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Research Article

Evaluating the Value of Blood D-Dimers in Pregnant Women with Preeclampsia as a Predictor for Onset of HELLP Syndrome: Case Control Study

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Abstract

Introduction: Preeclampsia is a common medical complication of pregnancy. It could be complicated by HELLP syndrome. HELLP syndrome is a multi-systemic disorder that complicates pregnancy with associated foeto-maternal morbidity and mortality. It could be a life-threatening obstetric complication. When diagnosed early and appropriate intervention instituted promptly, these complications can be picked early or even prevented.

Objective: This main aim of this study was to determine if the presence of blood D-dimers in women with preeclampsia is an early predictor of HELLP syndrome.

Methodology: This study was a prospective case-control study carried out at the Depart. of Obs. and Gyn., UCH and at AMTH, between November 2015 to April 2016. Ninety pregnant women with preeclampsia as cases and ninety with normal pregnancy as controls were recruited into the study before delivery and monitored till after delivery. Blood samples was collected for serum D-dimer assay. A structured proforma was utilised to extract socio-demographic, maternal obstetric history, and record results of tests. Data was collated and analysed using SPSS version 20. The level of significance was set at be $P < 0.05$.

Results: The mean age for cases was 31.4 years and controls was 31.3 years. The two groups were matched for GA. Caesarean section was the commoner route of delivery for preeclampsia patients. The mean d-dimer levels were elevated above the cut-off 0.5 mg/l in both groups. The pre-delivery was 3.37 mg/l and 1.47 mg/l and post-delivery was 3.22 mg/l and 3.14 mg/l for cases and controls respectively. This was statistically significant. (p-value < 0.001). Upon conclusion of the study, a higher proportion of the cases had elevated D-dimer levels (95.2%) compared to controls (89.5%). This was not statistically significant. (p-value 0.447). The prevalence of HELLP syndrome was 0.6% and only one patient with preeclampsia developed the syndrome while one patient without preeclampsia was diagnosed with the syndrome post-delivery. This was too low to perform a logistic regression and hence elevated D-dimer cannot be used to predict HELLP syndrome in the subjects from this study.

Conclusion: Elevated d-dimer levels were detected in patients with preeclampsia, but it was not predictive of HELLP syndrome due to low prevalence in our environment.

Keywords: *Preeclampsia; HELLP Syndrome Prediction; D-Dimer; University College Hospital; Adeoyo Maternity Teaching Hospital; Feto-Maternal Complications*

Abbreviations

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelet; UCH: University College Hospital; UI: University of Ibadan; AMTH: Adeoyo Maternity Teaching Hospital; GA: Gestational Age; Dept. of Obs. and Gyn: Department of Obstetrics and Gynecology; LDH: Lactate Dehydrogenase; ALT: Alanine Transaminase; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; ELISA: Enzyme Immunosorbent Assay; FBC: Full Blood Count

Introduction

Preeclampsia complicates 5 - 7% of all pregnancies [1]. Preeclampsia has been shown to lead to several complications both in the mother, the foetus and the perinatal period and may similarly affect the infant and child in the long term development. It is also the most common medical complications of pregnancy. HELLP syndrome has been regarded as a distinct entity and a complication of preeclampsia as well as normal uncomplicated pregnancy. HELLP syndrome is a multi-systemic disorder that complicates pregnancy and has a poor prognosis associated with significant feto-maternal morbidity and mortality. The syndrome is a serious complication in pregnancy characterized by haemolysis, elevated liver enzymes and low platelet count occurring in 0.5 to 0.9% of all pregnancies and in 10 - 20% of cases with severe preeclampsia [1].

Another study also documented it occurs in 0.2 - 0.6% of all pregnancies and the incidence is estimated at 10 - 20% of severe preeclamptic pregnancies [2]. The risk of recurrence in subsequent pregnancies is estimated at 19 - 27% [2]. In addition, Gleeson., *et al*. also published an incidence of 0.2 - 0.6% in Western countries compared to preeclampsia which occurs in 5 to 7% of all pregnancies. Superimposed HELLP syndrome develops in 4 to 12% of women with preeclampsia or eclampsia [3]. About a third of HELLP cases occur after the baby is born in the first week after delivery [3].

