**Haemostatic Function and Predictive Values for Pre-Eclampsia Severity of Pregnant Women in a Rural West African Town**

**Abstract**

Introduction: This study aimed to assess hemostatic function in preeclampsia using selected coagulation indices and to determine whether these indices are predictive of preeclampsia severity in a rural West African population.

Method: A hospital-based case-control study was conducted involving 65 women with preeclampsia as the test group and 65 age-, trimester-, and parity-matched normotensive, non-proteinuric pregnant Black women as controls. The preeclamptic group was classified as having mild or severe disease according to the American College of Obstetricians and Gynecologists (ACOG) criteria. The coagulation parameters assessed included platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), plasminogen activator inhibitor type-1 (PAI-1), fibrinogen, D-dimer, and mean platelet volume (MPV).

Results: Among the preeclamptic participants, 34(52.9%) had mild and 31(47.7%) had severe preeclampsia. In the second trimester, median plasma fibrinogen and D-dimer levels were significantly higher in the preeclamptic group compared to controls: 298.4 (217–408) mg/dL vs. 207.4 (134–256) mg/dL for fibrinogen (p<0.001), and 589.4 (278–1002) ng/mL vs. 102.0 (78–178) ng/mL for D-dimer (p<0.001). Mean PAI-1 levels were also elevated in preeclamptic women compared to controls in both the second trimester (6.41±2.4 vs. 4.73±1.5 ng/mL; p<0.001) and third trimester (10.61±2.6 vs. 7.21±1.6 ng/mL; p<0.001). Receiver Operating Characteristic (ROC) curve analysis indicated that third-trimester levels of PAI-1, fibrinogen, and D-dimer were significant predictors of preeclampsia severity (p < 0.05).

Conclusion: This study confirms prior findings of a progressive increase in fibrinogen, PAI-1, and D-dimer levels during pregnancy, with significantly higher levels observed in women with preeclampsia. These coagulation indices, particularly in the third trimester, may serve as useful biomarkers for predicting the clinical severity of preeclampsia.

**Keywords**: Pre-eclampsia, Haemostatic, Platelet, Severity, Coagulation

**1. Introduction**

Hemostasis is the physiological process by which blood loss from the vascular system is controlled through a complex interaction among the vessel wall, platelets, and plasma proteins [1]. It preserves vascular integrity by maintaining blood in a fluid state under normal circumstances and by preventing excessive bleeding in the event of vascular injury. Hemostasis involves the initiation and termination of coagulation in a tightly regulated manner, alongside the removal of formed clots. This process encompasses four interrelated components: vascular wall integrity, platelet function, coagulation, and fibrinolysis [2]. The components of the fibrinolytic system include proteases, serpine inhibitors, and receptors [1]. The proteases are plasminogen (PLG), Tissue plasminogen activator (tPA), urokinase plasminogen activator (UPA) [2]. The serpine inhibitors are plasminogen activator inhibitor type-1 (PAI-1), plasminogen activator inhibitor type-2 (PAI-2), and α2-antiplasmin. Most importantly, fibrinolysis follows the release of tissue plasminogen activator (tPA) from endothelial cells, which then binds to fibrin, thus enhancing its capacity to convert thrombus bound plasminogen into plasmin. Following thrombin generation and consequent activation of FXIII inter or intramolecular transamidation of the α or γ chains by factor XIII occurs and then the action of plasmin yields characteristic D-dimer, D-dimer–E fragments and oligomers of fragments X & Y (which are collectively called cross-linked FDP or XDP), in addition to X,Y,D,E. PAI-2 is a serpin inhibitor of tPA that is mainly produced by the placenta and can also be synthesized in monocytes and epidermal cells. It contributes to the inhibition of fibrinolysis during pregnancy. PAI-2 is not usually found in the plasma of non-pregnant subjects and levels are often low in pre-eclamptics due to placental insufficiency. In pregnancy, it is detectable in plasma from about the 8th week of pregnancy, rising to a peak at around the 33weeks and falling only slowly after delivery [2].Normal pregnancy is associated with significant changes in the coagulation and fibrinolytic systems, favoring a procoagulant state. These changes, particularly the increase in specific coagulation factors, serve as a physiological mechanism to reduce hemorrhagic risks during delivery.

