Research

# Association between haemostatic parameters at diagnosis and pregnancy outcome in women with pre-eclampsia in south-east Nigeria

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## Abstract

**Background:** Pre-eclampsia complicates 3-5% of pregnancies and is a global cause of perinatal and maternal death. In pre-eclampsia, activated maternal inflammatory response and immune dysfunction culminate in serious derangement in the coagulation and fibrinolytic systems. We aimed to determine if changes in the coagulation system predict severity and outcome of preeclampsia.

**Methodology:** This was a prospective self-controlled study of pre-eclamptic pregnant women recruited from 28 weeks and followed till delivery. At the point of diagnosis, blood sample for platelet count, prothrombin time and activated partial thromboplastin time was collected. Data was analyzed using IBM SPSS version 20 and p-value was set at ≤0.05.

**Results:** Thirty women with preeclampsia were followed up to delivery in this study. Their mean gestational ages were 33.87± 3.93 and 37.50±2.77 weeks at recruitment and delivery respectively. Of the complications seen in these women, maternal death 11(36.7%) was the most frequent maternal complication while prematurity 23 (76.7%) was the most frequent fetal complication. Ten (33.3%) subjects had thrombocytopenia, 7(23.3%) had isolated prolonged PT, 17(56.7%) had isolated prolonged APTT while 18(60.0%) had both prolonged PT and APTT. Maternal and fetal complications had no significant association with the PT and APTT of the study subjects.

**Conclusion:** The existence of thrombocytopenia and derangement in PT and APTT is common in preeclampsia. The prevalence of feto-maternal complications is high in preeclampsia. However, the coagulation derangement showed no associations with these complications and likely not predictors of poor pregnancy outcome.

## Keywords

Preeclampsia, maternal outcome, fetal outcome, thrombocytopenia, prothrombin time, activated partial thromboplastin time, coagulation screening tests

## Introduction

Pre-eclampsia is new onset hypertension and proteinuria after 20 weeks of gestation in pregnant women who previously lacked such features[1,2]. It could result in severe untoward multi-systemic maternal and perinatal morbidities and mortalities[3,4]. It has been associated with fetal growth restriction as well as thrombocytopenia and multi-organ dysfunctions such as: cerebral, visual, hepatic, renal and pulmonary complications in the mother[1,5]. The burden of pre-eclampsia is enormous as it complicates between 2% and 10% of pregnancies[3,6-8]. Being among the major global causes of perinatal and maternal deaths, about 500,000 and 76,000 perinatal and maternal deaths respectively have been attributed to preeclampsia globally every year[3-8].

Pre-eclampsia has been dubbed a disease of theories hence finding its precise pathophysiology has remained a mirage[1-3,7]. However, it appears that poor placentation,

vascular spasm and endothelial dysfunction are among the basic pathologies that have been identified in pre-eclampsia[9]. Pregnancy is a hypercoagulable state, a property which is vital to forestall postpartum haemorrhage, but pre-eclampsia is even a super hypercoagulable state with potential for utero-placental insufficiency, multi-organ micro thrombi formation and disseminated intravascular coagulopathy[1,3,4,6,8-13]. Activated maternal inflammatory response and immune dysfunction culminate in serious malfunction of the coagulation and fibrinolytic systems[11,12]. To achieve normalcy in organ and utero-placental perfusions during pregnancy, it is pertinent to maintain tranquility in the coagulation and anti-coagulation pathways[11,12]. It is, therefore, necessary to strike a balance between coagulation and fibrinolysis[11-13]. Ability to predict correctly and make timely diagnosis will help to prevent pregnancy complications in women with the disease[1-10]. Some available clinical and laboratory markers of severity of pre-eclampsia have not been able to reliably predict its outcome in all cases[1-5]. Quite recently, some biochemical substances such as soluble fms-like tyrosine kinase-1(sFlt-1), soluble endoglin (sEng), placental growth factors (PIGF) and the vascular endothelial growth factors (VEGF) that have shown promising results in prediction and early diagnosis of the disease are regrettably expensive and unavailable especially in low resource countries and settings such as ours[2,5]. Platelets and coagulation cascades activations have been shown to be among the major differential pathways for early-onset pre-eclampsia.[9,10] This is supported by the extent of thrombocytopenia and consumptive coagulopathy seen as the severity of pre-eclampsia increases[9].

