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Research article

Correlation of platelet parameters with adverse maternal and neonatal outcomes in severe preeclampsia: A case-control study

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ABSTRACT

Background: Pre-eclampsia (PET) is a potentially devastating multi-systemic disorder resulting in the generation of oxidative stress. Platelet activation causes vasoconstriction and release of inflammatory cytokines, resulting in an intensified inflammatory response, endothelial damage, and coagulopathy which culminate in adverse pregnancy outcomes.

Aim: To compare the platelet parameters between preeclamptic and normotensive pregnant women and their relationship to adverse outcomes in women with pre-eclampsia.

Materials and methods: This was a case-control study of platelet indices of 60 pre-eclamptic and 60 normotensive pregnant women recruited at 28 weeks and followed till delivery. A blood sample was collected at entry into the study and just before delivery. The sample was analyzed within 1 h of collection using the Mythic 18 hematological auto-analyzer. Data were analyzed using IBM-SPSS version 22. A P-value of <0.05 was considered statistically significant.

Results: The mean platelet count, Platelet distribution width (PDW), plateletcrit were statistically significantly different between normotensive and severe preeclamptic participants (p= <0.001). Statistically significant differences were not present in any of the platelet parameters between mild and severe PET. The odds of developing eclampsia was low at higher mean platelet count and plateletcrit levels above $161.36 \pm 73.74 \times 10^9$/L [p = 0.02, AOR = 0.27, 95% CI (0.08–0.88)] and $0.13 \pm 0.05\%$ [p = 0.001, AOR = 0.22, 95% CI (0.08–0.58)] respectively. Eclampsia was strongly associated with P-LCR (platelet-large cell ratio) above $23.15 \pm 4.92\%$ [p = 0.004, AOR = 11.00, 95%CI (1.48–89.02)]. Abruptio placentae had low odds at lower levels of mean plateletcrit. Pre-term birth was significantly lower at mean plateletcrit levels above $0.14 \pm 0.05\%$; admission into neonatal intensive care unit was strongly associated with a mean PLC ratio above $22.73 \pm 5.91\%$.

Conclusion: This study demonstrated significant differences in platelet count, plateletcrit, platelet distribution width, and P-LCR between pre-eclamptic and normotensive women. Increase in P-LCR is a risk factor for eclampsia although the effect size is low.

1. Introduction

Pre-eclampsia is a potentially devastating complication of pregnancy [1, 2] characterized by a new-onset of hypertension associated with thrombocytopenia, maternal multi-organ dysfunction, and fetal growth restriction [3, 4]. It is associated with the development of hypertension and proteinuria after 20 weeks of pregnancy in previously normotensive and non-proteinuric women [4, 5]. It complicates between 3% and 5% of pregnancies [1, 6, 7, 8]. It is one of the leading causes of maternal and perinatal morbidities and mortalities around the world [1, 2]. It is responsible for 76,000 maternal and 500,000 perinatal deaths annually [1, 6, 7, 8] and 192 maternal deaths daily [7]. These figures demonstrate the enormity of the ills of pre-eclampsia and the need to find ways of preventing the complications associated with it.

The etiology of preeclampsia is largely unknown but it has been associated with certain risk factors such as African descent, obesity, nutritional deficiencies, previous history of chronic hypertension, heredity, diabetes mellitus, autoimmune disorders, molar, and multiple

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gestations [4, 5, 9, 10]. Others include: primipaternity, primigravidity, teenage pregnancy, and age above 35 years [5, 9]. It is regarded as a disease of theories, and finding definitive pathophysiology remains elusive [1, 4, 5, 7, 8, 9, 10, 11]. Inefficient remodeling of the smooth muscles of the spiral arterioles of the uterine endometrium due to failure of the second wave of trophoblastic invasion has been implicated [4, 6, 10]. This leads to the persistence of high resistance vessels which are highly responsive to vasoactive substances causing turbulent blood flow and generation of oxidative stress causing widespread multi-organ endothelial damage [4, 6, 10]. Placental hypoperfusion and increased vascular permeability also contribute to the pathophysiology [11].

Platelets are small discoid anucleated cytoplasmic fragments derived from megakaryocytes that are primarily involved in hemostasis by adhering to sites of endothelial injury, leading to platelet aggregation [12, 13, 14, 15, 16]. Thrombocytopenia is the commonest hemostatic abnormality in pre-eclampsia and maybe the only initial manifestation predating other laboratory changes [14, 15]. Enhanced thrombopoiesis produces younger and larger platelets that are metabolically and enzymatically more active [12, 13]. The inflammatory response is intensified in pre-eclampsia by the induction of inflammatory cytokines by adherent platelets on endothelial cells culminating in severe hemostatic, vascular, and coagulation abnormalities that cause serious feto-maternal complications [17].