A study done in Bamako, Mali in Africa over a 4 year- period reported an incidence of 0.58% HELLP syndrome of 1559 patients admitted at Point G hospital Intensive care Unit between 1999 - 2002 [2].

The rate of these complications will depend on the population studied, the laboratory criteria used to establish the diagnosis, and the presence of associated pre-existing medical conditions or obstetric complications [4]. Because of the variable nature of the clinical presentation, the diagnosis of HELLP syndrome is generally delayed for an average of eight days [5]. Many woman with this syndrome are initially misdiagnosed with other disorders, such as cholecystitis, esophagitis, gastritis, hepatitis or idiopathic thrombocytopenia [6]. In one retrospective chart review of patients with HELLP syndrome, only two of 14 patients was admitted to entered the hospital with the correct diagnosis [5]. HELLP syndrome can be difficult to diagnose due to the variability of symptoms among patients (frequently patients have no symptoms other than general abdominal pain), and early diagnosis is key in reducing morbidity. If not treated in a timely manner, patients can become critically ill or die due to liver rupture/haemorrhage or cerebral oedema.

In making diagnosis of HELLP syndrome, blood is usually taken to assay for evidence of haemolysis (LDH assay), liver enzymes (alanine and aspartate transaminase) and platelet count. However, clinical suspicion and physical examination is necessary in addition to the blood tests in women with preeclampsia.

In a study conducted between 1991 and 1992, a positive D-dimer test in the presence of preeclampsia was reported to be predictive of patients who will develop HELLP syndrome [6]. Out of 81 preeclamptic women and 12 controls in the study conducted by Nieger., *et al*. it was discovered 43 of them who had positive d-dimer tests had increased risk of developing HELLP syndrome and also had other abnormalities such higher mean arterial pressure and their infants were born low birth weight with low Apgar scores.

To further show the clinical value of positive d-dimer in its ability to predict pregnant women who will develop features of HELLP syndrome, a study conducted in 1993 by Trofatter KF., *et al*. among 86 pregnant women. They noticed 33 women with positive d-dimer test had deranged liver enzymes, besides increased risk for early delivery, low birth weight and low Apgar score infant and high mean arterial pressure [7].

These two studies measured the levels of D-dimers in the pregnant women prior to delivery and established an association between elevated values of d-dimers and early onset of HELLP syndrome, low birth weight babies, low Apgar scores and high mean arterial blood pressure after delivery of the women.

We determined the levels of d-dimers both prior to delivery of women with or without preeclampsia and after their delivery and seek to establish if there was any relationship between changes in values of d-dimers.

Methodology

The study was a case-control study of pregnant women who presented at the Dept. of Obs and Gyn UCH Ibadan via the ANC and GE units in UCH and AMTH, Ibadan. The cases were patients with preeclampsia and the controls did not have preeclampsia or any other disease in the exclusion criteria. The pregnant women was categorised into Group A (Patients with preeclampsia) as cases and Group B (Patients without preeclampsia) as controls. Group A patients with preeclampsia (defined as systolic BP of 140 mmhg and or diastolic BP of 90 mmhg with at least 1+ proteinuria) admitted for the management of their disease were recruited and monitored from admission till delivery and discharge. We ensured they met the inclusion criteria (stated below). Group B were normal pregnant women without pre-eclampsia or any other disease condition in the exclusion criteria. They were also monitored till delivery and discharge from the hospital.

The inclusion criteria are pregnant women with preeclampsia (BP-140/90 mmhg and 1+ proteinuria), patients who give informed consent, singleton fetus, GA of 28 weeks gestational age and above, patients with features of severe preeclampsia such as epigastric or right hypochondriac pains, blurring of vision, persistent headaches.

The exclusion criteria are pregnant women who did not give their consent, those with any known bleeding disorder, DVT or pulmonary embolism, overt placental abruption, past or present history of coagulopathy, platelet disorders, haemoglobinopathy, suspected sepsis or malignancy, past or present history of liver disease or hepatitis, and women on anti-coagulant therapy.