From the foregoing, it is evident that changes in the coagulation system might play a significant role in determining severity of pre-eclampsia and prognosticating the feto-maternal outcomes of pregnancies complicated by pre-eclampsia. Therefore, evaluation of the haemostatic system by assessing platelet count, prothrombin time and activated partial thromboplastin time to determine their correlation with adverse perinatal and maternal outcomes in pre-eclamptic pregnancies is what this study is set out to achieve. This will help in instituting early intervention.

## Methodology

This is a prospective self-controlled study carried out at the obstetrics and gynecology department of Alex Ekwueme Federal University Teaching Hospital (AEFUTHA) Ebonyi state, Nigeria. The study participants were pregnant women with preeclampsia (BP >140/90mmHg and proteinuria >300 mg/day in previously normotensive patients). Women included in the study were consenting women with singleton pregnancies from 28 weeks gestation with pre-eclampsia. Patients on anticoagulant or antiplatelet drugs, those who were diagnosed with diabetes mellitus, chronic liver disease, bleeding disorders and hypercoagulable states, chronic hypertension, multiple pregnancies, intrauterine fetal death at presentation, abruption placenta and heart disease were excluded from the study.

The sample size for this study was calculated using the formula for cross-sectional designs:

$$n = \frac{Z^2 P(100-P)}{d^2}$$

Where:

n = minimum sample size.

Z = coefficient of Z statistics obtained from the standard normal distribution table. The confidence limit of 95% is 1.96

P = prevalence rate (in %)

d = sampling error tolerated (in %)

q = 100-p

Using the prevalence of pre-eclampsia to be 3%[3] at a confidence limit of 95% (d =5%) and Z of 1.96, the minimum size (n) is

$$\frac{1.96^2 \times 3*(100-3)}{5^2} = \frac{3.8416 \times 3*(97)}{25}$$

$$= 44.71 \approx 45$$

Consecutive patients that met eligibility criteria were recruited into the study until sample size was achieved. Patient's case notes and structured interviewer administered questionnaires were used to retrieve demographic and clinical information from the participants. These study subjects were followed up till delivery and both maternal and fetal complications, when occurred, were documented.

At the point of diagnosis of pre-eclampsia, venous blood samples were collected into ethylenediaminetetraacetic (EDTA) sample bottles for platelet count, and sodium citrate bottles for prothrombin time (PT) and activated partial thromboplastin times (APTT). The blood samples were transported immediately to the haematology research laboratory AEFUTHA where platelet count was done using automated haematology analyser Mindray BC300. The blood samples collected in sodium citrate bottles were immediately separated and platelet poor plasma obtained for PT and APTT analysis according to standard protocols. The levels of these coagulation parameters and platelet count were measured and compared with a known control value. Thrombocytopenia was defined as platelet count of

<100 x $10^9$/L, prolonged PT as > 14 seconds, and prolonged APTT as >40 seconds. Data were analyzed using the Statistical Package for the Social Sciences version 20 (IBM-SPSS, Armonk, NY, USA). Categorical data were summarized using proportion (percentage), while quantitative data were summarized using mean, standard deviation (SD) and range. Chi-square and Fisher's exact tests (where appropriate) were used to determine the association between clotting profile, maternal and fetal complications. The level of significance was set at p≤ 0.05

This study was approved by the Research Ethics Committee of Alex Ekwueme Federal University Teaching Hospital Abakaliki with approval number of AE-FETHA/REC/VOL/2/2019/153.

## Results

Thirty women with preeclampsia were followed up to delivery in this study. Their mean ± SD age was 28.9 ± 5.6 years and range of 15-38 years. Their mean gestational ages were 33.87± 3.93 and 37.50±2.77 weeks at recruitment and delivery respectively. Only 2 (6.7%) were nulliparous, 10 (33.3%) were grand multiparous and the remaining 18 (60%) had one to four previous deliveries. Twenty-two out of the thirty (73.3%) study participants had pre-eclampsia with severe features. Other socio-demographic data are summarized on table 1.