Reliable prediction and early diagnosis of pre-eclampsia are pivotal in preventing its complications thereby improving pregnancy outcome [3, 5, 10, 18, 19]. Planning for the most appropriate place and time of delivery is key for optimal management and prediction of adverse outcome [19]. Some clinical, biophysical, and biochemical indicators of severe disease such as epigastric pain, blood pressure, and serum uric acid respectively, have not shown consistent outcome or clinical usefulness for predicting adverse maternal and/or perinatal outcome [20]. Novel biomarkers such as soluble fms-like tyrosine kinase-1(sFlt-1), soluble endoglin (sEng), placental growth factors (PIGF) and the vascular endothelial growth factors (VEGF) have shown promising results but are unaffordable and not readily available in resource-poor settings [3, 4, 9, 10, 21, 22].

Platelet parameters are a combination of different platelet indices including platelet count with different predictive capacities [19, 20]. Platelet parameters have shown promising results in the prediction and diagnosis of pre-eclampsia [3, 4, 9, 10, 18, 21, 22, 23] but their role in the prediction of adverse feto-maternal outcome have not received adequate attention [3, 4, 9, 10]. Platelet count, a component of the platelet parameters, is one of the best-performing multivariable models for the prediction of composite maternal outcome in pre-eclamptic women [19]. Pre-eclampsia has been linked with platelet activation and significant hemostatic abnormalities which result in serious feto-maternal complications [22]. Its optimal management depends on prompt prediction, early diagnosis, and timely institution of standard treatment and termination of the pregnancy to prevent the onset of the cascade of events that will result in adverse outcome [19, 22]. Clinical features and common tests available for the care of pre-eclamptic patients lack strong evidence of clinical usefulness in predicting adverse outcome [7, 19]. The lack of reliable, affordable and globally acceptable marker(s) of severity and the adverse outcome is worrisome [24]. The soluble fms-like tyrosine kinase-1 to placental growth factor (sFLt-1/PIGF) ratio, a promising novel biomarker for predicting composite maternal outcomes, is unavailable and unaffordable by many patients in resource-poor settings [19]. It becomes necessary to try other biomarkers that are affordable to resource-constrained patients.

Platelet parameters are markers of platelet activation that have been found useful for predicting and diagnosing various medical conditions especially cardiovascular diseases including hypertensive disorders in pregnancy such as pre-eclampsia [25, 26]. However, their utility in predicting the severity and outcome of pre-eclampsia has not been fully exploited [24, 25]. They are simple, easy, and cheap with no extra cost to the patient since they are part of the full blood count utilized in the care of pre-eclamptic and are usually generated by hematological auto-analyzers [27, 28]. This study is aimed at comparing the platelet indices between the pre-eclamptic and normotensive pregnant women and also in determining the relationship between platelet parameters and adverse pregnancy outcomes in pre-eclamptic women.

2. Materials and methods

2.1. Study design

The study is a case-control. The cases were women with pre-eclampsia while control were matched normotensive pregnant women.

2.2. Study background

The study was carried out at the Alex Ekwueme Federal University Teaching Hospital, Abakaliki (AE-FUTHA) and St. Patrick's Mile 4 Hospital, Abakaliki, Ebonyi state. Ebonyi state is one of the five states of the South-East geopolitical zone of Nigeria with a population of about 2.17 million people and Abakaliki is the state capital [29]. Subsistent farming and petty trading are common occupations, especially among the rural dwellers. Literacy level and health indices are generally poor.

2.3. Study population

The study participants were normotensive pregnant women and those with pre-eclampsia from 28 weeks gestation that met the inclusion criteria and were managed at Mile 4 and Alex Ekwueme Federal University Teaching Hospitals, in Abakaliki, Ebonyi state. The study population was recruited between 10th August 2019 and 28th February 2020. Consecutive sampling method was used to recruit consenting pre-eclamptic women (cases) while purposive sampling method was applied for the controls that met the inclusion criteria. A detailed history was obtained and a thorough physical examination was carried out on each participant. Results of relevant investigations such as serum electrolytes, urea, and creatinine, coagulation profile, liver function test, fasting blood sugar, and blood group were retrieved from their case notes and also utilized in their management. Participants with pre-eclampsia were compared with low-risk normotensive pregnant women that received antenatal care or that delivered at the study centers. The cases were matched with controls of the same gestational age within one week of the cases.

2.4. Inclusion and exclusion criteria

Women included in the study were women with a singleton pregnancy from 28 weeks gestation with pre-eclampsia and consenting normotensive pregnant women from 28 weeks gestation. Those excluded were pregnant women with diagnosed diabetes mellitus, chronic liver disease, chronic renal disease, chronic hypertension, multiple pregnancies, bleeding disorders, heart disease, and those on anticoagulant/antiplatelet drugs.

The recruited controls were healthy and normotensive pregnant women that received antenatal care at the study centers who were matched with the cases for gestational age at a 1:1 ratio. For each case recruited, a control with corresponding gestational age or gestational age within one week of the case was recruited from the antenatal clinic, labor ward, or emergency unit. Only pregnant women from 28 weeks were recruited and two blood samples were collected for full blood count analysis: first at diagnosis of pre-eclampsia and then in the second stage of labor or just before induction of anesthesia for cesarean deliveries. For the controls, the first blood sample was taken at a corresponding gestational age or a gestational age within one week of the cases while the second sample was taken just as in the cases above. Each study participant had a unique code placed on her folder at recruitment to aid follow-

up. Participants with pre-eclampsia were subdivided into mild and severe groups and were followed up till discharge.