Primary outcome measure is the level of D-dimers and the development of HELLP syndrome.

The patients were recruited into the study after signing the informed consent form. The minimum gestational age for recruitment was 28 weeks, which is regarded as the age of viability in this environment. Their blood pressures were measured and mean arterial pressure calculated and recorded by the primary investigator or trained research assistant which included the antenatal clinic nurses and resident doctors. This was done for all the recruited patients to ensure standardization of values. Blood pressure was taken twice in the sitting position or supine position before the blood samples were collected for the serum blood D-dimer and prior to the institution of anti-hypertensive and other medications as per treatment protocol in the department for their disease and were monitored till delivery and discharge. The patient's name, age, parity and gestational age and foetal condition was ascertained and recorded. Any associated maternal clinical features such as headaches, blurring of vision or hypochondriac tenderness was noted in the data entry form. Patients that developed any condition while on admission were noted in the data entry form. Patients who developed HELLP syndrome were noted and the information filled on the data entry form. Patients were monitored till discharge or 4 days post-delivery whichever was first for features of HELLP syndrome.

At recruitment of patient: Blood and urine samples were taken from each group. The blood tests include sampled for D-dimers, LDH, ALT, full blood count and platelet, PT, APTT and peripheral blood film at recruitment. Serum samples were used for D-dimer assay using

the Micro-plate ELISA kit. Urinalysis (with the dipstick) was done. The results from the tests were recorded in the data entry form. D-dimer assay was done by the Micro-plate Elisa method, which has high sensitivity but low specificity and said to be the gold standard in measuring d-dimers in blood. The laboratory typically determined the diagnostic cut-off values for D-dimer from assay-specific reference curves established using the manufacturer's calibrators. (The ELISA KIT used for D-dimer assay was manufactured by Elabscience, HumanD2D (D-dimer) ELISA KIT, with a detection range of 78.13 - 5000 ng/ml). The cut-off for normal D-dimer for this study was 0.5 mg/l (500 ng/ml) based on the previous study [8]. Urinalysis was done with urine dipsticks to check presence of proteinuria. A dipstick urine measurement for protein was performed on clean catch midstream urine specimen collected from the patient. Testing was performed with multistix reagent strips (Bayer) and results were reported as negative, trace, 1+, 2+ or 3+. The second set of blood test was used for full blood count and platelet count, LDH, ALT, PT, APTT and peripheral blood film. LDH test was used to assess degree of haemolysis. It is noted to be a very sensitive test for degree of haemolysis as it is abundant in red cells. An increase in LDH isozymes 1 and 2 is more specific for red blood cell destruction. The reference range was based on the kit used for analysis. Full blood count was done, platelet count and other parameters such as the white cell count and packed cell volume was noted. Liver enzymes such alanine transaminase was checked for after taken samples from the patients in other to see which of the group developed HELLP syndrome.

The diagnostic criteria for full HELLP syndrome were abnormalities of all three tests LDH (> 600 IU/Litre), ALT (> 40 UI/Litres) and platelet count (< 150,000 cells/uL) according to the criteria by the University of Mississippi in 1999. While partial HELLP syndrome is when there is abnormality of at least one of the three parameters. This study used cut off of < 250 IU/L for LDH and ALT of < 33UI/L for females (bases on the Kit used for analysis and by manufactured by Leadman Multi-biochemistry, Beijing, China) and platelet count lower than 150,000/mm^3. The tests was done by along with the laboratory scientists, and pathology physicians in chemical pathology and haematology and they assisted in interpretation and correction of errors in the laboratory analysis of results from the scientist. Standardization of the test kits was done with the laboratory scientist/pathologist and the reference ranges were reviewed and set for high or normal D-dimer values in pregnancy. The results were entered onto the data entry form. At Delivery and within 24 hours, the same blood was taken to check for differences in values compared to the initial samples at recruitment and also to diagnose HELLP syndrome in the these patients.

