Original Article

Pregnancy associated coagulopathies in selected community hospitals in Southwest Nigeria

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Abstract

Background and Aim: Pregnancy is characterized by multiple changes in the coagulation system which occurs at different stages of the condition, representing one of the major triggers of maternal and foetal morbidity/mortality in the world during complicated incidences. This study determined the prevalence of coagulation disorders among pregnant women in Southwest Nigeria to buttress the need for prompt and accurate routine diagnosis of these disorders. **Methods:** Four hundred and five participants (405) attending some selected tertiary health facilities in Southwestern Nigeria were randomly recruited for the study, comprising two hundred and seventy (270) pregnant subjects and one hundred and thirty-five (135) apparently healthy age- and socio-economic status-matched non-pregnant women as controls. The platelet count was assessed; prothrombin time and activated partial thromboplastin time were assessed. Immunoturbidimetric and chromogenic techniques were also used to assess the level of D-dimer and activated protein C resistance. **Results:** Platelet count, PT and INR in all three trimesters were significantly ($p < 0.05$) reduced when compared to the non-pregnant control subjects. However, the level of circulating D-dimer was significantly ($p < 0.05$) increased in all three trimesters when compared with the control group, with observable steady increase in the second and third trimesters. Also, 13% of respondents had thrombotic predisposition and 14.8% with tendencies for consumption coagulopathy while 1.1% are APCr positive individuals. **Conclusion:** The study affirms the hypercoagulable state of pregnancy coupled with mild gestational thrombocytopenia which could be pointers to onset of coagulation disorders in some participants, subjects with coagulation profiles indicative of thrombotic tendencies and possible onset of consumption coagulopathy and the presence of activated protein C resistant in the region. A review of the coagulation monitoring strategies for pregnant women from primary care to include more definite assays and its proper implementation will immensely contribute to early diagnosis along with intervention for pregnancy associated coagulopathies in resource-limited settings.

Keywords: Coagulation disorders, disseminated intravascular coagulation, pregnancy, thrombosis

Introduction

Maternal mortality is a major public health emergency worldwide, remaining unacceptably high in the developing countries with approximately 810 women reportedly dying from pregnancy or childbirth related complications daily.[1] Nearly 99% of all maternal deaths occur in resource-limited settings with more than half of the deaths occurring in Sub-Saharan Africa and about one

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third in South Asia with most of the mortalities being otherwise preventable.[2] Globally, complications in pregnancy are a major contributor to negative pregnancy outcomes; including maternal and foetal morbidity and mortality if not promptly addressed. These pregnancy complications are grouped as direct and indirect causes of maternal mortality according to the WHO international classification of Disease, with the direct causes comprising abortion, coagulation disorders, hypertensive disorders (preeclampsia and eclampsia), pregnancy-related sepsis and the indirect causes comprising underlying medical disorders (acquired or inherited), HIV and other related viral infections.[1,3,4] Pregnancy is characterized by multiple changes in the coagulation system as the pregnancy progresses, with dramatic change in coagulation factor concentrations throughout the pregnancy and the largest changes observed at term gestation. Coagulation disorders represent one of the major triggers of poor pregnancy outcomes in the world, significantly contributing to maternal and foetal morbidity and mortality in developing countries.[5]

Disseminated intravascular coagulation (DIC) is a prominent systemic coagulation disorder which can occur in any clinical condition.[6] It is associated with pregnancy complications that often results from systemic activation of coagulation thereby causing fibrin deposition without specific localization and occurring intravascularly.[7,8] DIC causes massive and ongoing activation of coagulation capable of depleting platelets and coagulation factors, subsequently resulting in haemorrhage (consumption coagulopathy). Preeclampsia is the most common obstetric emergency associated with these series of coagulation activation predisposing women to DIC.[8,9] Haemorrhage can also result from eclampsia, abruptio placentae which causes vaginal bleeding in the latter half of pregnancy, haemolytic anaemia, elevated liver enzymes and low platelet (HELLP) syndrome associated with vaginal bleeding and numerous other complications including underlying ones.[8,10-13] Thrombocytopenia has been implicated as an indicator of DIC development,[14] especially when occurring due to HELLP syndrome.[15,16] DIC can be diagnosed via sensitive laboratory investigations; however, most of the laboratory assays are not routinely available or accessible in the developing countries along with enormous consequences due to their fragile health systems. DIC contributes significantly to maternal and perinatal morbidity and mortality with myriads of consequences.[17] It is therefore essential to focus attention on its prompt diagnosis and accurate monitoring for early intervention and patients management first from the primary care setting then to the specialist centres.

