

Original Article

Determination of coagulopathy complicating severe preeclampsia and eclampsia with platelet count in a University Hospital, South-South, Nigeria

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ABSTRACT

Background: Pre-eclampsia is a multisystemic disorder complicating pregnancy. It is associated with a significant burden on maternal and perinatal health, especially when complicated by coagulation abnormalities.

Objective: The objective of the study was to determine the level of thrombocytopenia that predicts a risk of abnormalities of coagulation indices in severe preeclampsia and eclampsia.

Materials and Methods: Haemostatic factors including platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT) and plasma fibrinogen were done for a cohort of 90 patients with severe preeclampsia and eclampsia at the Department of Obstetrics and Gynaecology, University of Benin Teaching Hospital, Benin City. Their demographic and laboratory data were analysed using the Statistical Package for Social Sciences version 20.0 and GraphPad InStat 3 software.

Results: Twenty-one (23.3%) of the 90 patients had eclampsia. Mean age was 29.78 ± 4.7 years, parity was 2.54 ± 1.6 and gestational age was 36.14 ± 2.9 weeks. Thrombocytopenia was found in 13 (14.4%) patients, whereas biochemical coagulopathy was found in 6 (6.7%) patients. Thrombocytopenia was 43% more likely with eclampsia than severe preeclampsia (47.6% vs 4.3, $P = 0.001$). Abnormal PT, APTT and plasma fibrinogen were more likely with platelet count below 80000 cell/ μ l ($P = 0.046$, $P = 0.014$ and $P = 0.001$, respectively). Eclampsia complicated with thrombocytopenia was associated with the most severe biochemical coagulopathy.

Conclusion: Thrombocytopenia frequently complicates eclampsia more than severe preeclampsia at platelet count levels below 80000 cell/ μ l. This level is discriminatory for biochemical coagulopathy, and it should prompt coagulation studies and warrant clinical vigilance.

Key words: Coagulopathy; eclampsia; platelet counts; severe preeclampsia; thrombocytopenia; University of Benin Teaching Hospital (UBTH).

Introduction

Coagulopathy results from an imbalance between the coagulation and fibrinolytic activities such that in hypercoagulable states, such as preeclampsia, activation of the thrombotic system leads to the development of multiple thrombi and rapid consumption of platelets, prothrombin,


fibrinogen and coagulation factors. Coagulation failure is one of the most dreaded complications of severe preeclampsia and eclampsia. Its evolution significantly increases the toll of

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the disease. Coagulopathy mainly develops as a component of the primary disease but may also arise from its complications such as intrauterine fetal death, abruptio placentae or primary postpartum haemorrhage. Coagulopathy may affect up to 15% of severe preeclampsia cases, and is believed to account for approximately 15% of maternal deaths from the condition.^[1-5]

Routine tests used to assess decompensated disseminated intravascular coagulopathy (DIC) have been considered to be of limited value in the preeclamptic and eclamptic population. It is advocated, especially in the developed world, that more sophisticated tests such as determinations of antithrombin III, thrombin-antithrombin III complex, D-dimer, factor VIII antigen/activity ratio and beta-thromboglobulin be conducted to detect compensated coagulopathy in preeclampsia.^[6-9] Despite this, routine laboratory indicators of DIC have remained thrombocytopenia, prolonged prothrombin time, prolonged activated partial thromboplastin time and reduction in the concentration of fibrinogen. In low resource settings, where the means to achieve full scale coagulation profile assessment is either lacking or non-existent, a greater reliance is placed on clinical observation for coagulopathy or the performance of bedside clotting time because this is rather inexpensive. However, the determination of prolonged clotting time will hardly be sufficient to hinge clinical decisions on. Hence, the use of platelet count appears to be more uniformly agreed as the basic investigation required for evaluating the risk of coagulopathy in severe preeclampsia.^[10-12]

The ease with which platelet count is done has led many authors to advocate its use as a screening test to identify potential candidates for further evaluation of coagulopathy. In this regard, platelet count can be assessed routinely for all patients with severe preeclampsia, and the result to be interpreted based on a cut-off value for considering a complete coagulation study to predict coagulation disorder. However, the level of platelet depletion that has clinical implication remains a matter of debate with some workers reporting levels as low as 50000 cell/ μ l without any significant adverse outcome,^[13,14] while others insist that less than 100,000 cell/ μ l warrants further evaluation.^[12]

Platelet count is a rapid, simple and cheap means of assessing haemostatic status compared to a complete coagulation profile, and its usefulness in detecting early coagulation disorder in conditions such as severe preeclampsia and eclampsia is no longer in doubt. What is not immediately apparent is the extent to or the accuracy with which thrombocytopenia can be used as a pointer to coagulation failure in preeclampsia in our environment.

