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Prothrombin time and Activated Partial Thromboplastin time in Pregnant Women in Southern Nigeria

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ABSTRACT

The incidence of bleeding during and after child birth has become an issue of concern in maternal health. Prothrombin time and activated partial thromboplastin time in antenatal women in the three trimesters were studied in Southern Nigeria. 120 subjects were recruited for the study, consisting of 30 pregnant women each at first, second and third trimesters and 30 non pregnant women as the control. The tests were carried out using standard techniques. The result of the PT showed no statistically significant ($P>0.05$) difference in the first and third trimesters except in the second trimester ($P<0.05$). Activated partial thromboplastin time increased significantly in all the trimesters when compared with the control group. A decrease in coagulation factors of the intrinsic pathway could be responsible for the prolonged APTT in all the trimesters.

INTRODUCTION

The process of haemostasis is a dynamic and delicate equilibrium between coagulation and fibrinolysis. Coagulation results from an interaction among vessel walls, platelets and coagulation factors (Norris, 2003). Following endothelial damage, platelets adhere to the subendothelium forming a platelet plug which then becomes permanent with fibrin deposition (Norris. 2003). Clot formation is limited by antithrombin (AT) and proteins C and S. The fibrinolytic system functions to maintain the fluid state through the breakdown of fibrin by plasmin. Plasmin is generated from plasminogen by the action of tissue plasminogen activator (t-PA). Pregnancy is associated with changes in haemostasis, including an increase in the majority of clotting factors, a decrease in the quantity of natural anticoagulants and a reduction in fibrinolytic activity. (Bremme, 2003; Dahlman *et al.*, 1985; O'Riordan and Higgins, 2003). These changes result in a state of hypercoagulability (Bremme, 2003; and O'Riordan and Higgins, 2003), are likely due to hormonal changes (Sattar *et al.*, 1999) and increase the risk of thromboembolism.

The increase in clotting activity is greatest at the time of delivery with placental expulsion; releasing thromboplastic substances (Dahlman *et al.*, 1985). These substances stimulate clot formation to stop maternal blood loss. As placental blood flow is up to 700ml/min, considerable hemorrhage can occur if clotting fails. Coagulation and fibrinolysis generally return to pre-pregnant levels 3–4weeks postpartum (Bremme, 2003; Dahlman *et al.*, 1985).

The prothrombin time was described by Quick in 1935 and the test was often referred to as 'Quick's Prothrombin Time. The prothrombin time was developed to measure prothrombin (Factor II) and hence its name. However, it subsequently became clear that it was sensitive to abnormalities of factors VII, X, V, II and fibrinogen. The activated partial thromboplastin time (APTT) is a global plasma coagulation test affected by abnormalities in the intrinsic (factors XII, XI, VIII, IX, prekallikrein, and high molecular weight kininogen) and common portions of the classic coagulation pathway. The concept of separate intrinsic and extrinsic pathways of coagulation is useful for understanding and diagnosing blood coagulation abnormalities in vitro, however it should be appreciated that in vivo there are interactions between the two pathways outside of the classic scheme. The APTT will generally be prolonged when a clotting factor level is less than 30-40%.

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Since the normal range for most clotting factors is 50-150% (and 70-130% for factor XI), a normal APTT does not rule out the possibility of a mild factor deficiency (Clinlab Navigator. 2003). As most coagulation factors increase in normal pregnancy, the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are shortened. The PT and its derived measure, international normalised ratio (INR), test for factors such as FII, FV, FVII, FX and fibrinogen. Some nutritional deficiencies and/or liver disease will decrease these factors prolonging the PT. Furthermore, PT and APTT may be artificially prolonged due to the presence of an antiphospholipid antibody (APLA), such as lupus anticoagulant. In fact, patients with APLA are prothrombotic. The APTT is considered a good screening test for deficiencies of FVIII, FIX, FXI and FXII. The APTT may be prolonged by the presence of an APLA and/or unfractionated/standard heparin (SH). To differentiate between the presence of an APLA and a factor deficiency, the patient's plasma is mixed 50:50 with normal plasma. If the APTT remains abnormal an APLA is present (Thornton and Douglas, 2010).

Pregnancy is a risk factor for venous thrombosis and the incidence of venous thromboembolism during normal pregnancy is 6-fold higher than in the general female population of child bearing age. Venous thromboembolism is an important cause of maternal morbidity and mortality. The coagulation cascade is in an activated state in pregnancy. Activation includes increased concentrations of all clotting factors, except factors XI, XIII, with increased levels of High molecular weight fibrinogen complexes. Changes in the haemostatic mechanism also involve decreased levels of anticoagulant proteins such as protein C and Protein S as well as enhanced thrombin generation and decreased fibrinolytic activity (Srimala *et al.*, 2013).

Although there are data regarding reference range of prothrombin time and activated partial thromboplastin time in normal pregnancy, to our own knowledge none has been reported in our environment, hence the present study was designed to investigate to what fashion normal pregnancy will affect prothrombin time and activated partial thromboplastin time tests in Southern Nigeria.