Preeclampsia is a hypertensive disorder of pregnancy that affects many pregnancies globally. It is defined by new-onset hypertension (diastolic blood pressure ≥110 mmHg on one occasion or ≥90 mmHg on two or more occasions at least 4 hours apart) and proteinuria (≥300 mg/day or a urinary protein/creatinine ratio ≥30 mg/mmol) occurring after 20 weeks of gestation in previously normotensive women [3]. Symptoms may persist for up to six weeks postpartum. Preeclampsia is associated with increased risks of preterm birth, intrauterine growth restriction, low birth weight, and perinatal mortality, and affects several pregnant women in the United States [4]. In developing countries, its prevalence ranges from 1.8% to 16.7% [4]. In Nigeria, reported prevalence rates include 8.8% in a study conducted in Jos, North-Central Nigeria [5] and 5–10% in South-West Nigeria [6]. Preeclampsia is could alter the coagulation system due to maternal immune dysregulation. Also, the inflammatory responses induced by preeclampsia could also affect the fibrinolytic system. In normal pregnancy, a balance is maintained between coagulation and anticoagulation to ensure proper uteroplacental perfusion. In preeclampsia, this balance may be disrupted, leading to microthrombi formation, impaired organ perfusion, and potential maternal and fetal complications [7].

Measuring markers of coagulation and fibrinolysis can help predict the onset and severity of preeclampsia [7]. Various indices, including fibrinogen, D-dimer (DD), plasminogen activator inhibitor type-1 (PAI-1), tissue plasminogen activator (tPA), soluble fms-like tyrosine kinase-1 (sFlt-1), and platelet distribution width (PDW), have been investigated as potential biomarkers [7–8]. Fibrinogen plays a critical role in identifying hemostatic failure and guiding replacement therapy in fibrinopenic states [9]. Additionally, elevated levels of cancer antigen-125, C-reactive protein, and plasma fibrinogen have been associated with the severity of preeclampsia. Genetic studies have revealed significant associations between preeclampsia and maternal or fetal DNA variants, including those in COL1A1, IL1A, and PLAUR genes [10]. Endothelial cell activation in preeclampsia promotes coagulation and increases vascular reactivity. Morphological changes in renal glomeruli, increased permeability, and elevated levels of endothelial activation markers such as E-selectin and VCAM-1 have also been documented [11].

Despite extensive research, conclusions on the effects of preeclampsia on the coagulation-fibrinolytic system remain inconsistent. This highlights the need to further investigate endothelial-derived fibrinolytic markers in preeclamptic patients to assess their role in disease pathogenesis and severity. This study, therefore, aims to evaluate variations in coagulation-fibrinolytic markers among preeclamptic women and determine their predictive value in assessing the severity of preeclampsia. Given the substantial burden of this condition in Nigeria, and its role in maternal and neonatal morbidity and mortality, identifying reliable biomarkers could improve risk stratification and outcomes.

**2. Methods**

Study Population

This hospital-based, case-control observational study was conducted at the Department of Obstetrics and Gynecology, Irrua Specialist Teaching Hospital (ISTH), located in Irrua, a rural community in Edo State, Nigeria (latitude 6.5438°N, longitude 5.8987°E). ISTH is a 375-bed tertiary hospital with an obstetric unit consisting of 48 obstetric and 42 gynecological beds, conducting an average of 1,600 deliveries annually. Antenatal clinics are held three times per week, with a booking clinic once a week and an average of 100 new bookings monthly.

The study population included pregnant women attending the antenatal clinic. The case group comprised women diagnosed with preeclampsia, while the control group included normotensive, non-proteinuric pregnant women. Participants were matched for age, gestational trimester, and parity.