**Table 1.** Maternal demographic and clinical characteristics

| Variable | Frequency |
|---|---|
| Age | |
| Mean | 28.9 ± 5.6 |
| Range | 15 – 38 |
| GA @recruitment (weeks) | |
| 28 – 33 | 13 (43.3) |
| 24 – 39 | 14 (46.7) |
| ≥40 | 3 (10.0) |
| GA @delivery (weeks) | |
| 28 – 33 | 13 (43.3) |
| 24 – 39 | 10 (33.3) |
| ≥40 | 7 (23.3) |
| Booking status | |
| Booked | 18 (60.0) |
| Not booked | 12 (40.0) |
| Educational status | |
| Primary | 6 (20.0) |
| Secondary | 14 (46.7) |
| Tertiary | 10 (33.3) |
| Religion | |
| Christian | 29 (96.7) |
| Islam | 1 (3.3) |
| Ethnicity | |
| Igbo | 26 (86.7) |
| Others | 4 (13.3) |
| Social Class | |
| I | 4 (13.3) |
| III | 9 (30.1) |
| IV | 10 (33.3) |
| V | 7 (23.3) |

Of the complications seen in these women, maternal death 11(36.7%) was the most frequent maternal complication while prematurity 23 (76.7) was the most frequent fetal complication from Table 2.

Haemostatic parameters in the subjects at recruitment showed that the mean ±SD for platelet count, Prothrombin time and activated partial thromboplastin times were 154±87.6 x $10^9$/L, 17.8 ±12.1 seconds and 46.4± 17.8 seconds respectively. 10(33.3%) subjects had thrombocytopenia, 7(23.3%) had isolated prolonged PT, 17(56.7%) had isolated prolonged APTT while 18(60.0%) had both prolonged PT and APTT.

**Table 2.** Distribution of maternal and fetal complications

| Complications | Frequency (%) |
|---|---|
| **Maternal** | |
| Eclampsia | 16 (53.3) |
| Abruption placentae | 9 (30.0) |
| ICU admission | 9 (30.0) |
| Mortality | 11 (36.7) |
| | |
| **Fetal** | |
| Prematurity | 23 (76.7) |
| Birth asphyxia | 15 (50.0) |
| NICU admission | 13 (43.3) |
| Perinatal mortality | 18 (60.0) |

Maternal and fetal complications had no significant association with the PT and APTT of the study subjects. The study observed that the odds that prolonged clotting time is associated with maternal and fetal complications is high except for maternal mortality from Table 3.

**Table 3: Association between clotting profile, maternal and fetal complications**

| | Prolonged Clotting time N = 18 | Normal Clotting time N= 12 | Total N = 30 | Statistics | P value | Odds ratio |
|---|---|---|---|---|---|---|
| Maternal | | | | | | |
| Eclampsia | 10 (62.5) | 6 (37.5) | 16 (100.0) | 0.089 | 0.765 | 1.25 |
| Abruptio placentae | 7 (77.8) | 2 (22.2) | 9 (100.0) | Fisher's | 0.249 | 3.18 |
| ICU admission | 5 (71.4) | 2 (28.6) | 7 (100.0) | Fisher's | 0.669 | 1.92 |
| Mortality | 6 (54.5) | 5 (45.5) | 11 (100.0) | 0.215 | 0.712 | 0.70 |
| | | | | | | |
| Fetal | | | | | | |
| Prematurity | 15 (65.2) | 8 (34.8) | 23 (100.0) | Fisher's | 0.392 | 2.50 |
| Birth asphyxia | 11 (73.3) | 4 (26.7) | 15 (100.0) | Fisher's | 0.264 | 3.14 |
| NICU admission | 9 (69.2) | 4 (30.8) | 13 (100.0) | Fisher's | 0.465 | 2.00 |
| Perinatal mortality | 12 (66.7) | 6 (33.3) | 18 (100.0) | 0.833 | 0.458 | 2.00 |

## Discussion

Preeclampsia is an obstetrics emergency with both maternal and fetal consequences. This study was conducted to determine the effect of preeclampsia on maternal platelet count and clotting profile (PT and APTT) and correlate them with maternal and fetal complications. We observed that these parameters are deranged in preeclampsia with up to 33.3 – 60.0% of study subjects having thrombocytopenia, or prolonged PT and/or APTT., however, this did not correlate with maternal outcomes.