2.5. Sample size determination

The minimum sample size was determined using the formula for case-control studies for the difference in two means.

$$N = \frac{r+1}{r}\frac{\sigma^2\left[Z\beta + Z\frac{\alpha}{2}\right]^2}{(\mu 1 — \mu 2)^2}$$

Where N is the sample size

r is the ratio of cases to controls. Assuming an equal number of cases and controls, r = 1

σ^2 = pooled variance of outcome variable = $\frac{S_1{}^2 + S_2{}^2}{2}$

S_1 = Standard deviation of cases; S_2 = Standard deviation of the controls

Zβ = desired power; typically 0.84 for power of 80%

$Z\frac{\alpha}{2}$ = desired level of statistical significance; set to a level of 0.05 at 95% confidence interval and equal to 1.96

μ1 = mean of platelet parameter for patients with pre-eclampsia (cases)

μ2 = mean of platelet parameter for normal patients (control)

$$\sigma^2 = \frac{(1\cdot 70)^2 + (0\cdot 8)^2}{2} = \frac{2.89 + 0.64}{2} = 1.765$$

From a study done by Alisi et al. [30] the mean and standard deviation of the platelet parameter PDW for pre-eclamptic cases and normotensive pregnant controls were 12.04 ± 1.70 fl and 11.32 ± 0.8 fl respectively. Therefore, the sample size was

$$N = \frac{1+1}{1}\frac{(1\cdot 765)\{1\cdot 96 + 0\cdot 84\}^2}{(12\cdot 04 — 11\cdot 32)^2} = 53\cdot 40$$

Ten percent attrition rate (5.3) was added, making it approximately 59. However, 130 participants were recruited for the study but 120 were analyzed (60 in each arm).

2.6. Study procedure

2.6.1. Measurement of blood pressure

Blood pressure was measured with mercury sphygmomanometer with standard cuff. Participants were made to sit comfortably on an armchair with a backrest and allowed to rest for 10 min before measuring the blood pressure with the right arm supported at the level of the heart. The cuff was placed two finger breaths above the brachial artery pulsation from the right antecubital fossa and the 'artery' mark was aligned with the bladder of the cuff, ensuring that about 80% of the arm circumference was encircled by the bladder. The brachial artery pulsation was palpated and the cuff inflated until the pulsation disappeared. The point of disappearance was noted as estimated systolic blood pressure. The cuff was then deflated completely and re-inflated to 20 mmHg above the estimated systolic level to occlude the brachial artery pulsation. The diaphragm of the stethoscope was placed over the brachial artery and the cuff was deflated at a rate of 2 mm Hg/s until regular tapping sounds were heard. Systolic (Korotkoff I) and diastolic (Korotkoff V) blood pressure readings were measured to the nearest 2 mmHg. Mild pre-eclampsia was diagnosed with systolic blood pressure (SBP) of 140–159 mmHg and/or diastolic blood pressure (DBP) of 90–109 mmHg measured on two occasions at least 4 h apart, with proteinuria while severe pre-eclampsia was diagnosed with single systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) reading of ≥160 mmHg and/or ≥110 mmHg respectively in association with significant proteinuria.

2.7. Sample collection

2.7.1. Blood sample

Aseptic universal precautions were observed and participants were made comfortable during sample collection. The left antecubital region was used for venipuncture. A tourniquet was applied for not more than 2 min about four finger breaths above the left antecubital fossa area for venipuncture. The area was swabbed with 70% alcohol (methylated spirit) and allowed to air-dry. A 21-gauge needle (5-ml syringe) was introduced into any prominent vein at the cubital fossa and once blood flow was established, the tourniquet was released and 4 mL of blood was collected into a labeled tube containing ethylene diamine tetraacetate, tripotassium (EDTA K_3) anticoagulant. Gentle pressure was applied with a ball of dry cotton wool over the puncture site to achieve hemostasis. The container was gently inverted 6 times for proper mixing of the blood sample with the anticoagulant and the specimen was transported to the laboratory in a sealed zip-lock type biohazard bag. At the laboratory, each collected blood sample was placed on a sample mixer that rotated at 20 turns per minute for 5 min to ensure proper mixing of the blood with the anticoagulant, and the test was performed within 1 h of sample collection using MYTHIC 18 with serial number 100218010266 and reference code M18C/UM-EN/017.