Recruitment was done via simple random sampling. Each clinic day, a list of all pregnant women in attendance was obtained. Women meeting the inclusion criteria were separated into two groups: those with preeclampsia and those without. From each group, eligible participants were randomly selected until the required sample size was achieved.

Preeclamptic participants were further categorized into two subgroups—non-severe and severe—based on clinical features and ACOG guidelines.

Sample Size Determination and Preeclampsia Criteria

The sample size was calculated using the formula for comparing proportions in a case-control study design:

Where;

n = sample size in the case-control group

r = ratio of controls to cases

Zβ = Represents the desired power (typically 0.84 for 80% power)

Zα = Represents the desired level of statistical significance (typically 1.96).

Þ = A measure of variability (similar to standard deviation) ()

(P1 – P2)2 = Effect Size (the difference in proportions)P1 is the proportion of cases exposed.

P2 is the proportion of exposed cases in the control group which is 10% (0.1) [6].

To get the proportion of cases exposed, P1 =

The odds ratio (OR) for those exposed in the control group is 4.0 [6].

Therefore, P1 = (4.0

P1 = 0.31

Þ = = = 0.21

Therefore, n =

Substituting into the formula, the minimum sample size n = 59 per group.

To account for potential attrition, 10% was added (6 participants), resulting in 65 participants per group.

A total of 65 women with preeclampsia who met the selection criteria were enrolled as cases. An additional 65 age-, trimester-, and parity-matched normotensive, non-proteinuric pregnant women were recruited as controls.

Preeclampsia was defined using the National High Blood Pressure Education Program Working Group criteria as a blood pressure of ≥140/90 mmHg and confirmed proteinuria (≥0.3 g/L in a 24-hour urine sample), occurring after 20 weeks of gestation in women without a history of chronic hypertension. Controls were healthy pregnant women with gestational age >20 weeks and without hypertension or proteinuria.

A structured, researcher-administered questionnaire was used to collect sociodemographic information, obstetric and medical history. General clinical examination, including weight and blood pressure measurement, was conducted before specimen collection. Participants requiring urgent medical attention were promptly referred to the managing consultant.

Specimen Collection

Symphysis-fundal height was measured using a non-stretchable measuring tape from the pubic symphysis to the uterine fundus and recorded in centimeters. Fetal heart rate was assessed using a Pinard stethoscope and documented in beats per minute.

All clinical procedures were performed in the presence of female chaperones. Each participant was comfortably seated, and venipuncture was performed under aseptic conditions. A total of 8.5 mL of venous blood was collected.

4.5 mL was placed in a 5 mL plastic tube containing 0.5 mL of 3.8% sodium citrate

4.0 mL was placed in a tube containing EDTA

The samples were gently mixed. Citrated blood was centrifuged at 1500 g for 15 minutes, and the supernatant was centrifuged again at 1500 g for another 15 minutes to obtain platelet-poor plasma (PPP), defined as plasma with platelet count <10 × 10⁹/L. PPP was aliquoted into labeled tubes and stored at −80°C until assay.

The EDTA sample was used for peripheral blood film preparation, platelet count, and mean platelet volume (MPV), all performed within 6–8 hours of collection. The same procedure was applied to samples from the control group.

Sharps were disposed of in puncture-proof containers without recapping, and all biomedical waste was appropriately segregated and discarded.

Laboratory Procedures

The following assays were performed on collected samples: Platelet count, Mean platelet volume (MPV), Prothrombin time (PT), Activated partial thromboplastin time (aPTT), Fibrinogen assay, D-dimer assay, and Plasminogen activator inhibitor type-1 (PAI-1) assay.

Platelet Count and MPV

These were measured using the Orphee Mythic 22 automated hematology analyzer (Model SN 510121-000086), which operates based on impedance principles. As cells pass between two electrodes, changes in electrical resistance generate pulses that correlate with cell size and count.