Over 33% of the women had thrombocytopenia in our study. Previous researchers reported a prevalence of 7.41 – 28.4%[14,15,16] of thrombocytopenia in preeclampsia. The differences in prevalence rates may be attributed to the gestational age of population under study, severity of preeclampsia and the platelet cut-off value used. Thrombocytopenia is thought to worsen with increasing gestational age in pregnancy and there may be normal platelet count in early pregnancy, as was similarly observed by Han et al and Thalor et al[17,18]. Han et al and Heilman et al also reported worsening thrombocytopenia in cases of severe preeclampsia when compared to mild preeclampsia[17,19]. Almost three-quarter of our study subjects had preeclampsia with severe features which may account for the higher rates of thrombocytopenia in this study. Unlike other studies[14-16], we used a platelet count cut-off of 100 x $10^9$/L which reflects the local cut-off value for thrombocytopenia in our environment. All these factors put together might have contributed to the differences in prevalence rates.

We observed that over half of our subjects had derangement in PT and APTT. The changes in PT and APTT reflect the disturbed coagulation activities in extrinsic and intrinsic pathways respectively[20]. Most of the clotting factors are normally synthesised in the liver, with significant disturbances in the hepatic function as seen during late pregnancy in preeclampsia, there is complex changes in the haemostatic system with net insufficiency of intrinsic and extrinsic coagulation[20,21]. The mean PT and APTT values from our study were 17.8 ±12.1 seconds and 46.4± 17.8 seconds respectively. Even though Han et al[17] reported lower values, they still observed a significant difference in the values between normal pregnant women and those with preeclampsia supporting the disturbance of both extrinsic and intrinsic coagulation pathways in pre-eclampsia. It is pertinent to note that we had a higher proportion of patients with severe preeclampsia just as reported by some other Nigerian studies[3,22]. Additionally, up to 40% of our patients were not booked, an observation that demonstrates an inadequate antenatal care and monitoring of these pregnant women.

The reported maternal outcomes in this study included abruptio placenta, admission in the intensive care unit and mortality which accounts for most of the cases. This is contrary to the observation by Ajah et al and Aadibha et al who reported 12.1% and no mortality respectively in their respective studies[2,23]. We noticed that most of their study participants were nulliparous whereas most of our subjects were multiparous. High parity has long been associated with poor maternal outcomes including mortality because of several factors stemming from maternal deprivation to lifestyle changes[24,25]. This might have contributed to the differences. The most frequent fetal/neonatal complication is prematurity. We reported a high rate of 76.7% in this study when compared to 28% reported by Hnat et al[26]. Birth asphyxia was also reportedly high in this study, occurring in up to 50% of

cases. Numerous conditions could predispose a baby to developing birth asphyxia. Notable of them are hypertension and placental insufficiency which is the basic pathology in preeclampsia[27]. Another risk observed in this study was placenta abruption reported in up to a third of the patients. This condition is known to further compromise fetal circulation predisposing to asphyxia[27]. There was equally a high rate of newborn intensive care unit (NICU) admission in our cohort which is higher that reports from previous research (14.6 – 27.3%)[28-30]. Even though our study did not report on the determinants of these complications in preeclampsia, the possible reasons for NICU admissions in preeclampsia has been summarized by Sibai[27] to include unfavourable cervix, prolonged labour, cervical ripening, and increased rates of chorioamnionitis, fetal distress[27].

Despite the high prevalence of poor obstetrics outcomes associated with preeclampsia which include the feto-maternal complications, our study showed no statistically significant associations between the coagulation profile and these complications. While the basic mechanism of these complications is related to placental insufficiency, the coagulation disturbances are majorly related to activation of the endothelium with activation of coagulation leading to consumption of platelets and some coagulation proteins, most notably in severe preeclampsia[15,16,27]. This may imply that degree of derangement in the coagulation screening tests in women with preeclampsia may not predict pregnancy outcome in this population warranting further studies that may explore other possible predictors.

A major limitation of this work is that we could not control for other causes of thrombocytopenia in pregnancy knowing that there are other causes of thrombocytopenia other than preeclampsia. Additionally, we did not have any booking or pre-inclusion platelet count for most of them. Being a hospital-based study, it is limited by the inherent bias and may not be representative of the general population.

Conclusion

Study showed that thrombocytopenia and derangement in PT and APTT occur commonly in preeclampsia. The coagulation derangement showed no associations with feto-maternal complications and may not serve as predictors of poor pregnancy outcome. Further studies to investigate possible predictors of preeclampsia and poor pregnancy outcomes are recommended.

## Authors' contribution

OCN conceptualized, designed and interpreted data of the study, BSU, OVO, CM and HCO contributed equally in the manuscript writing, HCO contributed in interpreting the data and writing the manuscript. All the authors gave approval of the final manuscript.

## Conflict of Interest

There was no conflict of interest

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