2.7.2. Mid-stream urine sample

Each participant was educated on the procedure and provided with a well-labeled wide-mouthed sterile urine container and pieces of towelettes (wipes) to clean her vulva. After hand washing, each participant opened the already labeled sterile container, ensuring that it was within reach and not contaminated. The perineum was washed with clean water and dried with a sanitary pad. The thumb and index finger of one hand were used to separate the labial folds to expose the urethral opening. Then using one towelette at a time, the patient wiped the sides of the inner fold and then the center from front to back, one at a time. The initial part of the urine stream was voided while the mid-stream was collected into a urine bottle. The specimen bottle was re-capped tightly, cleaned and the urine sent to the laboratory for analysis. Proteinuria was determined with urinalysis test strips, Combi-11 by Macherey-Nagel®. Significant proteinuria was regarded as ≥ 2+ of proteinuria on dipstick or 1+ of proteinuria plus urinary PH < 8 or specific gravity <1.030 in a random urine sample [4, 10, 23].

2.8. Analysis of data

The data generated from the study were analyzed with IBM-SPSS version 22 Chicago, Il, USA. Mean and standard deviation was used to represent the continuous variables (platelet parameters) while frequencies and percentages were used for the analysis of the categorical variables. The mean platelet parameter differences among the groups were compared with Analysis of Variance (ANOVA). Adjusted odds ratio at 95% confidence interval was used to evaluate the relationship between platelet parameters and adverse maternal and fetal outcomes. P-value <0.05 was considered statistically significant.

2.9. Ethical considerations

Ethical clearance was sought and obtained from the Health Research and Ethics Committee of AE-FETHA with approval number of AE-FETHA/REC/VOL/2/2019/153. Permission was also obtained from the Health Research and Ethics Committee of St. Patrick's Mile Four hospital, Abakaliki with an approval number of RE/M4H/39/19. The ethical principles of informed consent, confidentiality, beneficence, non-maleficence, and justice were strictly observed in the conduct of the study. The cost of the research was borne by the researcher.

3. Results

The study lasted for 6 months during which a total of 130 patients were recruited (60 cases and 70 controls). Ten participants in the control group were lost to follow-up and 120 were analyzed eventually; sixty in each of the case and control groups. Among pre-eclamptic participants, 24 (40.0%) had eclampsia, 17 (28.3%) had Abruptio placentae, 25 (41.7%) were managed in the intensive care unit and 2(3.3%) died while 28(46.7%) of the babies were delivered pre-term, 24 (40.0%) had birth asphyxia, 35 (58.3%) were admitted in the NICU and 15(25.0%) had perinatal death. Among the normotensive participants, 2(3.3%) had Abruptio placentae from trauma. One of the two that had Abruptio placentae was nursed in the ICU and was managed and discharged.

Table 1 below shows the socio-demographic characteristics of the participants in the two groups there was no statistically significant difference in socio-demographic characteristics of the participants. The mean ages of the participants, cases, and controls were 29.25 ± 5.04 years, 28.88 ± 5.00 years respectively while the mean gestational ages at recruitment and delivery were 33.87 ± 3.93 weeks and 37.50 ± 2.77 weeks respectively.

Table 2 depicts the comparison of the platelet parameters in normotensive, mild, and severe pre-eclamptic groups of the study at recruitment and just before delivery. ANOVA supplemented with a posthoc test was used to compare the mean among the groups. Statistically significant differences were observed among the groups in all the platelet parameters except the mean platelet volume (MPV). The posthoc test revealed statistically significant differences in mean platelet count (PC) between normotensive and severe pre-eclamptic participants at entry and just before delivery ($p = 0.001$ and <0.001 respectively). There was also a significant difference in the mean plateletcrit (PCT) levels between normal and severe pre-eclamptic participants at recruitment and just before delivery ($p = 0.001$ and <0.001 respectively) as well as between normal and mild pre-eclamptic women just before delivery ($p = 0.002$). Platelet distribution width (PDW) showed statistically significant differences in normotensive compared to severe pre-eclamptic participants at entry into the study and just before delivery ($p = 0.005$ and 0.04 respectively) while also showing a significant difference between normal and mild pre-eclampsia at entry ($p = 0.005$). Statistically significant differences were also noted in the platelet-large cell ratio (P-LCR) levels between normotensive and mild as well as between normotensive and severe pre-eclamptic participants at entry and between normal and mild pre-eclamptic cases just before delivery. No statistically significant difference in MPV was seen among the groups and none of the platelet parameters showed a significant difference between participants with mild and those with severe pre-eclampsia. There was a decline in the mean PC and PCT at entry (recruitment) and just before delivery in all the groups but the difference was not statistically significant. In contrast, there was an increment in the levels of MPV, PDW, and P-LCR in the groups between recruitment and just before delivery. These changes were also not statistically different.

Table 1. Comparison of socio-demographic characteristics of participants.