Prothrombin Time (PT)

PT was measured using a one-stage method with commercially available reagents (Chemelex S.A., Spain), following Owren’s method. Plasma samples were mixed with calcium and thromboplastin, and clotting time at 37°C was recorded. The assay evaluates the extrinsic and common coagulation pathways (Factors I, V, VII, and X) [12].

Activated Partial Thromboplastin Time (aPTT)

The aPTT was determined using commercially available reagents (Chemelex S.A., Spain) based on the Proctor and Rapaport method [13]. Plasma was preincubated with kaolin to activate contact factors, followed by the addition of phospholipids and calcium chloride. The test assesses the intrinsic and common pathways and is sensitive to anticoagulants and heparin.

Fibrinogen Assay

The Human Fibrinogen ELISA Kit (Cat. No. E-EL-H2106–H2108, Elabscience®, USA) was used based on the Sandwich-ELISA principle. The assay involves antigen-antibody binding, biotin labeling, and HRP-mediated color development measured at 450 ± 2 nm. Concentrations were calculated from a standard curve.

PAI-1 Assay

PAI-1 levels were quantified using the Human PAI-1 ELISA Kit (Cat. No. E-EL-H6104–H6106, Elabscience®, USA), employing the Sandwich-ELISA technique. Antibody-antigen interactions and enzyme-substrate reactions were measured spectrophotometrically at 450 ± 2 nm. PAI-1 concentrations were derived from the standard curve.

D-dimer Assay

The Human D-Dimer ELISA Kit (Cat. No. E-EL-H6145–H6147, Elabscience®) was used to measure plasma D-dimer levels using the Sandwich-ELISA technique. After the enzyme-substrate reaction, absorbance was measured at 450 ± 2 nm, and concentrations were calculated using a standard curve.

Data Analysis

Data from the structured questionnaires and laboratory results were entered into a master datasheet and analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Results were presented in tables and figures as appropriate. Categorical variables were compared using the Chi-square test, while continuous variables were analyzed using correlation analysis. A p-value of <0.05 was considered statistically significant.

Additionally, Receiver Operating Characteristic (ROC) curve analysis was used to assess the predictive performance (sensitivity and specificity) of hemostatic markers in determining the severity of preeclampsia.

**3. Results**

The mean age of the preeclamptic participants was 31.32 ± 6.4 years, while that of the control group was 30.35 ± 4.8 years. The majority of participants in both groups were married, attained tertiary education, and practiced Christianity (Table 1).

Table 1: Socio-demographic characteristics of study participants

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pre-eclampsia****(n=65)** | **Normotensive****(n=65)** | **Total** **(n=130)** |  |  |
|  | **n(%)** | **n(%)** | **n(%)** | **χ2** | **p-value** |
| **Age group (Years)**20-2425-2930-3435-39≥40Mean±SD | 7(10.8)20(30.8)18(27.7)12(18.5)8(12.3)31.32±6.4 | 7(10.8)20(30.8)18(27.7)12(18.5)8(12.3)30.35±4.8 | 14 (10.8)40 (30.8)36 (27.7)24 (18.5)16 (12.3) | 0.0000.975\* | 1.0000.331 |
| **Marital status**MarriedSingle | 62(95.4)3(4.6) | 63(96.9)2(3.1) | 125(96.2)5(3.8) | 0.208 | 0.648 |
| **Educational level**SecondaryTertiary | 19(29.2)46(70.8) | 15(23.1)50(76.9) | 34(26.2)96(73.8) | 0.637 | 0.425 |
| **Religion**ChristianityIslam | 56(86.2)9(13.8) | 59(90.8)6(9.2) | 115(88.5)6(9.2) | 0.678 | 0.410 |

\*Independent student t-test

**Clinical Features of Study Participants**

Table 2 presents the clinical features observed among pre-eclamptic and normotensive pregnant women attending the antenatal clinic at Irrua. Pallor was observed in 17(13.1%) participants at presentation. edema, headache, and abdominal pain were significantly more common among the pre-eclamptic group compared to the normotensive controls.