Other thrombotic disorders could also arise in pregnancy resulting in deep vein thrombosis (DVT); a rare but fatal complication in pregnancy whose occurrence varies widely and reported as one of the leading causes of maternal morbidity in some Western countries[18-20] Several factors have been associated with DVT risk in pregnancy with hypercoagulability as a major predisposing factor, prolonged bed rest or immobility, pelvic or leg trauma, and obesity, preeclampsia, Caesarean section, instrument-assisted delivery, haemorrhage, multiparity, varicose veins, a previous history of a thromboembolic event, and hereditary or acquired thrombophilias are some known factors associated with DVT risk in pregnancy.[18-20] Furthermore, haemoglobin (Hb) variants including HbS, C, D, Lepore, unstable haemoglobins and many others depending on the gene affected and the region they are discovered can also be associated with coagulation complications in pregnancy.[21,22] Sickle cell syndrome poses a high risk of poor pregnancy outcomes characterised by specific complications with more severe course in homozygous HbS women. There is however a reduced risk of pregnancy complications in the HbSC genotype women compared to the homozygous HbS women albeit having greater risk of complications than the apparently healthy HbAA genotype pregnant women.[22-24] The litany of physiological changes associated with pregnancy have made the application and interpretation of haemostatic screening assays in pregnancy particularly challenging as these complex changes are not detectable by classic routine coagulation/platelet assays.[25] This study therefore evaluated the prevalence of coagulation disorders among pregnant women in Southwest Nigeria.

Materials and Methods

Study design and subjects selection

This cross sectional study was carried out at the Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Osogbo; Osun State and Federal Teaching Hospital, Ido-Ekiti, Ekiti State Nigeria. Both healthcare institutions are modern teaching hospitals that are attended as both primary care hospitals and referral centers in communities around Osun State, Ekiti State and some other localities in Oyo and Ondo States of Southwest Nigeria. A total of four hundred and five participants (405) were randomly recruited for this study from these facilities using simple random sampling method between November, 2018 and April, 2019. The study participants comprised two hundred and seventy (270) pregnant women attending antenatal clinics of these hospitals who were selected equally from each facility and another one hundred and thirty-five (135) age-and socio-economic status matched apparently healthy non-pregnant women from the hospitals vicinity as control subjects. LAUTECH Teaching Hospital, Osogbo, Nigeria on 20th May,2018 with protocol number LTH/EC/2018/05/415. Federal Teaching Hospital, Ido Ekiti, Ekiti state, Nigeria on 6th March, 2018 with protocol number ERC/2018/02/13/1015.

Pregnant women with a history or symptoms of pre-eclampsia, eclampsia, gestational diabetes, hypertension and any other previous pregnancy complications as well as those on anticoagulant therapy were excluded from the study and selection criteria for the controls were same with the study subjects. Ensuring participants have no symptoms or signs related to acute illness in the preceding one month. Ethical approvals were obtained from the Ethics Committees of both hospitals. Validated semi-structured, interviewer-administered questionnaire were administered to determine the clinical history and gestational age of the` pregnancy. Written informed consents were thereafter obtained from each study participant before

commencing the study. Blood samples were collected by a single measurement from subjects across the three trimesters of the pregnant population recruited for the study.

Sample preparation

Six (6) ml of whole blood was collected intravenously with 3 ml each dispensed into ethylene diamine tetra acetic acid (EDTA) anticoagulated bottle and 1/10 volume of 3.8% sodium citrate anticoagulated bottles and mixed properly. The sodium citrated blood was centrifuged at low speed to obtain platelet poor plasma which was dispensed into two eppendorf tubes and stored at -20°C for subsequent analysis of the coagulation biomarkers. The EDTA anticoagulated blood was immediately analysed for the platelet count and haemoglobin electrophoresis.

Haematological analysis

Platelet count of participants was analysed using the Mindray Haematology autoanalyser 5000BC[26] with suitable cell packs according to the manufacturer's instruction and the haemoglobin genotype electrophoresis determined using the alkaline electrophoresis as described by the International Council for Standardization in Haematology.[27,28]