Variable	Case (n = 60,%)	Control (n = 60,%)	P-value
Age (years)			0.85
16–20	2 (3.3)	4(6.7)	
21–25	3 (5.0)	5(8.3)	
26–30	30 (50.0)	21(35.0)	
31–35	14(23.3)	20(33.3)	
36–40	11(18.3)	10(16.6)	
Parity			0.39
0	24 (40.0)	20 (33.3)	
1–4	31 (51.7)	33 (55.0)	
≥5	5 (8.3)	7 (11.7)	
Entry GA (weeks)			0.52
28–33	22 (36.7)	25 (41.7)	
34–39	27 (45.0)	27 (45.0)	
≥40	11 (18.3)	8 (13.3)	
Delivery GA (weeks)			0.15
28–33	13 (21.7)	8 (13.3)	
34–39	36 (60.0)	37 (61.7)	
≥40	11 (18.3)	15 (25.0)	
Educational level			0.38
Primary	10 (16.7)	9 (15.0)	
Secondary	27 (45.0)	22 (36.7)	
Tertiary	23 (38.3)	29 (48.3)	
Social class			0.18
1	9 (15.0)	11 (18.3)	
2	6 (10.0)	13 (21.7)	
3	19 (31.7)	17 (28.3)	
4	16 (26.6)	10 (16.7)	
5	10 (16.7)	9 (15.0)	
Tribe			0.28
Igbo	54 (90.0)	51 (85.0)	
Hausa	2 (3.3)	1 (1.7)	
Yoruba	1 (1.7)	2 (3.3)	
Others	3 (5.0)	6 (10.0)	

G.A = Gestational Age.

Table 3 demonstrates the correlation of platelet parameters **(recruitment and delivery)** with adverse maternal outcomes in pre-eclampsia. The study observed a very strong association between eclampsia and elevated mean platelet-large cell ratio [$p = 0.004$, AOR = 11.00, 95%CI (1.48–89·02)]. It was also noted that the odds of developing eclampsia among pre-eclamptic participants at higher levels of PC and PCT were also significantly lower [$p = 0.02$, AOR = 0.27, 95% CI (0.08–0.88)] and [$p = 0.001$, AOR = 0.22, 95% CI (0.08–0.58)]. The study also observed that the odds of having abruptio placentae and being admitted in the ICU were significantly lower at higher plateletcrit values. None of the platelet parameters were positively associated with maternal mortality in this study.

Table 4 represents the relationship between the various platelet parameters **(recruitment and delivery)** and the four adverse perinatal outcome measures assessed in the study. It was observed that the odds of preterm delivery in women with pre-eclampsia were significantly low at higher mean PCT levels [$p = 0.001$, AOR = 0.14, 95% CI (0.04–0.49)] whereas an association was observed between high mean P-LCR and NICU admission [$p = 0.01$, AOR = 5.16, 95% CI (1.39–19.21)]. None of the parameters was statistically significant for birth asphyxia and perinatal death.

4. Discussion

The potential of the platelet parameters to predict the severity of pre-eclampsia and its associated feto-maternal complications has been evaluated in different studies. This study evaluated five platelet parameters to determine their relationship with the severity of pre-eclampsia and perinatal and maternal complications. A progressive decrease in mean platelet count was noted in mild and severe pre-eclamptic compared to normotensive participants at recruitment into the study. This was also true among the groups at delivery. This relationship between platelet count and severity of pre-eclampsia could be due to the increased platelet destruction associated with pre-eclampsia. Similar findings were reported by Freitas et al, [16] Al Sheeha et al. [22]Abbas et al. [31]and Alisi et al. [30] which supports increased platelet destruction with increasing severity of pre-eclampsia. Other studies also documented a similar decline in platelet count with increasing severity of pre-eclampsia [23, 32, 33, 34, 35, 36, 37]. It is also observed that statistically significant differences were present between the mean PCT and PDW in the pre-eclamptic group compared to the controls at both recruitment and

Table 2. Comparison of the platelet parameters among normotensives and pre-eclamptic women at entry and just before delivery.

Variable	Normotensive (n = 60)	MPE (n = 18)	SPE (N = 42)	F-Value	P-value	Tukey's post-hoc test	P-value
PC($\bar{x}$,SD)10^9/L Entry	193.0(55.06)	167.7(90.5)	144.5(61.9)	7.19	0.001*	N vs MPE	0.308
						N vs SPE	0.001*
						MPE vs SPE	0.401
Delivery	182.5(52.15)	167.3(96.7)	128.4 (57.6)	9.37	<0.001*	N vs MPE	0.638
						N vs SPE	<0.001*
						MPE vs SPE	0.541
PCT($\bar{x}$, SD)% Entry	0.18 ± 0.06	0.15 ± 0.07	0.13 ± 0.05	6.68	0.002*	N vs MPE	0.223
						N vs SPE	0.001*
						MPE vs SPE	0.585
Delivery	0.17 ± 0.07	0.11 ± 0.06	0.09 ± 0.05	19.89	<0.001*	N vs MPE	0.002*
						N vs SPE	<0.001*
						MPE vs SPE	0.541
MPV($\bar{x}$, SD)fl Entry	8.62 ± 1.11	9.16 ± 1.07	8.96 ± 0.85	2.45	0.09	N vs MPE	0.134
						N vs SPE	0.238
						MPE vs SPE	0.775
Delivery	9.91 ± 1.5	9.37 ± 1.61	9.54 ± 1.15	1.42	0.24	N vs MPE	0.329
						N vs SPE	0.402
						MPE vs SPE	0.899
PDW($\bar{x}$, SD)fl Entry	13.05 ± 2.14	14.75 ± 1·80	14.59 ± 1.83	9.63	<0.001*	N vs MPE	0.005*
						N vs SPE	0.001*
						MPEvs SPE	0.957
Delivery	14.80 ± 2.40	16.45 ± 3.53	16.32 ± 3.72	3.83	0.02*	N vs MPE	0.120
						N vs SPE	0.042*
						MPEvs SPE	0.988
P-LCR($\bar{x}$, SD)% Entry	16.08 ± 4.11	21.60 ± 6.80	21.97 ± 5.06	20.70	<0.001*	N vs MPE	<0.001*
						N vs SPE	<0.001*
						MPEvs SPE	0.961
Delivery	23.56 ± 4.93	19.95 ± 7.57	22.41 ± 6.02	2.74	0.068	N vs MPE	0.056
						N vs SPE	0.584
						MPEvs SPE	0.289