Table 2: Clinical features observed among pregnant women attending the antenatal clinic, Irrua

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Clinical Features** | **Pre-eclampsia****(n=65)** | **Normotensive****(n=65)** | **Total****(n=130)** |  |  |
|  | **n(%)** | **n(%)** | **n(%)** | **χ2** | **p-value** |
| Palor | 13(20.0) | 4(6.2) | 17(13.1) | 5.482 | **0.019\*** |
| Jaundice | 4(6.2) | 1(1.5) | 5(3.8) | 1.872 | 0.171 |
| Cyanosis | 3(4.6) | 0(0.0) | 3(2.3) | 3.071 | 0.080 |
| Oedema | 14(21.5) | 3(4.6) | 17(13.1) | 8.188 | **0.004\*** |
| Headache | 7(10.8) | 1(1.5) | 8(6.2) | 4.795 | **0.029\*** |
| Epigastric pain | 1(1.5) | 0(0.0) | 1(0.8) | 1.008 | 0.315 |
| Dysuria | 2(3.1) | 1(1.5) | 3(2.3) | 0.341 | 0.559 |
| Frequency | 3(4.6) | 4(6.2) | 7(5.4) | 0.151 | 0.698 |
| Abdominal pain | 4(6.2) | 0(0.0) | 4(3.1) | 4.127 | **0.042\*** |
| Visual disturbance | 2(3.1) | 0(0.0) | 2(1.5) | 2.031 | 0.154 |

**Comparison of Hemostatic Parameters**

There were no statistically significant differences in platelet count, mean platelet volume (MPV), prothrombin time (PT), or activated partial thromboplastin time (aPTT) between preeclamptic women and normotensive controls at the time of diagnosis in the second trimester. However, plasma levels of plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and D-dimer were significantly higher in the preeclamptic group compared to the controls (p < 0.05 for each parameter) (Table 3).

Table 3: Comparison of hemostatic parameters between preeclamptic and normotensive pregnant women at diagnosis (second trimester), attending the antenatal clinic at Irrua

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre-eclampsia****(n=65)** | **Normotensive****(n=65)** |  |  |
|  | **Mean±SD** | **Mean±SD** | **t-value** | **P** |
| Platelet count (x 106) | 209.03±70.4 | 208.51±55.9 | 0.047 | 0.963 |
| MPV (fl) | 9.18±1.1 | 9.04±1.0 | 0.756 | 0.451 |
| Prothrombin time (secs) | 12.45±1.1 | 12.34±0.8 | 0.617 | 0.538 |
| INR | 1.05±0.1 | 1.04±0.1 | 0.436 | 0.663 |
| APTT (sec) | 37.45±1.3 | 37.37±1.1 | 0.359 | 0.720 |
| PAI 1 (ng/ml) | 6.41±2.4 | 4.73±1.5 | 4.842 | **<0.001\*** |
|  | **Median (Q1-Q3)** | **Median (Q1-Q3)** | **Man Whitney** |  |
| Fibrinogen (mg/ml) | 298.4 (217-408) | 207.4 (134-256) | -5.518 | **<0.001\*\*** |
| D-DIMER (ng/ml) | 589.4 (278-1002) | 102.0 (78-178) | -8.028 | **<0.001\*\*** |

t-value = Independent student t test; \*\*=Man Whitney test

In the third trimester, plasma levels of MPV, PAI-1, fibrinogen, and D-dimer remained significantly elevated in preeclamptic women compared to their matched normotensive counterparts (p < 0.05 for each), as shown in Table 4.

