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Review Article

D-dimer Levels Among Pregnant Women of African Descent Attending Antenatal Clinic in a Tertiary Hospital in Sokoto, North Western Nigeria

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Abstract

Introduction: Monitoring of coagulation status in pregnancy is crucial to ensure effective haemostatic management, goal-directed therapy, improved outcomes and successful delivery. D-dimer values are thought to predict prothrombotic states of an individual and there exist an association between hypercoagulability markers like D-dimer and increased risk of coronary events. In this study we evaluated the D- dimer levels among pregnant women of African descent in Sokoto, North Western Nigeria.

Methods: Manual D-dimer latex suspension method was used for detecting the presence of D-dimer (Helena, UK). This semi- quantitative method was used in determining the plasma concentration of the D- dimer following the manufacturer's instructions.

Results: Seventy-five consecutively-recruited pregnant women aged 18-40 years and mean age of 27.12± 5.31years constituted the subjects for this case-control study. Twenty -five aged- matched non-pregnant women were monitored as controls. About 12% of the pregnant women had normal D-dimer values (<250 ng/mL), 24% of the pregnant women had elevated D-dimer levels (250-500 ng/mL), while 64% of the pregnant women were found to be at risk of thrombosis (D-dimer > 500 ng/mL). We observed a positive and significant correlation between D-dimer values and gestation age ($r = 0.42$, $p < 0.01$). All the 25 non- pregnant women had a moderate D- dimer level of between 250-500 ng/ml. This study indicates that a significant number of pregnant women in the 2nd and 3rd trimester have positive D-dimer results with 33 (44.0%) potentially at risk of thrombosis.

Conclusion: Our finding indicates that 12% of pregnant women had normal D-dimer values (≤250 ng/mL), 24% had moderate D-dimer (250-500 ng/mL) while 64% were potentially at risk for thrombosis (D-dimer > 500 ng/mL). D –dimer level among pregnant women of African descent seems to rise during pregnancy predisposing them to potential thrombotic complications. We recommend that pregnant women at risk in the area be under the care of a qualified obstetrician and that D-dimer levels in such women be monitored during pregnancy to reduce the risk of thrombotic complications.

Keywords: D-dimer; Pregnancy; African; Pregnancy; Sokoto; Nigeria

Introduction

Haemorrhage is one of the major causes of maternal mortality and morbidity worldwide [1]. It is responsible for 44% of maternal death in Africa [2]. More than 536,000 women die every year from pregnancy-related complications in sub Saharan Africa [3].

Physiological changes in pregnancy affect the coagulation and fibrinolytic systems. Many of the clotting factors increase and anticoagulation factors decrease causing augmented coagulation and decreased fibrinolysis. However, pre-existing coagulopathies may affect the course of pregnancy and nature of the coagulopathy may also be modified by pregnancy. These changes in coagulation may affect the mode of delivery.

Monitoring of coagulation status in pregnancy is crucial for effective haemostatic management, goal-directed therapy, and improved outcomes [4]. Laboratory-based screening is used routinely to assess coagulation status in obstetric patients. The tests consist of platelet count; PT, APTT, D-Dimer, and plasma fibrinogen levels in the developed world [5]. In many countries in sub-Saharan Africa (SSA), a significant number of women do not attend antenatal clinics and are often delivered at home by traditional birth attendants (TBA's) and there is a high rate of often unreported haemorrhage- related maternal mortality due to absence of vital laboratory tests, equipment and qualified laboratory personnel to carry out haemostatic monitoring during pregnancy and prior to delivery.

Pregnancy is also a risk factor for venous thrombosis. Venous thromboembolism is an important cause of maternal morbidity and mortality in hospitalized patients. D-dimer values can be used to predict prothrombotic (such as atrial fibrillation) associated with intracardiac thrombosis and embolism [6-8] and there is rapid normalization of D-dimer values after cardio version [7] or warfarinization [8] in patients with atrial fibrillation. A recent meta-analysis of prospective studies reported an association between the hypercoagulability marker D-dimer and an increased risk for coronary events [9] which occurs when there is an imbalance between procoagulant and anticoagulant activities of haemostasis molecules. Pregnancy is a hypercoagulable state. Various strategies incorporating D- dimer testing for emergency evaluation of Pulmonary Embolism (PE) in combination with spiral computed tomography (CT) and pretest clinical probability have been proposed [11-13]. Circulating concentrations of fibrin D-dimer reflect the extent of fibrin turnover in the circulation, as this antigen is present in several degradation products from the cleavage of cross-linked fibrin by plasmin [14,15]. Highly elevated D-dimer values occur in various disorders in which the coagulation system is excessively activated, such as acute venous thromboembolism [16]. It has been suggested that modestly elevated circulating D-dimer values reflect minor increases in blood coagulation, thrombin formation and turnover of cross-linked intravascular fibrin and that these increases may be relevant to coronary heart disease (CHD) [15].