PC = platelet count, PCT = plateletcrit, MPV = mean platelet volume, PDW = platelet distribution width, P-LCR = platelet-large cell ratio, S.D = standard deviation, L = liters, fL = femtoliters, N=Normotensive, MPE = Mild Pre-eclampsia, SPE = Severe Pre-eclampsia. Vs = versus, * statistically significant when $p < 0.05$.

delivery of the patients. Mean PCT decreased while mean PDW increased with increasing severity of pre-eclampsia. The observed decline in PCT may be due to accelerated platelet destruction while increased PDW, a marker of platelet activation, suggests an ongoing increased marrow activity. Similar findings were noted in other studies [16, 22, 23, 30, 31, 32].

P-LCR was also statistically lower in normotensive compared to mild and severe pre-eclamptic participants at recruitment of the participants which also suggests increased bone marrow turnover following platelet destruction as more immature platelets are produced to mitigate the increased platelet destruction. The study, however, observed a decline in P-LCR in mild pre-eclampsia compared to normotensive patients as well as an increment in severe compared to mild pre-eclampsia at delivery. These observed differences were not statistically significant. This finding is not in agreement with the findings of other studies [16, 22, 23, 30, 31, 33, 36, 38] This may be due to the relatively short time interval between collection of blood samples and instituting intervention strategies in an attempt to prevent complications in this study. MPV, however, did not show any statistically significant difference in cases compared to controls at both recruitment and delivery. This is in contrast to the findings in other studies [16, 22, 30, 31, 34, 35, 36]. Significantly higher MPV have been noted in pre-eclampsia compared to control in studies that collected a smaller quantity of blood into EDTA bottle [32]. Four milliliters of blood was used in this study as against 2 mL in some studies that observed significantly higher MPV (10.15 ± 1.10fl) [31], 11.55 ± 0.86fl [36]. Higher MPV values have also been observed in samples analyzed after 2 h of blood collection as the platelets tend to swell up with prolonged contact with EDTA, MPV is essentially a measurement of platelet size [16, 39].

From this study, no statistically significant differences were observed in the platelet parameters in mild compared to severe pre-eclampsia. This is in contrast to the findings of other studies [23, 32, 35] and may be due to short time intervals between recruitment and delivery in women with mild and severe pre-eclampsia in this study compared to other studies. This study observed that eclampsia has higher odds of occurrence with higher P-LCR and this finding was statistically significant. Other studies have also documented maternal complications with increasing P-LCR [34, 36] suggesting that high P-LCR may signify accelerated production of young and large platelets due to increased marrow activity to replace destroyed platelets. It was noted that there was a lower odd of occurrence of Eclampsia with participants who had higher mean PC. This suggests that individuals with reduced mean PC are more likely to have Eclampsia as a complication of their disease condition. This finding was statistically significant and agrees with findings from other studies [23, 32, 33, 34, 35, 36, 37]. This study also found that Eclampsia, Abruptio placentae, and maternal admission into intensive care unit were significantly associated with lower mean PCT. This phenomenon occurs more with increasing severity of pre-eclampsia such as in Eclampsia and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome and so supports the finding of this study. These findings are in agreement with other studies [32, 35, 38], supporting increased marrow platelet production in severe pre-eclampsia.

Eclampsia also has higher odds of occurrence with higher MPV but this association was not statistically significant. None of the parameters

Table 3. Relationship between platelet parameters and adverse maternal outcome in pre-eclampsia.