Table 4: Comparison of hemostatic parameters between preeclamptic and normotensive pregnant women in the third trimester, attending the antenatal clinic at Irrua

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre-eclampsia****(n=65)** | **Normotensive****(n=65)** |  |  |
| Platelet count | 231.28±77.0 | 238.71±67.4 | -0.585 | 0.559 |
| MPV (fl) | 9.41±1.2 | 8.8±0.8 | 3.552 | **0.001\*** |
| Prothrombin time (secs) | 12.68±1.0 | 12.54±0.9 | 0.858 | 0.393 |
| INR | 1.07±0.1 | 1.05±0.1 | 0.982 | 0.328 |
| APTT (secs) | 38.25±1.4 | 37.88±1.1 | 1.647 | 0.102 |
| PAI 1 (ng/ml) | 10.61±2.6 | 7.21±1.6 | 8.949 | **<0.001\*** |
| Fibrinogen (mg/ml) | 610.8 (392-798)# | 308.8(218-399)# | -7.061 | **<0.001\*\*** |
| D-DIMER (ng/ml) | 809.0(438-1547)# | 103.0 (86-234)# | -8.223 | **<0.001\*\*** |

**Hemostatic Parameters by Severity of Preeclampsia**

Table 5 shows that the median plasma levels of fibrinogen and D-dimer were significantly higher in women with severe preeclampsia compared to those with mild preeclampsia (p < 0.05).

Table 5: Hemostatic parameters of preeclamptic pregnant women attending the antenatal clinic in Irrua at second trimester, stratified by severity of preeclampsia

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mild(n=31)**Mean±SD | **Severe(n=34)**Mean±SD | P |
| Platelet count (X109) | 233.82.82±82.5 | 228.48±71.8 | 0.783 |
| MPV (fL) | 9.13±1.3 | 9.22±1.0 | 0.758 |
| Prothrombin time (sec) |  12.42±1.1 |  12.47±1.2 | 0.857 |
| INR | 1.04±0.1 | 1.05±0.1 | 0.857 |
| APTT (sec) | 37.58±1.3 | 37.32±1.3 | 0.434 |
| PAI 1 (ng/ml) | 6.00±2.0 | 6.78±2.6 | 0.184 |
| Fibrinogen (mg/ml) | 297.2(213-310)# | 301.4(233-500)# | 0.058 |
| D-DIMER (ng/ml) | 376.0(205-874)# | 699.0(401-1023)# | **0.041\*** |

\*\*=Man Whitney test;  #=Median (Q1-Q3)

Table 6 also shows that the median plasma levels of fibrinogen and D-dimer were significantly higher in women with severe preeclampsia compared to those with mild preeclampsia in the third trimester (p < 0.05).

Table 6: Hemostatic parameters of preeclamptic pregnant women attending the antenatal clinic in Irrua, in the third trimester, stratified by severity of preeclampsia

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mild(n=31)** Mean±SD | **Severe(n=34)** Mean±SD | **p** |
| Platelet count (X109) | 214.50±7.6 | 203.03±63.1 | 0.516 |
| MPV (fL) | 9.36±1.1 | 9.46±1.3 | 0.720 |
| Prothrombin time (sec) | 12.51±0.9 | 12.82±1.0 | 0.197 |
| INR | 1.06±0.1 | 1.09±0.1 | 0.255 |
| APTT (sec) | 37.94±1.4 | 38.53±1.4 | 0.094 |
| PAI 1 (ng/ml) | 10.54±2.3 | 10.67±2.9 | 0.839 |
| Fibrinogen (mg/ml) | 501.0(335-628)# | 745.1(501-1000)# | **0.001\*\*** |
| D-DIMER (ng/ml) | 555.0(262-1131)# | 1062(567-1797)# | **0.010\*\*** |

\*\*=Man Whitney test;  #=Median (Q1-Q3)

Figure 1 shows the area under the curve (ROC) for Platelet count, MPV, PT, INR, APTT, PAI-1, Fibrinogen, and D-dimer. 95% CI for PAI-1 is 0.629 - 0.802 (ng/ml), for Fibrinogen is 0.704 - 0.857 (mg/ml) and 0.854 - 0.962 (ng/ml) for D-dimer, in predicting preeclampsia severity. The ***p<0.05*** for PAI-1, Fibrinogen, and D-dimer.