There paucity of data on D- dimer levels among pregnant women in Sokoto, Nigeria. It is not known to what extent pregnancy affects D- dimers levels of pregnant women in Sokoto State, Nigeria. The aim of this study was to generate evidenced-based data on the fibrinolytic marker (D-dimer) in pregnant women to facilitate the obstetric and haematology-related care offered to pregnant women in Sokoto State in particular and Nigeria in general.

Aim of study

The aim of this study is to determine the D- dimer concentration among pregnant women of African descent in Sokoto, North Western, Nigeria.

Materials and methods

Study Area

This study was conducted in the Haematology Department of Usmanu Danfodiyo University Teaching Hospital Sokoto State. The hospital is a tertiary health facility rendering quality healthcare services to the people from Sokoto and the surrounding states of Kebbi and Zamfara State. Sokoto is a city located in the extreme Northwest of Nigeria, near to the confluence of the Sokoto River and the Rima River. The metropolitan city lies between longitude 05 11 to 13 03 East and latitude 13 00 to 13 06 North and covers an area of 60.33km. It is in the dry Sahel surrounded by sandy savannah with an annual average temperature of 28.3°C (82.9 °F). It is one of the hottest cities in the world. The warmest months are February to April and the rainy season is from June to October, during which showers are the common occurrence. Sokoto state has a population of 3.7 million people based on 2006 census. It is made up of two major ethnic groups namely, Hausa and Fulani. Apart from Hausa and Fulani, there are the Zabarmawa and Tuareg minority in the border local government areas. Agriculture, fishing and local crafts (blacksmithing, weaving, dyeing, carving and leather works) play an important role in the economic life of the people of Sokoto [17].

Sample Population

Seventy-five consecutively-recruited pregnant women aged 18-40 years and mean age of 27.12± 5.31 years visiting the Usmanu Danfodiyo University Teaching hospital for antenatal care constituted the subjects for this case-control study. Twenty -five aged- matched non-pregnant women (mean age 27.24 ± 4.23) were monitored as controls. The control participants were selected from the female staff of the teaching hospital

and the university.

Study Design

This is a descriptive case-control study designed to investigate D-dimer concentration among pregnant women of African descent in Sokoto, North Western Nigeria.

Inclusion criteria

The following women who met the inclusion criteria; age ≥ 18years, confirmed pregnant by a qualified obstetrician and willingness to give a verbal informed consent to participate in study were recruited after counselling.

Exclusion Criteria

All non-pregnant, non-adult (<18 years), pregnant non-consenting pregnant women were excluded form participation as subjects in the study.

Ethical issues:

Ethical approval was obtained from the ethical committee of the Usmanu Danfodiyo University Teaching Hospital, Sokoto. Verbal informed consent was obtained from all study participants.

Sample Collection

For each subject a tourniquet was applied around the arm, the antecubital fosa was disinfected with cotton wool soaked in methylated spirit. About 2.7mls of venous blood was collected using 5mls syringe into sodium citrate anticoagulated tubes. The sample was centrifuged at 3,000rpm and the plasma was then separated and used for determination of D- dimer concentrations qualitatively and semi-quantitatively.

Methods for D- Dimer estimation

Qualitative method:

Exactly 20µl of test plasma was placed in circles on a test card. Exactly 20µl of manual D-dimer latex suspension was placed in a nearby area of each circle. The sample and manual D-dimer latex was quickly mixed using a clean mixing stick for each sample and a timer was simultaneously started, the test card was rocked gently and agglutination was observed. Positive and negative agglutination were compared with the results obtained using the positive and negative control plasma included in the kit.

Semi- quantitative method:

The D-dimer concentration for all positive result was carried out by serially diluting 100 µl of the citrated plasma with imidazole buffer. Each dilution mixed with the latex suspension on a test card as per the quantitative method. The D-dimer concentration was then determined.