Sample collection and processing

D-dimer assay was done by the micro-plate Elisa method: Specimen used was citrated platelet-poor plasma. Five (5 mls) of venous blood with a 20G needle was collected into a 3.2% (0.32M) tri-sodium citrate anticoagulant tube and filled to the correct volume. The ratio of anticoagulant to blood will be 1:9 part. The blood was double spinned at 1500G for 15 minutes and the plasma was separated and transferred to a plain tube and stored at -20^0C before analysis. D-dimer was analysed by immunoassay using ELISA, micro-plate reader (Stat fax®.4200 Awareness technology).

10 mls of blood was collected from each patient with a 20g needle. This was distributed as follows: 2.5 mls into a paediatric size K EDTA bottle for FBC studies and peripheral blood film examination; 2.5 mls into a paediatric size lithium heparin bottle for LDH, ALT. Then 5 mls of blood collected into sodium citrate bottle for PT/APTT test which was same sample prepared and used for d-dimer assay. FBC studies and peripheral blood film examination was done within 6 hours of collection. The heparinized sample and the citrate sample were centrifuged at 3000G for 15 minutes and the separated plasma was stored a -20^0C until analysis which was done within 2 weeks of collection. However, to prepare a platelets-poor plasma sample for analysis, we double spined at 1500G for 15 minutes the sample collected into the sodium citrate bottle for analysis.

FBC and other biochemical analysis was done on automated platforms.

The sample size was calculated using formular for comparing mean difference assuming a power of 90%, at 0.05 level of significance to detect a mean difference of 1.2 mg/L in D-dimer levels between preeclamptic women and normal pregnant women. Sample size was 80 patients per group and allowing for attrition of 10%. 90 women would be recruited in each group.

Analysis of data was done by computer using the Statistical Package for Social Sciences (SPSS-16 for Windows Version). The variables were summarized using frequencies, proportions, means and standard deviation. The Chi-square test and student t-test were used to test for associations and differences in characteristics between the case and control groups. Logistic regression could not be done to determine significant predictors for HELLP syndrome because of the low prevalence of HELLP syndrome in this study as only one patient in each group had the syndrome. Level of significance will be set at p value < 0.05.

Ethical consideration

Approval was obtained from the Joint Institution Review Committee (IRC) of the UCH/UI. Ethical approval was also gotten from the Oyo State ethical committee since some of the patients were recruited from AMTH. Consent form was interpreted and explained to the participants in their local language if they don't understand English to obtain their consent and they were allowed to sign guided by the investigator or research assistant.

Results

Baseline characteristics of participants

The baseline characteristics of participants are as shown in table 1 below. There were significant differences seen in the level of education, booking status, number of pregnancies, number of deliveries and route of delivery between cases and controls. The mean age among cases was 31.4 and controls was 31.3 years. Majority (98.9 - 100%) of the participants were married in both groups. Tertiary and secondary education were the common highest levels of education in both groups. The overall mean gestational ages were similar as well. Caesarean section was the main route of delivery for cases while vaginal delivery was commoner for controls.

Variable	Case No (%)	Control No (%)	All No (%)	Chi Square/T Test	P-Value
Age Mean (SD)	 31.4 (4.5)	 31.3 (12.1)	 31.3 (9.1)	 0.060	 0.952
Marital Status Married Single	 87 (98.9) 1 (1.1)	 89 (100) 0	 176 (99.4) 1 (0.6)	 1.017	 0.313
Level of education None Primary Secondary Tertiary	 3 (3.4) 5 (5.7) 39 (44.3) 41 (46.6)	 0 15 (18.8) 31 (38.8) 34 (42.5)	 3 (1.8) 20 (11.9) 70 (41.7) 75 (44.6)	 9.208	 0.027
Booking Status Booked Unbooked	 70 (77.8) 20 (22.2)	 85 (94.4) 5 (5.6)	 155 (86.1) 25 (13.9)	 10.452	 0.001
Route of admission Antenatal clinic Emergency	 61 (67.8) 29 (32.2)	 71 (79.8) 18 (20.2)	 132 (73.7) 47 (26.3)	 3.327	 0.068
Mean Gestational Age (weeks)	 34 +/- 4.2	 33.8 +/- 4.0	 29.8 - 38.2		
No of pregnancies Range Mean (SD)	 1 - 7 2.3 (1.4)	 0 - 9 2.8(1.7)	 0 - 9 2.5 (1.5)	 -2.100	 0.037
No of deliveries Range Mean (SD)	 0 - 4 0.9(1.1)	 0 - 6 1.4(1.3)	 0 - 6 1.1 (1.2)	 -2.235	 0.027
Route of delivery S. vaginal delivery Caesarean section	 31 (35.2) 57 (64.8)	 63 (72.4) 24 (27.6)	 94 (53.7) 81 (46.3)	 24.3	 < 0.001