Coagulation assay

Coagulation biomarkers including Prothrombin time (PT) and Activated partial thromboplastin time (APTT) were assessed using Diagen (Diagnostic Ltd., UK) reagents Lot T85 and the International Normalized Ratio (INR) calculated as specified for Diagen reagent, Diagnostic Ltd.[28] The plasma concentration of D-dimer was evaluated quantitatively by Immunoturbidimetric determination of fibrin degradation using Cobas Tina quant D-Dimer Gen 2 reagent (Cat No. 05077753-190) on Cobas C111 (Roche) analyser in which 5 ul of plasma sample was diluted with 10 ul of water diluents, 90 ul of reagents R1 (TRIS/HCl buffer: 250 mmol/L) and SR (Latex particles coated with monoclonal anti-human D-Dimer antibodies (mouse)) were added to the dilution respectively, then the analyser was operated based on manufacturers' instructions which were strictly adhered to for the procedure. The level of activated Protein C resistance was determined using COATEST™ APC™ Resistance V assay Cat No. 82312063 (Chromogenix, Diapharma, Bedford, USA) as described by the manufacturer and also applied in similar study.[29] The frozen plasma samples were rapidly thawed at 37°C in a standardised way ensuring negligible loss of activity of labile coagulation factors and absence of cryoprecipitate then a sufficient volume of CaCl2 and APC/CaCl2 was pre-warmed at 37 ± 0.5°C. Exactly 50 ul of sample plasma or control plasma with 200 ul of V-DEF Plasma were pre-diluted (1:4) (the pre-diluted plasma were analysed within 45 minutes as required by the manufacturer), then one volume (100 ul) of the pre-diluted plasma and an equal volume (100 ul) of the APTT reagent was added in a tube at 37°C for 5 minutes. Thereafter, one volume (100 ul) of $CaCl_2$ was added simultaneously timing of clot formation was started and recorded. A second analysis was performed on the plasma, exchanging $CaCl_2$ with APC/$CaCl_2$ and the time for clot formation was recorded.

The factor V related APC ratio for the samples and controls were calculated as:

APC -V ratio = Clot time APC/$CaCl_2$/Clot time $CaCl_2$

Statistical analysis

Data were analysed using SPSS version 25.0. Student "t"-test was used to compare means and other variables and Analysis of variance (ANOVA) was used to determine the level of uniformity among the study groups at $P < 0.05$. Chi-square test was used to test for association between categorical variables, with the level of significance set at ≤0.05.

Results

Coagulation assessment of pregnant and non-pregnant participants

Coagulation biomarkers which include platelet count, PT, INR, APTT, D-dimer and APC-V ratio were assessed in the pregnant and non-pregnant control groups [Table 1]. There was a significant decrease ($p < 0.05$) in the platelets of the pregnant group compared to the non-pregnant control group with some pregnant participants having notable decrease in platelet count. The PT and INR were reduced significantly ($p < 0.05$) in the pregnant group than the non-pregnant control group. Plasma level of D-dimer was significantly ($p < 0.05$) increased in the pregnant group compared to the control (non-pregnant) group. However, the APTT and APC-V ratio showed no significant ($p > 0.05$) difference among the various study groups. Likewise, there was no significant ($p > 0.05$) difference in the coagulation biomarkers across the three trimesters of the pregnant group when compared together.

Furthermore, 13% of the study participants (35 subjects) had decreased PT/INR, APTT and elevated D-dimer level collectively, while 14.8% of the study population (39 subjects) had increased PT/INR, APTT and D-dimer levels. Three (3) participants

Table 1: Coagulation profile of pregnant and non-pregnant subjects

Variables	Group		*P*
	Control	Pregnant	
Plt ($\times 10^9$/L)	289.11±41.15	169.33*±41.83	0.000
PT (s)	13.48±1.37	10.50*±1.36	0.000
INR	1.19±0.28	1.08*±0.14	0.000
APTT (s)	33.67±1.75	33.88±5.92	0.690
D-dimer (ugFEU/ml)	0.49±0.12	1.85*±0.99	<0.001
APC-V ratio	2.68±0.72	2.66±0.84	0.660

Plt: Platelet count; PT: Prothrombin time; APTT: Activated Partial Thromboplastin time; INR: International normalised ratio; APC-V: Activated protein C-factor V ratio. Values represent mean±SD (n=405) and are significantly different at P<0.05. * Significantly different from Control group at P<0.05

comprising two pregnant subjects who were part of the 13% with collective decreased PT/INR, APTT and increased D-dimer, and one control non-pregnant subject having normal PT/INR, APTT and increased D-dimer had reduced APC-V ratio (<2.0) within the study period thereby giving a 0.7% prevalence of APCr [Figure 1].

Coagulation assays across haemoglobin genotypes

The haemoglobin (Hb) genotypes of the pregnant and non-pregnant groups were assessed and represented in Table 2. There were more HbAA (198) than the HbAS (72) subjects in the study respectively. No significant ($p > 0.05$) difference in the platelet count, INR, APTT and D-dimer of the various haemoglobin genotypes when compared across board. However, the APC-V ratio was significantly ($p < 0.05$) decreased in the HbAS compared to the other groups.