Statistical analysis

Data obtained from the study participants were subjected to descriptive statistics (mean, standard deviation and median). Differences between the subject and control groups for the measured parameters were determined using the t-test. Correlation was compared using linear regression analyses. Statistical analyses were carried out using SPSS software version 18.0 (SPSS Inc, Chicago, IL). A probability value of $p \leq 0.05$ was considered as significant in all statistical comparisms.

Results

Seventy-five consecutively-recruited pregnant women aged 18-40 years and mean age of 27.12± 5.31years constituted the subjects for this case-control study. Twenty -five aged-matched non-pregnant women were monitored as controls. About 12% of the pregnant women had normal D-dimer values (<250 ng/mL), 24% of the pregnant women had elevated D-dimer levels (250-500 ng/mL), while 64% of the pregnant women were found to be at risk of thrombosis (D-dimer > 500 ng/mL). Out of the 66 pregnant women with positive D-dimers, 48 (64%) were potentially at risk of thrombosis. Table 1 show the prevalence of D- Dimer positive result among pregnant women and non-pregnant women. We observed a positive and significant correlation between D-dimer values and gestation age ($r = 0.42$, $p < 0.01$). All the 25 non- pregnant women show a D-dimer levels of between 250-500 ng/ml.

Table 1. Prevalence of D- Dimer Positive Result among pregnant women and non-pregnant women.

Pregnancy Status	D-dimer Result			
	Negative (≤ 250 ng/ml) N (%)	Moderate (250-500ng/ml) N (%)	Significantly (>500ng/ml) N (%)	Raised
Pregnant	9 (12)	18 (24)	48 (64)	
Non-Pregnant	0 (0)	25 (100)	0 (0)	

The result also show that a significant number of pregnant women in the 2nd and 3rd trimester had positive D-dimer results 33 (44.0%) and 24 (32.0%) respectively compared to women in the first trimester 9 (12%) (p=0.01). Table 2 shows D- dimer positivity among pregnant women based on trimester.

Table 2. D- dimer positivity among pregnant women according to trimester.

D-dimer Result	1st Trimester N (%)	2nd Trimester N (%)	3rd Trimester N (%)	Total
Negative (≤ 250 ng/ml)	0 (0.0%)	3 (4.0%)	6 (8.0%)	9 (12%)
Positive (> 250 ng/ml)	9 (12.0%)	33 (44.0%)	24 (32.0%)	66 (88%)
Total	9 (12.0%)	36 (48.0%)	30 (40.0%)	75(100%)

Table 1shows that 9 (12.0%) of the pregnant women are negative to the D- dimers while 66 (88.0%) had detectable D- dimers. All the 25 non pregnant women showed a moderate D- dimer level of 250-500ng/ml. Table 2 indicates that all the 9 (12%) pregnant women in the first trimester were positive for D- dimer, 33 (44.0%) and 24 (32.0%) women in their third trimester had a positive D- dimer result. D-dimer concentration (ng/ml) at various dilutions among the pregnant subjects showed that at 12% had D-dimer concentration of ≤ 250 ng/ml, 24% had 250-500ng/ml, 28% had 500-1000ng/ml, 12% had 1000-1200ng/ml and 24% had 1200-2000ng/ml respectively. While among the non-pregnant control group, 100% had a concentration of 250-500 ng/ml.

Table 3. Values showing D-dimer concentration at various dilutions of pregnant (study group) and non-pregnant (control group) women.

Dilutions	Negative	Neat	1:2	1:4	1:8
Concentrations (ng/ml)	≤250	250-500	500-1000	1000-1200	1200-2000
Pregnant	9(12.0%)	18(24.0%)	21(28.0%)	9(12%)	18(24%)
Non-pregnant	0(0%)	25(100%)	(0%)	(0%)	(0%)

Clinically significant D-dimer concentration of 1200-2000ng/ml was significantly concentrated among pregnant women in the second 9(12%) and 3rd trimester 9(12%) compared to the first trimester 0(0%). Table 4 show that 18(24.0%) of the pregnant women had a positive and significant plasma dilution of 1:8 corresponding to D-dimer concentrations of 1200 – 2000ng/ml.

Table 4. D –dimer positivity at various plasma dilutions among pregnant women at different trimesters.