This study, therefore, is aimed at determining the platelet count that predicts coagulopathy in patients with severe preeclampsia and eclampsia in University of Benin Teaching Hospital (UBTH), Benin City.

Materials and Methods

This prospective, self-controlled cohort study was conducted in the Department of Obstetrics and Gynaecology, UBTH, Benin City, Edo State, Nigeria, between December 2010 and March 2011, with the approval of the hospital's Ethics and Research Committee. The participants were all patients admitted with a diagnosis of severe preeclampsia or eclampsia and billed for stabilisation and delivery according to our standardized Labour Ward protocol.^[15] Informed consent was obtained individually from the patients or their relatives. Patients with intrauterine foetal death at presentation, known coagulation disorders such as the haemophilias, immune thrombocytopenic purpura, inherited thrombocytopenia and von Willebrand disease, abruptio placentae, acute or chronic liver disease such as hepatitis, thromboembolic disorders and other hypercoagulable states, such as sickle cell disease, were excluded from the study.

UBTH is a tertiary health care facility located in Edo State, which serves as a major referral center in Nigeria, attracting patients from at least three neighboring states of Kogi, Ondo and Delta. Patients are also referred from both government-owned and private hospitals within Edo State. Within the hospital, the major portal of entry for pregnant women is the General Practice Clinic (GPC) from where they are referred to the Antenatal Clinic for booking, however in emergency situations, patients are admitted via the Emergency Unit of the Hospital to the Labor Ward. On an average, between 100 and 150 patients are booked for antenatal care every week in the hospital, while follow-up attendance rate is between 250 and 500 patients per week. The delivery rate in the hospital in the last 5 years has been approximately 2700 per year, which gives an average monthly delivery rate of 225. The hospital has a total antenatal and postnatal bed capacity of 82 spaces, and 8 functioning delivery rooms in the Labor Ward. There are 2 operating theatres attached to the Labor Ward.

In this study, patients who had antenatal care in UBTH were referred to as 'booked' and those not registered in UBTH as 'unbooked'. Preeclampsia is defined as gestational hypertension plus proteinuria of 300 mg or more in 24 hour urine sample collection or persistent proteinuria of at least 30 mg/dl (at least 1+ on dipstick) in random urine samples.^[5] Eclampsia is defined as the onset of seizures and/or unexplained coma during pregnancy, intrapartum or postpartum period in patients with signs and symptoms

of pre-eclampsia.^[5] In this study, the diagnosis of eclampsia was entertained when the patient was admitted to the Labor Ward either in coma or after a seizure in association with clinical evidence of the syndrome of preeclampsia, without any other obvious cause of coma or seizure. Their clinical management comprised seizure prophylaxis, blood pressure control and fluid replacement, correction of electrolytes derangement, intrauterine resuscitation and delivery by the most expedient route.

Venous blood samples were obtained for bedside clotting time, electrolytes, urea and creatinine, liver function tests and full blood count, in addition to platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT) and plasma fibrinogen level. Preparation and analysis of the blood samples for coagulation indices were carried out immediately in conjunction with our colleagues in the Haematology Department of the Hospital. Thrombocytopenia was defined as platelet count $<100,000$ cell/ μ l, prolonged PT as >16 seconds, prolonged APTT as >40 seconds, and hypofibrinogenemia as <2 g/dl. In this study, 'biochemical coagulopathy' was defined as the abnormality of at least one of these 3 coagulation parameters evaluated.

Sociodemographic and laboratory information obtained were documented in structured pro-forma, and were used to generate a database for analysis. The data was subjected to statistical analysis with a personal computer using the Statistical Package for the Social Sciences version 20.0 (SPSS IBM Corp, Armonk, NY) and GraphPad InStat 3 (GraphPad Software Inc., San Diego, CA). Univariate analysis was conducted using Chi-square test or Fisher's Exact Test as appropriate. Cross tabulations were conducted to determine associations. *P* value of <0.05 was considered significant.

