial thromboplastin time, TAT: Thrombin antithrombin complex

Table 6: Correlation between TAT, Maternal age and Haematological Parametersin women with Preeclampsia

	Preeclampsia-eclampsia		Controls	
	r	P value	r	P value
Maternal age	0.082	0.495	0.081	0.506
BMI	0.006	0.959	0.203	0.092
Birth weight	-0.230	0.068	0.212	0.124
WBC	0.230	0.052	-0.161	0.182
Granulocyte	0.209	0.078	-0.137	0.259
Lymphocyte	0.052	0.666	0.080	0.511
Monocyte	-0.111	0.353	-0.228	0.058
Haemoglobin	0.076	0.523	0.125	0.303
Haematocrit	0.056	0.645	0.049	0.690
Platelet	-0.406	<0.001	-0.163	0.177
PT	0.300	0.010	0.157	0.195
APTT	0.201	0.091	0.006	0.958

TAT: Thrombin antithrombin complex, WBC: White blood cell count, BMI: Body mass index, PT: Prothrombin time, APTT: Activated partial thromboplastin time

Table 7: Logistic Regression of TAT and Preeclampsia adjusted for maternal age

	B	S.E	P	OR	95% CI
Preeclampsia	1.667	0.443	<0.001	5.293	2.222 – 12.605
Age group	-0.086	0.192	0.654	0.918	0.630 – 1.336
APH	-19.592	17392.2	0.999		
PROM	19.424	10443.7	0.999		
Sepsis	-38.369	20634.7	0.999		
HELLP	-17.497	38903.1	1.000		
DIC	-20.872	32979.7	0.999		
PPH	-19.488	10443.7	0.999		
Mortality	18.813	16658.2	0.999		

APH: Antepartum haemorrhage, PROM: Premature rupture of membrane, HELLP: Haemolysis, elevated liver enzymes, low platelets, DIC: Disseminated intravascular coagulopathy, PPH: Postpartum haemorrhage

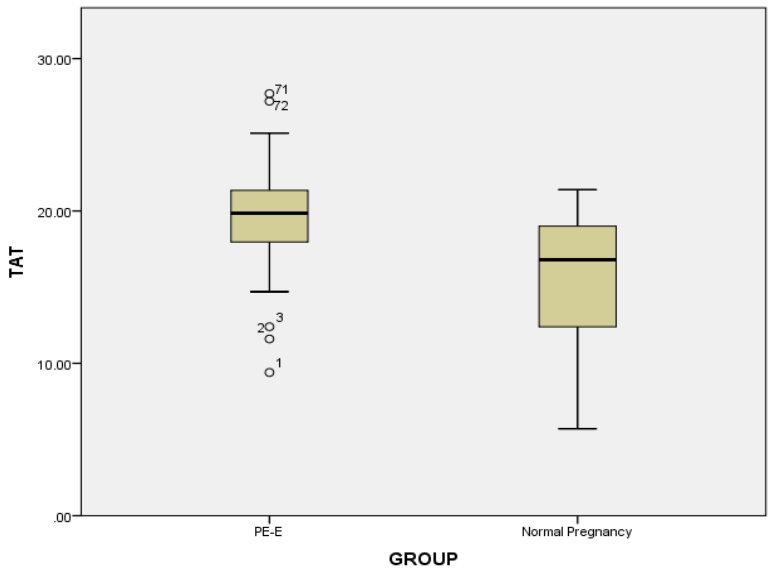
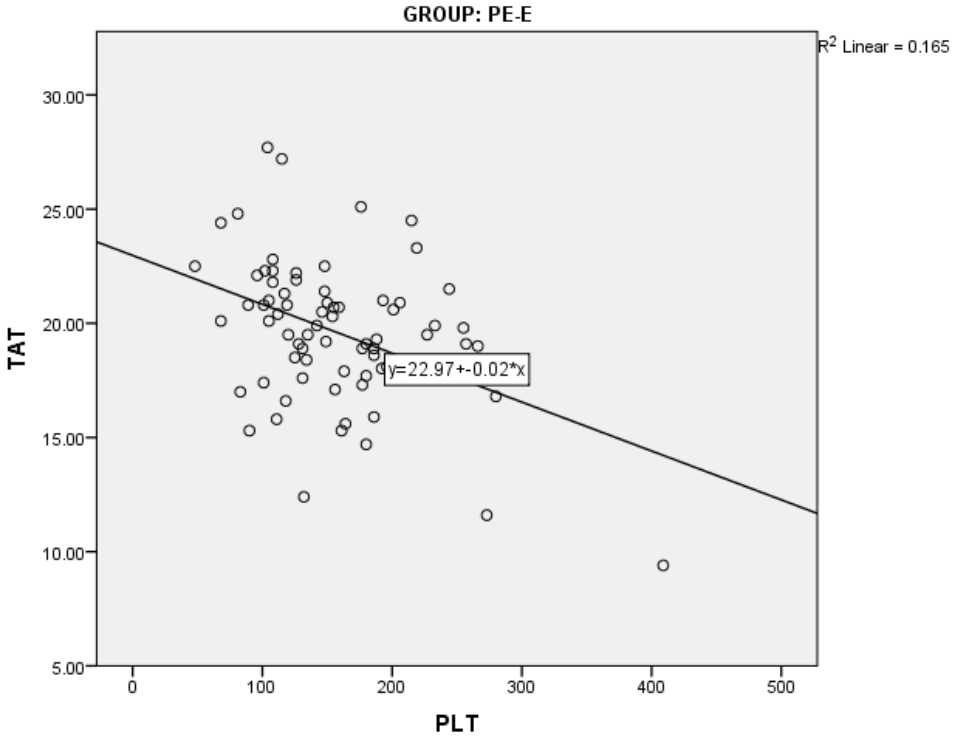


Figure 1: Boxplot of TAT Concentration in the Study Population



TAT: Thrombin antithrombin complex, PLT: Platelet count,
PE-E: Preeclampsia-eclampsia

Figure II: Scatterplot showing the Correlation between TAT complex and Platelet count in women with Preeclampsia

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