	Maternal complication			
	Eclampsia			
Variable	Yes (n = 24)	No (n = 36)	AOR(95%CI)	P-value
PC($\bar{x}$ ± SD)10^9/L	122.50 (58.42)	161.36 (73.74)	0.27(0.08–0.88)	0.02
PCT($\bar{x}$ ± SD)%	0.10 (0.05)	0.13 (0.05)	0.22(0.08–0.58)	0.001
MPV($\bar{x}$ ± SD)fl	9.48(0.98)	9.10 (0.97)	4.60(0.57–36.55)	0.11
PDW($\bar{x}$ ± SD)fl	15.76 (2.43)	15.11 (2.37)	0.84(0.29–2.38)	0.74
P-LCR($\bar{x}$ ± SD)%	23.15 (4.92)	20.84 (6.14)	11.50 (1.48–89.02)	0.004
	Abruptio placentae			
	Yes (n = 17)	No (n = 43)		
PC($\bar{x}$ ± SD)10^9/L	143.67 ± 56.02	151.23 ± 99.39	0.75(0.19–2.96)	0.68
PCT($\bar{x}$ ± SD)%	0.12 ± 0.06	0.13 ± 0.04	0.23(0.08–0.64)	0.003
MPV($\bar{x}$ ± SD)fl	9.36 ± 1.14	9.21 ± 0.93	1.69(0.35–8.05)	0.50
PDW($\bar{x}$ ± SD)fl	15.55 ± 2.38	15.37 ± 2.50	1.92(0.52–7.08)	0.32
P-LCR($\bar{x}$ ± SD)%	22.04 ± 6.49	21.66 ± 5.52	1.26(0.42–3.77)	0.67
	Maternal mortality			
	Yes (n = 2)	No (n = 58)		
PC($\bar{x}$ ± SD)10^9/L	115.00 (37.47)	146.87 (70.98)	0.88(0.82–1.94)	0.52
PCT($\bar{x}$ ± SD)%	0.09 (0.04)	0.12 (0.05)	0.30(0.02–3.42)	0.30
MPV($\bar{x}$ ± SD)fl	9.28 (0.99)	8.65 (0.56)	0.85(0.79–2.92)	0.47
PDW($\bar{x}$ ± SD)fl	15.53 (1.16)	15.50 (2.43)	0.76(0.69–3.89)	0.34
P-LCR($\bar{x}$ ± SD)%	21.79 (5.85)	21.12 (1.52)	0.71(0.64–1.84)	0.28
	ICU admission			
PC($\bar{x}$ ± SD)10^9/L	Yes (n = 25)	No (n = 35)		
PCT($\bar{x}$ ± SD)%	130.50 ± 62.19	156.75 ± 74.29	0.49(0.15–1.63)	0.24
MPV($\bar{x}$ ± SD)fl	0.11 ± 0.05	0.12 ± 0. 05	0.36(0.15–0.86)	0.01
PDW($\bar{x}$ ± SD)fl	9.35 ± 0.97	9.12 ± 1.00	0.69(0.22–2.16)	0.52
P-LCR($\bar{x}$ ± SD)%	15.93 ± 2.41	14.90 ± 2.28	1.08(0.38–3.02)	0.87
PC($\bar{x}$ ± SD)10^9/L	21.89 ± 4.90	21.57 ± 6.37	1.52(0.55–4.17)	0.41

PC = platelet count, PCT = plateletcrit, MPV = mean platelet volume, PDW = platelet distribution width, P-LCR = platelet-large cell ratio, S.D = standard deviation, ICU = Intensive care unit, $\bar{x}$ = mean.

Table 4. Relationship between platelet parameters and adverse perinatal outcome in pre-eclampsia.

	Perinatal complication			
	Preterm delivery		AOR (95%CI)	P-value
Variable	Yes (n = 28)	No (n = 32)		
PC($\bar{x}$ ± SD)10^9/L	121.69 (50.19)	166.92 (78.70)	0.84(0.04–1.49)	0.79
PCT($\bar{x}$ ± SD)%	0.10 (0.04)	0.14 (0.05)	0.14(0.04–0.49)	0.001
MPV($\bar{x}$ ± SD)fl	9.43 (1.01)	9.10 (0.95)	0.65(0.15–2.73)	0.56
PDW($\bar{x}$ ± SD)fl	15.99 (2.98)	15.07 (1.65)	0.85(0.19–3.80)	0.83
P-LCR($\bar{x}$ ± SD)%	23.37 (5.12)	20.36 (5.99)	1.80(0.52–6.19	0.34
	Birth asphyxia			
	Yes (n = 35)	No (n = 25)		
PC($\bar{x}$ ± SD)10^9/L	141.75 ± 60.53	151.91 (83.62)	2.33(0.56–9.70)	0.23
PCT($\bar{x}$ ± SD)%	0.11 ± 0.05	0.12 ± 0.05	0.62(0.21–1.82)	0.38
MPV($\bar{x}$ ± SD)fl	9.38 ± 1.13	9.18 ± 0.88	0.80(0.19–3.37)	0.76
PDW($\bar{x}$ ± SD)fl	16.02 ± 1.83	15.15 ± 2.67	2.20(0.40–11.94)	0.35
P-LCR($\bar{x}$ ± SD)%	21.86 ± 5.45	21.63 ± 6.30	1.92(0.52–7.04)	0.31
	NICU admission			
	Yes (n = 35)	No (n = 25)		
PC($\bar{x}$ ± SD)10^9/L	144.34 ± 74.44	147>88 ± 65.17	1.52(0.42–5.44)	0.51
PCT($\bar{x}$ ± SD)%	0.12 ± 0.05	0.13 ± 0.05	0.56(0.19–1.61)	0.28
MPV($\bar{x}$ ± SD)fl	9.40 ± 1.07	9.06 ± 0.83	1.14(0.27–4.76)	0.85
PDW($\bar{x}$ ± SD)fl	16.24 ± 1.83	14.46 ± 1.96	0.81(0.17–3.79)	0.79
P-LCR($\bar{x}$ ± SD)%	22.73 ± 5.91	20.42 ± 5.35	5.16(1.39–19.21)	0.01
	Perinatal mortality			
	Yes (n = 15)	No (n = 45)		
PC($\bar{x}$ ± SD)10^9/L	123.43 ± 74.74	153.27 ± 67.81	0.36(0.09–1.41)	0.13
PCT($\bar{x}$ ± SD)%	0.10 ± 0.06	0.13 ± 0.04	0.28(0.07–1.15)	0.06
MPV($\bar{x}$ ± SD)fl	9.26 ± 1.06	9.25 ± 0.97	0.61(0.13–2.84)	0.53
PDW($\bar{x}$ ± SD)fl	15.62 ± 2.27	15.15 ± 2.79	1.00(0.17–5.57)	1.00
P-LCR($\bar{x}$ ± SD)%	22.45 ± 5.68	21.54 ± 5.83	1.29(0.30–5.44)	0.72