**Figure 1:** Receiver operating characteristic (ROC) curve for Pre-eclampsia using plasma levels of Platelet count, MPV, PT, APTT, PAI-1, Fibrinogen, and D-dimer in the second trimester.

Figure 2 shows the area under the curve for Platelet count, MPV, PT, INR, APTT, PAI-1, Fibrinogen, and D-dimer in predicting preeclampsia severity in the third trimester. The *p<0.05* for PAI-1, Fibrinogen and D-dimer in the third trimester.

**Figure 2:** Receiver operating characteristic (ROC) curve for plasma levels of Platelet count, MPV, PT, APTT, PAI-1, Fibrinogen, and D-dimer predicting severity of preeclampsia in third trimester.

**4. Discussion**

The prevalence of preeclampsia is typically higher at the extremes of reproductive age, particularly in women younger than 18 years or older than 35 years [14]. However, this study found that most preeclamptic participants were between 25 and 34 years old. This finding aligns with previous research showing the lowest risk of preeclampsia in the 20–24-year age group, with increasing risk beyond that age [15]. Sociodemographic factors such as educational level and religion may influence the age at which preeclampsia manifests.

Edema was a notable clinical finding in this cohort. Endothelial cell activation or dysfunction, precipitated by antiangiogenic factors, metabolic changes, and inflammatory leukocyte mediators, contributes to the development of preeclampsia. Proinflammatory cytokines such as interleukin-2 (IL-2), interferon-gamma (IF-γ), transforming growth factor-beta (TGF-β), and tumor necrosis factor-alpha (TNF-α) may play roles in the oxidative stress associated with preeclampsia. This oxidative stress leads to the production of reactive oxygen species, which damage endothelial cells, alter nitric oxide synthesis, and disrupt prostaglandin balance. Consequences include increased microvascular coagulation (causing thrombocytopenia), enhanced capillary permeability (leading to edema), and proteinuria. Abdominal pain, observed in many preeclamptic participants, may be due to hepatic involvement. It typically presents as right upper quadrant or epigastric pain and tenderness, and can be associated with hepatic infarction. Even with extensive hepatic involvement, clinical signs may remain subtle [16].

Platelet count decreased progressively with the severity of preeclampsia in both the second and third trimesters, likely due to increased platelet destruction as the condition advances. Conversely, mean platelet volume (MPV) increased in preeclamptic women, indicating heightened platelet turnover and marrow response to peripheral consumption. This observation is consistent with the findings of Umezuluike et al. and Thalor et al. [17-18]. MPV may therefore be a useful biomarker in differentiating preeclamptic from normotensive pregnancies. In normal pregnancy, a hypercoagulable state is characterized by shortened prothrombin time (PT) and activated partial thromboplastin time (APTT), which assess the extrinsic and intrinsic coagulation pathways, respectively. However, this study found PT and APTT values within the normal reference range for both cases and controls during the second trimester, possibly reflecting a balance between increased coagulation and counter-regulatory anticoagulant mechanisms in preeclampsia. A slight prolongation of PT and APTT was observed in the third trimester among preeclamptics, consistent with studies by Han et al. [7] and Emeka-obi et al. [19].

Endothelial dysfunction is central to the pathophysiology of preeclampsia and is associated with increased levels of fibrinolytic proteins, their inhibitors, and degradation products. In this study, plasma levels of plasminogen activator inhibitor-1 (PAI-1) were significantly elevated in preeclamptic participants compared to normotensive controls and were notably higher in severe cases. This supports the findings of Agersnap et al., who in a systematic review found increased PAI-1 levels in eight of eleven studies [20], and a similar study by Emeka-obi et al. [19] in the eastern part of Nigeria. In contrast, Pegoraro et al., studying Black South African women, did not find a significant role for the PAI-1 4G allele in preeclampsia risk, although they could not rule out its contribution [21]. Udenze et al., in a study from southwestern Nigeria, observed elevated PAI-1 levels in early preeclamptic pregnancies but found them to be poor indicators of disease severity possibly due to lack of third-trimester follow-up [22].