Results

Out of the 90 women recruited, 69 (76.7%) had severe preeclampsia and 21 (23.3%) had eclampsia whereas 13 women of this cohort had thrombocytopenia. Hence, the frequency of thrombocytopenia was 14.4%. Six patients had abnormal coagulation indices giving a biochemical coagulopathy rate of 6.7%. The majority (65.6%) of the patients were unbooked, which included all the 21 (23.33%) eclamptics and 38 (42.22%) severe preeclamptics. Thus, 44.9% of those with severe preeclampsia were unbooked patients. The mean platelet count was $163,000 \pm 72$ cell/ μ l, mean PT was 14.04 ± 3.2 s, mean APTT was 33.97 ± 3.1 s and mean fibrinogen level was 3.23 ± 0.5 g/dl.

The mean maternal age was 29.78 ± 4.7 years (range: 19 to 43), the mean parity was 2.54 ± 1.6 (range: 0 to 6), and

the mean gestational age was 36.14 ± 2.9 weeks (range: 24 to 41), with almost 90% presenting after 32 weeks [Table 1]. The maternal age, parity and gestational age were not significantly different between the preeclamptics and those with eclampsia. Similarly, thrombocytopenic patients did not differ in terms of age, parity and gestational age from the other patients with normal platelet count ($P = 0.730$, $P = 0.136$ and $P = 0.772$, respectively) [Table 1].

The mean platelet count of patients with thrombocytopenia was over two-fold lower than patients with normal platelet count (82800 ± 12075 cell/ μ l vs $188,000 \pm 64523$; $P = 0.001$). Hypofibrinogenemia was found in 31% of the thrombocytopenic patients but not in those with normal values ($P = 0.001$). Similarly, prolonged PT and APTT were seen in 46% and 23%, respectively, only in association with thrombocytopenia ($P = 0.001$ and $P = 0.001$, respectively) [Table 2].

Table 1: Maternal demographic characteristics in relation to thrombocytopenia

Variables	Thrombocytopenic		Normal		<i>P</i>
	<i>n</i> =13	(%)	<i>n</i> =77	(%)	
Age (years)					
≤19	1	(7.7)	4	(5.2)	0.730
20-35	11	(84.6)	60	(77.9)	
>35	1	(7.7)	13	(16.9)	
Parity					
0	5	(38.5)	43	(55.8)	0.136
1-4	8	(61.5)	27	(35.1)	
>4	-	-	7	(9.1)	
Gestational age (weeks)					
20-32	1	(7.7)	11	(14.3)	0.772
33-36	5	(38.5)	33	(42.9)	
≥37	7	(53.9)	33	(42.9)	

Table 2: Frequency and severity of abnormal plasma fibrinogen, APTT and PT in relation to thrombocytopenia

Variables	Thrombocytopenic		Normal		<i>P</i>
	<i>n</i> =13	(%)	<i>n</i> =77	(%)	
Fibrinogen (g/dl)	2.54 ± 0.76		3.54 ± 0.25		0.001*
< 2.0	4	(30.8)	0	(0.0)	
2.0-4.0	9	(69.2)	77	(100.0)	
>4.0	0	(0.0)	0	(0.0)	
APTT (second)	35.92 ± 5.11		33.13 ± 2.26		0.001*
<26	0	(0.0)	0	(0.0)	
26-40	10	(76.9)	77	(100.0)	
>40	3	(23.1)	0	(0.0)	
PT (second)	17.31 ± 5.63		12.52 ± 1.22		0.001*
<11	0	(0.0)	0	(0.0)	
11-16	7	(53.9)	77	(100.0)	
>16	6	(46.2)	0	(0.0)	

PT - Prothrombin time; APTT - Activated partial thromboplastin time; * - Statistically significant values

Thrombocytopenia above 80,000 cell/ μ l was associated with 15% risk of prolonged PT but not prolonged APTT or abnormal fibrinogen level. Platelet count between 50000 and 80000 cell/ μ l was associated with 100% risk of abnormal PT and fibrinogen level and 75% risk of prolonged APTT ($P = 0.046$, $P = 0.001$ and $P = 0.014$, respectively). Thrombocytopenia below 50000 cell/ μ l was not found in this study [Table 3].

The occurrence of eclampsia increased the risk of coagulopathy. Patients with eclampsia were 43% more likely to have thrombocytopenia than those with severe preeclampsia (47.6% vs 4.3, RR 10.95, 95% CI 3.32 to 36.16; $P = 0.001$). The mean platelet count and mean fibrinogen level were 21% lower and 18% lower, respectively, in patients with eclampsia than in patients with severe preeclampsia ($144,000 \pm 78662$ cell/ μ l vs $182,000 \pm 65846$, $P = 0.031$; and 2.92 ± 0.78 g/dl vs 3.54 ± 0.26 , $P = 0.001$, respectively). Similarly, the mean PT and mean APTT in eclampsia were 20% and 5%, respectively, higher than in severe preeclampsia (15.57 ± 5.03 s vs 12.49 ± 1.16 , $P = 0.001$; and 34.76 ± 4.18 s vs 33.16 ± 2.42 , $P = 0.030$, respectively) [Table 4].