Discussion

Pregnancy complications has been described as the leading cause of maternal mortality in Southern Asia and sub-Saharan Africa with Nigeria having the second highest number of annual maternal deaths, constituting 14% of all maternal deaths globally.[4,30] The impact of pregnancy on some basic coagulation biomarkers was analysed by evaluating some haemostatic screening assays, circulating levels of D-dimer in the plasma of control and pregnant groups. The reduction in platelet counts of the pregnant group with indicators of mild thrombocytopenia in some participants is suggestive of gestational thrombocytopenia; a leading cause of thrombocytopenia in pregnancy. This platelet reduction is thought to result from dilutional effects of increased plasma volume in pregnancy and destruction of platelets passing over the damaged trophoblast surface of the placenta.[31] Reduced platelet count is considered one of the early markers for all coagulation disorders like preeclampsia and DIC, subsequently necessitating the frequent investigation of thrombocytopenia in pregnancy at various points in patients with such history.[32,33] A low platelet can also be associated with several diseases including pregnancy specific and non-pregnancy related disease such as preeclampsia, HELLP syndrome, or idiopathic thrombocytopenic purpura (ITP) as well as an indicator to other associated coagulation disorders.[34]

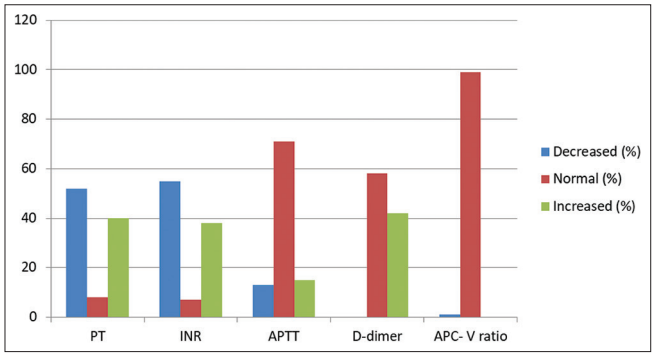

Figure 1: Effects of pregnancy on the markers of coagulation. PT: Prothrombin time; APTT: Activated Partial Thromboplastin time; INR: International normalized ratio; APC-V: Activated protein C –factor V ratio

Pregnancy is characterized by hypercoagulability resulting from an increased production of coagulation factors with reduced fibrinolysis leading to reduced PT, INR and elevated D-dimer level.[31,32] The pregnant group in this study also had reduced PT/INR with some of the pregnant subjects having low PT with increased APTT and elevated D-dimer levels than the non-pregnant control group correlating with the studies by Einass *et al.* and Akinsegun *et al.*[31,32] Pregnancy associated hypercoagulability is considered physiological, preserving placental function in pregnancy and prevents significant blood loss during delivery. This may however increase the risk of thrombosis and placental vascular complications subsequently.[32] D-dimer is a by-product of crosslinked fibrin degradation and its presence represents activation of the fibrinolytic system. The increased D-dimer level in the pregnant group may result from interactions between several fibrinolytic factors possibly to counter the increase in coagulation factors as observed in normal pregnancy,[35] with the endothelial-derived PAI-1 increasing during the later stage of pregnancy. Although detectable during the first trimester, placenta-derived PAI-2 also increases substantially throughout pregnancy.[35,36] These changes reflect an impaired fibrinolytic system which if it is consistent and detected early enough can be used to rule in/out pulmonary embolism and deep venous thrombosis using the primary care rule by Van del *et al.* (2011).[37] There was no significant difference in the APC-V ratio of the pregnant subjects in this study, which result from the infrequent APC resistance in this region. This may, therefore, account for the normal range of APC-V ratio among the study groups; nevertheless a study has established the presence of APC resistance in Nigeria.[29]

Although no significant difference in the coagulation biomarkers across the three trimesters of the pregnant group, the platelet count, PT, APC-V ratio and INR were however higher in the first trimester than the others. The gradual reduction in these coagulation biomarkers with increasing gestational age suggests an increased rate of coagulation in the system, evidenced

Table 2: Coagulation assessment of the various haemoglobin genotypes

Hb Genotypes	Platelet (10^9/L)	Variables				
		PT (secs)	INR	APTT (secs)	D-dimer (ugFEU/L)	APC-V ratio
AA (*n*-198)	176.72±45.60	11.12±1.79	1.88±0.51	31.46±5.96	0.83±0.91	2.56±0.63
AS (*n*-72)	161.97±48.94	11.11±1.66	1.81±0.50	33.06±5.88	0.89±1.22	2.20±0.37
P	0.113	0.216	0.535	0.348	0.952	0.010*