Table 1: *Baseline characteristics of participants.*

Maternal clinical features

Table 2 shows the maternal clinical features of participants upon recruitment. Significant differences were seen for some variables. A higher proportion of the cases reported having headache, blurring of vision, epigastric pain and respiratory distress. Cases also reported a significantly higher mean systolic, diastolic and mean arterial blood pressure compared to controls at baseline.

Variable	Case No (%)	Control No (%)	All No (%)	Chi Square/T Test	P-Value
Headache					
Yes	42 (46.7)	1 (1.1)	43 (23.9)	51.363	<0.001**
No	48 (53.3)	89 (98.9)	137 (76.1)		
Blurring of vision					
Yes	12 (13.3)	1(1.1)	13 (7.2)	10.032	0.002**
No	78 (86.7)	89(98.9)	167 (92.8)		
Epigastric pain					
Yes	15 (16.7)	1 (1.1)	16 (8.9)	13.445	<0.001**
No	75 (83.3)	89 (98.9)	164 (91.1)		
Respiratory distress					
Yes	2 (2.2)	0	2 (1.1)	2.023	0.155
No	87 (97.8)	89 (100)	176 (98.9)		
Jaundice					
Yes	1 (1.1)	0	1 (0.6)	1.017	0.313
No	88 (98.9)	90 (100)	178 (99.4)		
Systolic blood pressure Mean (SD)	160.7 (21.6)	110.9 (13.3)	196.5 (817.1)	18.521	< 0.001
Diastolic blood pressure Mean (SD)	100.7 (13.2)	68.6 (11.0)	84.6 (20.1)	17.576	< 0.001
Mean arterial blood pressure Mean (SD)	93.6 (16.1)	64.6 (8.1)	79.1 (19.3)	15.156	< 0.001

Table 2: *Maternal clinical features.*

***: Fishers Exact.*

D dimer levels among participants

The D dimer readings among pregnant women and its comparison across groups is presented in table 3a and 3b below. The mean D-Dimer levels for all participants at onset of the study was 2310.2 (SD = 1715.1) ng/ml and ranged between 39.1 - 5000 ng/ml. The mean D dimer levels for participants at the end of the study was 3169.1 ng/ml (SD = 1337.1) and ranged between 31.2 - 5000 ng/ml. Comparison of pre-delivery D dimer readings between cases and controls revealed that cases had a higher mean D Dimer reading of 3373.2 ng/ml (SD = 1277.0) compared to that of the control with a mean of 1471.1 ng/ml (SD = 1547.5). They both ranged between 39.1 - 5000 ng/ml. This was statistically significant at $p < 0.001$.

Group	D Dimer value (in ng/ml) Mean (SD)		T test	P-value
	Cases No (%)	Control No (%)		
Pre-delivery Range	3373.2 (1276.9) (39.1 - 5000)	1471.1 (1547.5) (39.1 - 5000)	7.852	< 0.001
Post-delivery Range	3219.8 (1027.6) (136.7 - 5000)	3141.1 (1493.1) (31.3 - 5000)	0.215	0.831

Table 3a: *Comparison of mean D-dimer levels among groups.*

D Dimer level	Group		Total	Chi square	P-value
	Cases No (%)	Control No (%)			
Pre-delivery					
Elevated	56 (93.3)	48 (63.2)	104 (76.5)	16.968	< 0.001
Normal	4 (6.7)	28 (36.8)	32 (23.5)		
Post-delivery					
Elevated	20 (95.2)	34 (89.5)	54 (91.5)	0.579	0.447
Normal	1 (4.8)	4 (10.5)	5 (8.5)		

Table 3b: *Comparison of D-dimer levels among groups.*

Also, comparison of mean post-delivery D dimer readings between cases and controls showed cases had a higher mean D-Dimer reading of 3219.8 (SD = 1027.6) ng/ml and ranged between 136.7 - 5000 ng/ml compared to that of the control with a mean of 3141.1 (SD = 1493.1) ng/ml and range between 31.3 - 5000 ng/ml. This was not statistically significant at p = 0.831.