Dilutions	N	Negative	Neat	1:2	1:4	1:8
D-Dimer Concentration (ng/ml)		≤250	250-500	500-1000	1000-1200	1200-2000
1st trimester	9(12.0%)	0(0.0%)	0(0.0%)	6(8.0%)	3(4.0%)	0(0.0%)
2nd trimester	36(48.0%)	3(4.0%)	9(12.0%)	9(12.0%)	6(8.0%)	9(12.0%)
3rd trimester	30(40.0%)	6(8.0%)	9(12.0%)	6(8.0%)	0(0.0%)	9(12.0%)
Total	75(100%)	9(12.0%)	18(24.0%)	21(28.0%)	9(12.0%)	18(24.0%)

Discussion

In this present study, we observed that 9 (12.0%) of the pregnant women were negative for the D- dimers while 48 (64%) had detectable D- dimers of >500ng/ml. All the 25 non pregnant women showed a D-dimer value 0f <500ng/ml. The high prevalence of detectable D-dimer concentration of >500ng/ml among 64% of pregnant subject re-affirms previous report that pregnancy itself is a hypercoagulability state [18]. A hypercoagulable state occurs when there is an imbalance between procoagulant and anticoagulant activities of haemostasis molecules [18-19]. Pregnancy is known to cause physiological changes in the body systems including the CNS which may lead to distress. Poverty and insecurity being experienced in the Northern part of the country also add to psychosocial distress among pregnant women in the area. Psychosocial factors might mediate their adverse impact on coronary arteries by eliciting a hypercoagulable state via changes in sympathetic nervous system activity. A recent meta-analysis of prospective studies reported an association of the hypercoagulability marker D-dimer with an increased risk for coronary events [9]. The relationship between psychosocial stress and CAD was considered one of the most important pathophysiologic issues in the field of cardiovascular medicine [20].

D- Dimer concentration is said to be higher in the elderly [21-22], and correlates positively with indicators of inflammatory processes like the C - reactive protein (CRP) and may reflect inflammatory states [23]. Previous report indicate that there were significant associations between D-dimer values with two circulating markers of inflammation but not with clinical evidence of CHD at baseline [6,7]. Conversely, the possibility that D-dimer values can predict prothrombotic states is suggested by preliminary associations and venous thrombosis and other conditions (atrial fibrillation) associated with intra cardiac thrombosis and embolism [7-8].

We also observed an elevated concentration of D- dimer compared with the control group. This finding is consistent with previous report in the Niger Delta of Nigeria by Jeremiah and colleagues [24] which indicated that a greater proportion (26.7%) of their cohort of pregnant women had elevated levels of D-dimer and that a high percentage of pregnant women (10.0%) may be at risk of thrombosis. Another study also observed the same progressive increase of fibrinogen and D-dimer throughout pregnancy [25]. Similarly, Hasen and colleagues [26] found a significant rise in D-dimer from first to second trimester and from second to third trimester.

In clinical application, a cut-off level of < 0.5 µg (500ng/ml) D-dimer/ml plasma is predictive for ruling out deep venous thrombosis and pulmonary embolism [27]. In this present study, about 12% of the pregnant women had normal D-dimer values (<250 ng/mL), 24% of the pregnant women had elevated D-dimer levels (250-500 ng/mL), while 64% of the

pregnant women were found to be at risk of thrombosis (D-dimer > 500 ng/mL). This figure is much higher than values observed by Jeremiah and colleagues [24] which indicated that about 63.3% of their cohort pregnant women had normal D-dimer values (0–200 ng/mL), 26.7% of the pregnant women had elevated D-dimer levels (201–499 ng/mL), while 10.0% of the pregnant women were found to be at risk of thrombosis (D-dimer > 500 ng/mL). The higher thrombotic risk observed in this study may due the effect of pregnancy or/ and the presence of an underlaying hypercoagulable activity. Our cohort of pregnant women particularly those at risk of thrombosis will need to be monitored properly for thromboembolic disorders including DVT and PE. It has been observed earlier that even within the normal range, D-dimer may predict coronary events in apparently healthy individuals [28] and in patients with atherosclerotic disease,[29] suggesting that increased fibrin turnover occurs along a continuum of severity, spanning health, a hypercoagulable state, and overt thrombosis [30].