Preeclampsia is known to increase the production of coagulation factors such as fibrinogen and factors VIII, IX, and X. Fibrinogen levels in preeclamptic women were significantly higher than in normotensive controls in this study, and levels were even more elevated in women with severe preeclampsia. These findings are consistent with previous studies [23-24]. The predictive power of fibrinogen for disease severity improved as pregnancy progressed, with the area under the curve (AUC) increasing from 0.780 in the second trimester to 0.859 in the third, which align with the study by Sultana et al. [25]. Williams et al. also reported increased fibrinogen and factor VIII activity in women with preeclampsia compared to those with normal pregnancies [26]. Although fibrinogen normally increases during pregnancy, the levels observed in this study likely exceed physiological limits and suggest pathological hypercoagulability.

D-dimer, a marker of fibrinolysis, increases during normal pregnancy due to low-grade intravascular coagulation. In this study, preeclamptic women especially those with severe disease had significantly higher D-dimer levels than normotensive controls, consistent with findings from other researchers [19, 27- 28]. Pinheiro Mde et al., in a meta-analysis, confirmed that D-dimer levels rise significantly in the third trimester in women who develop preeclampsia [27]. Lucena et al. observed that D-dimer increases throughout gestation, peaking earlier in women who develop preeclampsia [29]. In the present study, the AUC for D-dimer as a predictor of severe preeclampsia was 0.918, indicating high diagnostic performance. Baboolall et al. proposed a higher D-dimer threshold in the third trimester to reduce false positives, also highlighting the utility of PAI-1 in predicting severity [30].

Receiver operating characteristic (ROC) curve analysis confirmed that PAI-1, fibrinogen, and D-dimer levels were predictive of preeclampsia severity in both the second and third trimesters. These findings align with those of Han et al. [7]. Severe preeclamptics had markedly elevated values of these markers compared to mild cases and normotensive controls. The predictive ability of PAI-1 supports the theory that severe preeclampsia may represent a state of fibrinolytic failure, as shown in other studies [31]. Increased PAI-1 may result from angiotensin II stimulation at the placental bed, secondary to heightened renin-angiotensin system activity during pregnancy, likely driven by estrogen.

MPV was significantly higher in severe preeclamptic women during the third trimester, while platelet counts remained relatively stable, possibly due to elevated thrombopoietin levels. These findings underscore the involvement of the hemostatic system in preeclampsia and support the role of PAI-1, fibrinogen, and D-dimer as predictive biomarkers.

**Conclusion**

This study confirms that mean platelet volume (MPV) is significantly elevated in women with preeclampsia, particularly in the third trimester. Plasma levels of PAI-1, fibrinogen, and D-dimer were also significantly higher in preeclamptic subjects compared to normotensive pregnant women, with levels increasing with disease severity. Among these markers, fibrinogen and D-dimer demonstrated the highest predictive value for severe preeclampsia. Therefore, these hemostatic parameters can serve as useful tools in assessing the severity of preeclampsia, and their elevation supports the concept that severe preeclampsia is associated with fibrinolytic dysfunction.

Ethical Approval and Consent to Participate

Ethical approval for this study was obtained from the Ethics and Research Committee of the Irrua Specialist Teaching Hospital, Irrua, Nigeria (Protocol No: ISTH/HREC/20200308/078). Written authorization was also obtained from the Heads of the Departments of Hematology and Blood Transfusion, and Obstetrics and Gynecology. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants after the purpose of the study and the procedures involved were clearly explained to them in a language they best understood.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT) have been used during the writing or editing of manuscripts.

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