D-dimer levels among participants was grouped into elevated and normal based on the 0.5 mg/l criteria (Table 3b). The conversion factor of ng/ml to mg/l is 1000 for d-dimer levels. Results reveal that a higher proportion of the cases had elevated D-dimer levels (93.3%) compared to controls (63.2%) at the onset of the study. This was statistically significant at the onset of the study (p < 0.001). At the post-delivery, a higher proportion of the cases had elevated D-dimer levels (95.2%) compared to controls (89.5%). This was not statistically significant.

Prevalence of HELLP syndrome among participants: The prevalence of HELLP syndrome among participants is shown in figure 1 below. Only one participant (0.6%) a case was diagnosed with HELLP syndrome at the onset of the study. This was also the case at the end of the study where one participant in the control group tested positive for HELLP syndrome.

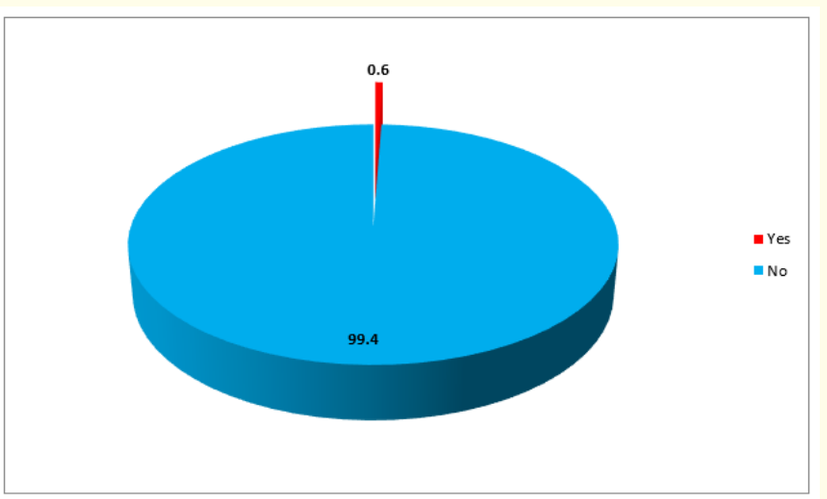

Figure 1: *Prevalence of HELLP syndrome among participant (pre and post).*

Discussion

The summary of the key findings from this study revealed that the mean D-dimer levels among participants with preeclampsia were higher than those without preeclampsia prior to delivery (3373.2 ng/ml SD = 1277.0 vs 1471.1 ng/ml SD = 1547.5 $p < 0.001$). HELLP syndrome was rare in this study as prevalence was 0.6% and D-dimer levels could not be used to predict onset of HELLP syndrome as only one participant from each group had the syndrome and logistic regression could not be done. The mean arterial blood pressure (MAP) was higher for the cases 93.6 mmhg (SD = 16.1) compared to the control which was 64.6 mmhg (SD = 8.1).

The study showed that plasma D-dimer levels, though high in patients with preeclampsia compared to those without the disease, cannot be used to predict onset of HELLP syndrome.

The mean age of both patients with preeclampsia and normal pregnancies were similar and most of the patients in the study were booked and admitted via the antenatal clinic. The main route of delivery of patients with preeclampsia was caesarean section as compared to vaginal delivery in patients with normal pregnancy. This is supports the study by Linhares., *et al*. that showed patients with a history of pre-eclampsia were 2.5 times more likely to have caesarean delivery (OR = 2.5; $p < 0.02$).