The combination of eclampsia and thrombocytopenia further increased the severity of biochemical coagulopathy. Mean fibrinogen level was 1.5-fold higher in 10 eclamptics without thrombocytopenia than 11 eclamptics with thrombocytopenia (3.47 ± 0.25 g/dl vs 2.31 ± 0.69 , $P = 0.001$). Again, the mean PT and APTT were 1.5-fold and 1.1-fold, respectively, more prolonged in eclamptics with thrombocytopenia than those without thrombocytopenia (18.80 ± 5.59 s vs 12.64 ± 1.57 ,

$P = 0.002$; and 36.40 ± 5.52 s vs 33.27 ± 1.56 , $P = 0.087$, respectively) [Table 4].

Only one of the patients showed clinical features of coagulopathy and had abnormalities of all the coagulation parameters with a platelet count of 68000 cell/ μ l.

Discussion

Disseminated intravascular coagulopathy is among the leading causes of mortality in preeclampsia and eclampsia.^[4,5] A high index of clinical suspicion coupled with early laboratory confirmation remains the primary approach in the execution of an effective preventive modality. The incidence of thrombocytopenia among the patients we studied was 14.4%. Biochemical coagulopathy was noted in 6.7%. Majority of the patients were unbooked, younger than 35 years and at advanced gestational ages. Eclampsia was significantly associated with unbooked status and a higher risk of coagulopathy than severe preeclampsia. The risk of hypofibrinogenemia, prolonged PT and prolonged APTT increased with worsening thrombocytopenia.

The higher contribution of the unbooked patients to our population of severe preeclamptics and eclamptics is consistent with reports of other studies.^[16,17] This observation demonstrates that inadequate antenatal care and monitoring, especially in peripheral centers, together play a key role in progression to severe disease which culminates in eclampsia. Nulliparity as a risk factor for preeclampsia and eclampsia was also seen in our study.^[17,18] Similar to what we found, the advanced gestational age at recruitment in severe preeclampsia and eclampsia has been ascribed to the occurrence of late-onset but rapidly progressive disease in our environment.^[16-18]

The 14.4% rate of thrombocytopenia we found probably reflects the level of coagulopathy complicating preeclampsia and eclampsia in our study population, considering that only patients with thrombocytopenia had abnormalities of the coagulation indices studied. Even so, the 6.7% rate of biochemical coagulopathy found in our study is higher than

Table 3: Pattern of disorders of PT, APTT and plasma fibrinogen based on severity of thrombocytopenia

Variables	Severity of thrombocytopenia (cell/ μ l)			P
	<50000	50000-80000 n=4 (%)	81,000-9,999 n=9 (%)	
Prolonged PT	-	4 (100.0)	2 (22.2)	0.046*
Prolonged APTT	-	3 (75.0)	- (0.0)	0.014*
Low fibrinogen	-	4 (100.0)	- (0.0)	0.001*

PT - Prothrombin time; APTT - Activated partial thromboplastin time; * - Statistically significant values

Table 4: Contribution of eclampsia to coagulation abnormalities

Variables	Severe Pre-eclampsia (n=69)	Eclampsia (n=21)		P
		Eclampsia with Thrombocytopenia (n=10)	Eclampsia without Thrombocytopenia (n=11)	
Platelet count (per μ l)	$182,000 \pm 65846$	79400 ± 11596	$203,000 \pm 65479$	0.031*
PT (s)	12.49 ± 1.16	18.80 ± 5.59	12.64 ± 1.57	0.001*
APTT (s)	33.16 ± 2.42	36.40 ± 5.52	33.27 ± 1.56	0.030*
Fibrinogen (g/dl)	3.54 ± 0.26	2.31 ± 0.69	3.47 ± 0.25	0.001*

PT - Prothrombin time; APTT - Activated partial thromboplastin time; * - Statistically significant values

the 2% reported by Barker *et al.*,^[19] lower than 14.7% reported by Sharma *et al.*^[11] but much lower than 50% found by Pritchard *et al.*^[3] The varying combinations of coagulation-fibrinolytic indices studied, the peculiarities of the population studied as well as the individual predisposition to coagulopathy may have significant impact on the results obtained, as well as their interpretation; and these may account for the different rates between studies.