The negative predictive value for the manual D – dimer for thrombosis is high [7]. In clinical studies done by group of researchers on normal subjects, patients with phlebographically confirmed DVT, patients with DIC and patients with pre- eclampsia the following results were obtained; out of 101 normal individuals, only 1 was positive at neat for the D – dimer while 100 of them were negative. Of 48 DVT patients, 3 were negative; 10 were positive at neat; 7 at ½ dilution, 14 at ¼ dilutions and 14 at 1/8 dilutions. 29 DIC patients had the following results; 0 negative, 3 positive at neat; 3 positive at ½; 4 at ¼ and 19 at 1/8 dilutions. In pre- eclampsic patients, 6 were investigated and were found to be: 2 negative for the D – dimer; 1 was positive at neat and 3 were positive at ½ and there was no observable agglutination at other dilutions [30]. In our study, we found 48 (64%) of the Pregnant women had agglutination at plasma dilutions of above ½ suggesting that a significant number of pregnant women may be at risk of various complications ranging from DVT, PE, CHD and pre – eclampsia.

In this study, we observed that 64% of our cohort of pregnant subjects are at risk for thrombosis (with a cut-off value of >500 ng/mL D-dimer concentration). Our finding is higher a risk of 10% observed in a previous report [24]. Pregnancy has been identified as one of the risk factors for thrombosis, with the risk increasing by a factor of 4.2 during pregnancy and rising to 14.4 in the postpartum period. The pregnancy-related high risk of thrombosis has been reported to persist for up to six weeks after delivery [31-32]. Our finding is consistent with reports from other parts of the world, which indicates that pregnancy predisposes women to a risk of thrombosis [33-36]. The interpretation of the D-dimer level depends on which test is used to perform the assay, as well as the cut-off values used [37]. Current recommendations suggest that a D-dimer test should be used in combination with other tests, such as compression ultrasonography and chest radiographs [38-39].

Another significant observation in this study is the progressive rise in the D-dimer concentration during the second and third trimesters of pregnancy. This observation is consistent with findings from previous reports [40-41]. D-dimer test has historically been used to determine increased fibrinolytic activity in various physiological and therapeutic states. An elevated D-dimer level in a patient's blood indicates two physiological processes: the presence of an intravascular thrombus and the normal degradation (fibrinolysis) of the thrombus [42]. The increase in the D-dimer is often due to interplay between several fibrinolytic factors. From the physiological point of view, tissue plasminogen activator converts plasminogen into plasmin, which cleaves fibrin and fibrinogen, yielding fibrin degradation products. A plasmin inhibitor (α2-antiplasmin) and plasmin activator inhibitor type 1 and type 2 (PAI-1 and PAI-2) prevent excess fibrin degradation by plasmin. Endothelial-derived PAI-1 increases during the later stages of pregnancy, whereas placenta-derived PAI-2, detectable in the plasma during the first trimester, increases substantially throughout pregnancy [43]. These changes that occur during normal pregnancy is an indication that the fibrinolytic system is impaired in pregnancy. The plasminogen level and D-dimers and fibrin degradation products tend to increase during pregnancy while the α2-antiplasmin level decreases. These physiological changes may be responsible for the higher D-dimer levels observed in the second and third trimester of pregnancy among our cohort of pregnant women [43]. Recent reports [44-45] suggest the need of adapting reference D-dimer values during the different trimesters of pregnancy as in general, high levels are seen in a trimester-dependent way.

Conclusion

Our finding indicates that 12% of pregnant women had normal D-dimer values (≤250 ng/mL), 24% had moderate D-dimer (250-500 ng/mL) while 64% were potentially at risk for thrombosis (D-dimer > 500 ng/mL). D –dimer level among pregnant women of African descent seems to rise during pregnancy predisposing them to potential thrombotic complications. We recommend that pregnant women at risk in the area be under the care of a qualified obstetrician and that D-dimer levels in such women be monitored during pregnancy to reduce the risk of thrombotic complications.

Limitations

Test used for this study was agglutination and semi quantitative method and other risk factors associated with elevated D- dimers such as smoking, high body mass index, atherosclerosis among others were not considered. A negative manual D- dimer test does not completely rule out thrombosis. A negative predictive value for patients with suspected DVT has been found to be 94% with the manual D- dimer. Detection of elevated D –dimer should ideally be used together with other clinical information to form a diagnosis. Agglutinations with

samples containing normal D- dimer levels may occasionally occur due to non- specificity. A small number of samples, when mixed with the latex, may exhibit white flakes which should not be confused with agglutination. No international standard for D –dimer exist for now for numerical values. We did not determine actual thrombin levels. It would have been of interest to correlate our observation with actual thrombin levels A larger cohort study may be required to further confirm these observations.

Conflict of interest

The authors report no conflicts of interest in this work.

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