PC = platelet count, PCT = plateletcrit, MPV = mean platelet volume, PDW = platelet distribution width, P-LCR = platelet-large cell ratio, S.D = standard deviation, NICU = Neonatal intensive care unit, AOR = Adjusted Odds ratio, CI = Confidence interval.

was statistically associated with maternal death. This disagrees with the findings in other studies [23, 32, 33, 35, 36, 37] which could be attributable to the early use of antihypertensive drugs in the management of the cases in this study which were predominantly booked patients. The study also revealed that PCT was significantly associated with pre-term delivery among women with pre-eclampsia. This suggests that participants with higher PCT had lesser odds of preterm delivery in this study. There were also higher odds of NICU admission for neonates of pre-eclamptic mothers with increasing P-LCR in this study. However, none of the parameters were significantly associated with birth asphyxia and perinatal death. It may be deduced that poor platelet indices like PCT and P-LCR in maternal circulation may be associated with adverse perinatal outcomes. These adverse outcomes associated with PCT and P-LCR were also noted in other studies [32, 34]. The similarity may be attributed to the pathogenesis of pre-eclampsia where in an attempt to mitigate enhanced destruction of platelets, immature platelets are produced from the marrow into the circulation.

5. Conclusion

This study demonstrated significant differences in PC, PCT, PDW, and P-LCR in the cases compared to controls. Similarly, PC, PCT, and P-LCR showed significant differences in adverse pregnancy outcomes in participants with mild and severe pre-eclampsia. The study has shown that assaying these parameters may help determine adverse maternal and perinatal outcomes but may not help determine the severity of the disease. The lack of significant difference in platelet parameters between recruitment and delivery may as well be due to the relatively short interval between those time points (33.87 ± 3.93 weeks & 37.50 ± 2.77 weeks) and may not essentially imply time independence of platelet parameters in management of pre-eclampsia.

6. Recommendations

From the findings of this study, generation of platelet parameters is recommended in diagnosing pre-eclampsia and determining the development of adverse feto-maternal outcome. This will help in early disease identification and timely institution of interventions to prevent progression to severe disease thereby reducing the incidence of adverse outcomes. However, large-scale studies are needed from early pregnancy to determine the mean platelet parameter values among pregnant women of all trimesters since women in the first two trimesters were excluded from this study. This will also help in studying the role of these indices in the prediction and early diagnosis of pre-eclampsia.

7. Limitations of the study

Our study is limited by the study population recruitment from 28 weeks of gestation which made it impossible to determine the pre-inclusion platelet indices of the cohort of women studied. However, we theorized that normotensive women earlier in pregnancy as well as in women developing pre-eclampsia before 28 weeks gestation have a normal parameter. The study was a hospital-based study with its bias and as such the findings from our study might not be a true representation of the general population of the study area. This research could be carried out in all trimesters of pregnancy and in a larger population to know if any differences could be observed from the findings of this study. A non-probability sampling method was used and this might be a source of selection bias. It (non-probability sampling) was however adopted because of the low prevalence rate of preeclampsia in the study area that will enable us to complete the patient's enrollment and follow up the patient in optimal time.

Declarations

Author contribution statement

Benjamin S. Umezuluike and Chidebe C. Anikwe: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Chinedu C. Ifemelumma, Bobbie C. A. Iwe, Oluomachi C. Nnachi and Ikechukwu B. O. Dimejesi: Analyzed and interpreted the data; Wrote the paper.

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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