This study showed an increase in d-dimer levels pre-delivery and post-delivery among all patients in this study. The mean D-Dimer reading for all respondents at onset of the study, prior to delivery was 2310.2 (SD = 1715.1) and ranged between 39.1 - 5000 ng/ml. The mean D dimer readings for participants at the end of the study, after delivery was 3169.1 (SD = 1337.1) and ranged between 31.2 - 5000 ng/ml. When comparing the d-dimer level of patients with preeclampsia and those without preeclampsia before and after the study, there was a higher level of d-dimer in the blood of patients with preeclampsia (mean D Dimer reading of 3373.2 ng/ml, SD = 1277.0) compared to those without preeclampsia (mean of 1471.1 ng/ml, SD = 1547.5). This was statistically significant at $p < 0.001$. However, following delivery, the levels of d-dimers in preeclamptic patients was still higher than that in patients with normal pregnancies but it was not statistically significant ($p = 0.831$).

This study has confirmed that patients with preeclampsia have elevated d-dimer levels compared to patients without preeclampsia. Since normal pregnancy has been shown to be a hypercoagulable state and the levels of d-dimers has been shown to increase progressively and increases with increasing gestational age as reported in separate studies by Kline, Heffner and Kovac and their colleagues [8-10]. Hence we can deduce that there is higher level of hypercoagulable state in patients with preeclampsia since they have higher d-dimer levels.

Patients without preeclampsia had an increase in their d-dimer levels from a mean of 1471.1 ng/ml to 3141.1 ng/ml. This may be explained due to the fact that the delivery process is associated with bleeding whether vaginal delivery or caesarean delivery and hence the levels of d-dimers, a form of fibrin degradation product increased.

Heffner., *et al*. showed in their study suggested a cut-off d-dimer levels for healthy woman was 0.5 mg/l [10] but comparing this to values from patients from this study with normal pregnancy (1.47 mg/l and 3.14 mg/l) and preeclampsia (3.37 mg/l and 3.22 mg/l) both before and after delivery showed an increase and proves pregnant women generally have hypercoagulable state. This study showed a higher proportion of patients with preeclampsia had elevated d-dimers compared to patients with normal pregnancy if 0.5 mg/l was taken as the normal values for healthy women. This was statistically significant ($P < 0.001$).

The diagnosis of HELLP syndrome in this study was made using the three standard parameters: LDH as prove of haemolysis, low platelet and ALT for liver enzymes. The method used in the laboratory to assay for LDH and ALT (which is more specific for liver diseases than AST) in this study has reference intervals of 0 - 250 iu/L and 0 - 33 iu/L for females respectively [11,12]. The values above the range was regarded as evidence of haemolysis and liver diseases respectively. Platelet count lower than 150,000/mm^3 as low. The study revealed

prevalence of HELLP syndrome to be 0.6%. Only one patient with preeclampsia was detected to have HELLP syndrome at the onset of the study. This was also the case at the end of the study where one patient with normal pregnancy was diagnosed to have HELLP syndrome after delivery. The prevalence of HELLP syndrome from this study was low which is similar to other studies that detected low prevalence among pregnant women as reported by Haram, Mihu and Gleeson and colleagues [1-3]. Since only one patient among patients who had preeclampsia developed HELLP syndrome, this answers the first specific objective of the study to determine the number of patients with preeclampsia that develops HELLP syndrome. The low incidence of HELLP syndrome; made it statistically illogical to be able to calculate the predictive of value of d-dimer for HELLP syndrome or do a logistic regression. This answers the main or general objective of this study to check the value of d-dimers in patients with preeclampsia as a predictor for HELLP syndrome.

The patients with normal pregnancy had their mean d-dimer increase from admission till after delivery but only patient had HELLP syndrome; while the preeclampsia group had their mean d-dimer reduce slightly but HELLP syndrome was missed at admission in patient. In addition, there are contrasting findings from various researches on the predictive value of d-dimers. The study in France by Marcq., *et al*. reported that d-dimer levels at admission has a poor predictive value for HELLP syndrome [13]. The while the study by Nieger in the US also showed D-dimer had poor positive predictive value however high negative predictive value [6]. Unlike in this study, the number of patients with HELLP syndrome that were d-dimer positive was high. It could be because the study was done among Caucasians were HELLP syndrome is higher as compared to Africans. Mihu., *et al*. in their study noted low incidence HELLP syndrome among blacks compared to Caucasians [3].