HCT: Haematocrit, Hb. Conc: Haemoglobin concentration, Plt: Platelet count, PT: Prothrombin time, APTT: Activated Partial Thromboplastin time, INR: International normalised ratio, APC-V: Activated protein C-factor V ratio. Values represent mean±SD (*n*=405) and are significantly different at $P<0.05$. * Significantly different from Control group at $P<0.05$

by the increase in D-dimer levels from the second trimester through the third trimester. This increase in D-dimer and fibrin degradation products concentration is suspected to results from the increased plasminogen levels and a corresponding decrease in the α2-antiplasmin during pregnancy which then enhances fibrinolysis, resulting in increased D-dimer levels with gestational age. Activation of coagulation in pregnancy is maximal at the third trimester, and similar to this study; lowest PT results have been reported in the third trimester of pregnant women.[38,39] APTT was also increased across the trimesters in the pregnant group, which may therefore explain the increased consumption of the coagulation factors in most of the subjects. This contradicts the findings of Ibeh *et al.* (2015),[40] where APTT was reduced in the third trimester compared to the first trimester. However, D-dimer levels increased across the trimesters. A major complication of haemoglobinopathy is endothelial dysfunction and tissue injury, occurring as a result of prolonged inflammation and oxidative stress.[41] HbSS and HbSC pregnant women present with maternal and foetal complications that results in morbidity and mortality if specialized multidisciplinary and personalized antenatal monitoring and management of the patients are not properly engaged.[42,43] In this study however, the HbAA and AS had no significant effect on the coagulation biomarkers, however, there was a reduced APC-V ratio in the HbAS pregnant subjects.

Additionally, 13% of the pregnant subjects had reduced platelets, PT/APTT and increased D-dimer concentration with associated pain in the lower extremities which are indicators of thrombotic incidences in DVT. These could indicate development of thrombosis in pregnant subjects' deep vein as the lower extremities pain present in some of the subjects prior to pregnancy became aggravated during pregnancy. In this study, 14.8% of the pregnant subjects had reduced platelet, prolonged PT/APTT and elevated D-dimer level, and this may indicate an onset of consumption coagulopathy which if not well managed could result in pregnancy complications or mortality. Exactly 0.7% of the participants with or without thrombotic tendencies were positive for the activated protein C resistance, supporting the lower extremities pain experienced by some study subjects. This is consistent with other studies on the prevalence of APC resistance among the Nigerian and Lebanese population respectively[43,44] as well as some supporting observation from some other regions.[45] The findings of this study underscore the prevalence of APC resistance in the indigenous population in this region despite the dearth of information on the condition in Africa. One limitation of the study is the recruitment of participants basically from the tertiary health institutions which may not adequately represent the total population of parturients in Southwest Nigeria. We were also not able to follow-up on participants' delivery outcome for further assessment of a correlation between coagulation and pregnancy outcomes.

Conclusion and Recommendation

The hypercoagulable state of pregnancy was reaffirmed in this study with pregnant subjects having significantly reduced coagulation indices and increased D-dimer levels when compared with controls. The notably reduced platelet in some participants is suggestive of gestational thrombocytopenia which is a marker of onset of pregnancy induced coagulation disorders such as preeclampsia. The presence of activated protein C resistance was also established through this study at a prevalence rate of 0.7% while 13% and 14.8% of the participants had coagulation biomarkers relating to thrombotic disorders and onset of consumption coagulopathy.

A holistic review of the monitoring respectively and evaluation strategies for pregnant women during antenatal clinics to include more definite assays such as the D-dimer as well as routine monitoring of coagulation profile would extensively reduce complicated incidences leading to maternal mortality in this region. Proper implementation of monitoring approaches will therefore contribute immensely to early diagnosis and intervention for pregnancy-associated coagulopathies when evaluating female reproductive health through specific diagnostic tests at the the primary care setting before referral to specialist centres when needed. Further studies with larger participants' size are therefore recommended to assess the correlation of pregnancy outcomes with coagulation disorders and other haemoglobin variants.

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The authors certify that they have obtained appropriate consent from all participants. In the form that each participant gave their consent for their clinical information to be reported in the journal and they understood that their names and initials will not be published as due efforts will be made to conceal their identity.

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Conflicts of interest

There are no conflicts of interest.

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