Similar to what we found, many researchers have reported thrombocytopenia to be the most common haemostatic abnormality in this group of patients. We found a lower rate than the 28% to 50% reported by many previous workers.^[1-3,19-21] Though our figure was higher than 10% reported by Riaz *et al.*,^[22] few studies agree with our rate of 14%.^[1,10] This variation is probably explained by the arbitrary cut-off definition of thrombocytopenia adopted by each researcher, so that higher rates are expected when a lower cut-off of 100,000 cell/ μ l is utilised. This understanding will seem to suggest that our participants will have a much lower thrombocytopenia rate should cut-off be set at 150,000 cell/ μ l.

The development of coagulopathy in preeclampsia appears to occur early, progressing over the course of the disease to involve with varying degrees, the coagulation parameters, especially in those with early-onset disease.^[23] Thrombocytopenia was predictive of the risk of coagulopathy in this study. Biochemical coagulopathy was unlikely at platelet count above 88000 cell/ μ l, however, the rate progressively increased for any particular parameter, with multiple parameters involvement, as thrombocytopenia decreased further below 80000 cell/ μ l. Abnormal PT was common as the mean platelet count started to reduce, whereas APTT and fibrinogen abnormalities were noticed at lower levels of thrombocytopenia. Thrombocytopenia below 50000 cell/ μ l was not found in this study, an observation that further suggests the progressive nature of coagulopathy in preeclampsia, such that a critical level of reduced platelet number and/or function is required to set off the chain of events leading to abnormal biochemical coagulopathy. Hence, dangerously low values of thrombocytopenia are averted by prompt diagnosis and appropriate treatment. One of our patients with a platelet count of 68000 cell/ μ l was found to have abnormalities of PT, APTT and fibrinogen level and showed clinical evidence of DIC. Aforementioned confirms that the more severe the thrombocytopenia, the more likely the occurrence of coagulopathy and consequent poor prognosis.

The finding that only participants with low platelet count were found to have biochemical coagulopathy has

previously been documented by other workers.^[11,12,19] Conversely, in a retrospective review of laboratory data obtained from 80 patients with hypertensive disorders of pregnancy in Pennsylvania, USA, minor abnormalities of PT, APTT and fibrinogen level were reported as frequent, even in patients with normal platelet count; however, these abnormalities were found mostly in patients with severe preeclampsia and eclampsia.^[24] Prieto *et al.* also reported that no correlation was found between levels of platelet count and those of PT, APTT or fibrinogen.^[25] However, consensus seems to favour the earlier involvement of platelets. Hence, it appears safe to monitor platelet count initially in the course of management, and to include coagulation indices when platelet count level decreases below 80000 cell/ μ l.

Again, our finding that thrombocytopenia occurred more when eclampsia supervened had been previously documented by Jambhulkar *et al.*^[10] Previous researchers have also shown that biochemical coagulopathy appeared to be more severe with the development of eclampsia or other major complications such as abruptio placentae and intrauterine fetal death.^[4,8,10,12,23] Our findings also support this observation, and this suggests that early determination of the risk of coagulopathy and the ongoing evaluation to predict disease progression will assist in reducing morbidity and mortality contributed by preeclampsia and eclampsia.^[26-29] Hence, coagulopathy was increased further in patients who had a combination of thrombocytopenia and eclampsia in our study.

The factors found to be associated with a significant risk of biochemical coagulopathy in preeclampsia in this study were severe disease, worsening thrombocytopenia and evolution to eclampsia. We also established the relationship between thrombocytopenia below 80000 cell/ μ l and the progressive risk and multiple involvements of PT, APTT and fibrinogen level abnormalities. To reduce the burden of coagulopathy in preeclampsia and eclampsia, coagulation studies will be necessary in the evaluation to determine the severity and need for correction. However, in peripheral settings where facilities may be lacking to conduct a coagulation study, assessment of platelet count will suffice in detecting significant thrombocytopenia, which should then prompt referral to more equipped centers.

A larger sample size, prospective case-control design to compare mild preeclampsia with severe preeclampsia, in a multicenter collaborative effort will probably improve the external validity of the results of our study.

Conclusion

In conclusion, the critical level of thrombocytopenia necessitating coagulation study in severe preeclampsia and eclampsia is 80000 cell/ μ l in our patients. The risk of coagulopathy increases with worsening thrombocytopenia and development of eclampsia. This will help to identify patients who may develop coagulopathy and require immediate referral to reduce maternal and perinatal mortality and morbidity rates.

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Conflicts of interest

There are no conflicts of interest.

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