The diagnosis of HELLP syndrome was missed in the patient with preeclampsia and the syndrome was only picked by the study and the patient had management for preeclampsia and was promptly delivered. Studies by Rahman., *et al*. and Schroeder., *et al*. have shown that diagnosis of HELLP syndrome could be missed or delayed as in the case of this patient [4,5], this may be attributable to the non-specific symptom of patients with the disease and low index of suspicion in health care professionals due to the low prevalence of the disease in this environment and among blacks. The development of HELLP syndrome in the patient with normal pregnancy in this study after delivery could also confirm that HELLP syndrome is a separate disease entity and may occur in the absence of preeclampsia or antecedent hypertension as previously reported in separate studies by Dotsch, Sibai and Reubinoff and their colleagues [14,15]. This patient was monitored for a longer period in the hospital and necessitated invitation of the haematology team and further investigation to co-manage her. Yucesoy., *et al*. conducted a study at the College of Medicine, Koceli and noted the diagnosis of HELLP syndrome could depend on the sample size of the population studied, location of the study and duration as can be seen to be 11% in a large study done Turkey over 7 years [16].

There is conflicting evidence of the usefulness of D-dimers in predicting HELLP syndrome depending on the population being studied and the prevalence of HELLP syndrome in that population; this study makes use of D-dimers for screening test for HELLP syndrome among blacks, where the prevalence is low a test that is not useful. However, considering other conflicting findings from studies by Nieger., *et al*. [6] in the US and Marcq., *et al*. [13] in France, there is need to conduct a more robust systematic review of all evidences with larger sample size of all evidences across various population to determine the usefulness of the predictive value of D-dimers for HELLP syndrome. These studies including this one had few sample size and for a rare disease in Africa and among blacks, there is need to have a larger sample size to be able to detect the presence of HELLP syndrome. This is one of the limitations of this study since about 180 participants were recruited due to constraints of funding and time needed to monitor the participants and complete the study. There is need to conduct a well-funded larger study to establish the role of D-dimers in the care of patients with preeclampsia, which is more common among blacks than HELLP syndrome before it can be introduced in patient care as a routine screening test for HELLP syndrome. The study in France by Marcq., *et al*. [13] used ELISA technique for screening for D-dimer which is the same screening kit used in this study and the findings were similar. This is one of the strength of this study because it had similar conclusions as a study done in Europe. ELISA kit is cheaper with high sensitivity and specificity and hence could be introduced as a routine testing kit on a large scale. Unlike the monoclonal antibody technique used by Nieger., *et al*. which is expensive and cannot be readily used in a large scale for routine testing. A meta-analysis

of 194 studies on the usefulness of the diagnostic value of D-dimers in patients with preeclampsia revealed it was elevated compared to normotensive patients especially in the third trimester [17].

This study revealed a number conflicting findings regarding the predictive value of D-dimers for HELLP syndrome compared to some other studies by Neiger and Trofatter. The usefulness of elevated D-dimers in predicting foetal and perinatal complications was also negative hence there is need for further comprehensive research with larger sample size as well as systematic review across different populations where there is varied prevalence of HELLP syndrome, to guide the introduction of D-dimer assay as a screening tool in patients with preeclampsia as a health policy and change clinical practice.

Conclusion

Elevated d-dimer levels were detected in patients with pre-eclampsia but it was not predictive of HELLP syndrome due to low prevalence in our environment. Hence, routine assay for D-dimer levels should not be recommended for screening for HELLP syndrome in patients with preeclampsia among blacks; and thorough review is necessary for all pregnant women in order to be able to detect HELLP syndrome because of its associated feoto-maternal and perinatal complications particularly in patients with preeclampsia and could be missed, masked by other disease condition or even in patients without preeclampsia.

There is need for further larger studies among Caucasians and blacks and systematic reviews to establish the predictive value of D-dimers and guide the introduction of the routine assay of D-dimers in clinical practice.

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Conflict of Interest

The authors declare no there is no conflict of interest.

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