SUBJECTS AND METHODS

Blood samples were randomly collected from 90 apparently healthy uncomplicated pregnant women who attended the routine ante-natal clinics in Southern Nigeria and from 30 apparently healthy non pregnant women, which served as controls. Both subjects and controls were randomly chosen from the general population of women. All subjects gave informed consent to participate in the study. 7 ml of venous blood was collected from each subject, 4.5 ml dispensed into 0.5 ml 3.2% trisodium citrate anticoagulant bottle and mixed by gentle inversion. This was spun for 10 minutes at 3000 rpm; the supernatant citrated plasma was collected and used to determine the prothrombin time and activated partial thromboplastin time tests using standard techniques as described by Dacie and Lewis (2001). The remaining 2.5 ml of blood was dispensed into plain specimen bottle and was used for blood grouping. All samples were analyzed within two hours of collection.

Prothrombin time test (Dacie and lewis, 2001)

Specimen was centrifuged to obtain platelet poor plasma. 0.2ml of thromboplastin-calcium reagent was pipetted into pre warmed test tube; 0.1ml of patient's plasma was added to it and the stop watch started simultaneously. The tubes were gently tilted for exactly 2-3 seconds interval back and forth in the water bath at 37°C until clot was formed and time recorded. Each test and control plasma was performed in duplicate.

Activated partial thromboplastin time test (Dacie and Lewis, 2001)

Specimen was centrifuged to obtain platelet poor plasma. 0.1ml of plasma was pipetted into test tube; 0.1ml of kaolin/platelet substitute was added to it. The contents of the tube were mixed quickly and placed in a 37^0C water bath for 5 minutes. 0.1ml of pre warmed calcium chloride was added into the tube and the stop watch started simultaneously. The tubes were gently tilted for exactly 3-5 seconds interval back and forth in the water bath till clot was formed and time recorded. Each test and control plasma was performed in duplicate.

STATISTICAL ANALYSIS

Data collected were analyzed using SPSS 17.0 of windows statistical package. P-value ≤0.05 were considered as significant while P-values >0.05 were considered not significant.

RESULT

Tables 4.1 and 4.2 show comparison of mean ±standard deviation of prothrombin and activated partial thromboplastin time and control group of pregnant women in different trimesters Prothrombin time (PT) in the first, second and third trimesters did not rise above the control. There was a significant reduction in the PT value during the second trimester.

Table 4.1: Comparison of Mean ± SD of prothrombin time (PT) values of the test and control group

Control (Sec)	First Trimester (Sec)	Second Trimester (Sec)	Third Trimester(Sec)
13.39 ± 1.51	13.12 ± 1.32	12.14 ± 0.79 *	13.24 ± 1.12

* Indicates significant difference where p value is ≤ 0.05

Table 4.2: Comparison of Mean ± SD of Activated partial prothrombin time (APPT) values of the test and control group.

Conrol (Sec)	First Trimester (Sec)	Second Trimester (Sec)	Third Trimester(Sec)
32.78 ± 1.40	35.97 ± 1.24*	38.88 ± 1.28*	35.02 ± 1.17*

* Indicates significant difference where p value is ≤ 0.05

The activated partial prothrombin time (APPT) values increased during pregnancy when compared with the control. A significant increase in APPT was observed during pregnancy particularly during the second trimester.

DISCUSSION

Haemostasis in normal pregnancy involves a complex network of interactions with positive and negative feedback loops, integrating blood vessels; platelets, coagulation factors, coagulation inhibitors and fibrinolysis and has evolved to maintain the integrity of the vasculature. Normal pregnancy is associated with substantial changes in the tissue factor pathway and in the wider haemostatic system. Normal pregnancy is characterized by impressive changes in the activating and inhibitory pathways of coagulation and fibrinolysis resulting in an accelerated, but well balanced, process of thrombin formation and resolution. These changes serve to protect the mother from the hazard of bleeding imposed by placentation and delivery, but they also carry the risk of an exaggerated response, localized or generalized, to coagulant stimuli. Hemorrhage occupies an important position in the etiology of maternal mortality and therefore, remains a major problem.There is activation of blood coagulation and a simultaneous increase in fibrinolysis without signs of organ dysfunction during normal pregnancy. These changes increase as pregnancy progresses. During delivery there is consumption of platelets and blood coagulation factors including fibrinogen (Strimala *et al.*, 2013).

In this study, prothrombin time assesses the extrinsic pathway of coagulation and is sensitive to factors VII, X, V, II and fibrinogen. Also partial activated thromboplastin time assesses the intrinsic pathway of coagulation and is sensitive to deficiencies of factors I, II, VIII, IX, X, XI, XII. The result of the present study reveals that prothrombin time showed no statistically significant difference when first and third trimesters were compared with the control group. This indicates that pregnancy is not likely to have any adverse effect on prothrombin time. This result is consistent with an earlier report by Cerneca *et al.,* (1997) who recorded no change in the mean prothrombin time values among pregnant women while there was a statistically significant difference when second trimester was compared with the control group. This was in line with the earlier report by Buseri *et al.,* 2008, Temal *et al*., (2007) who recorded an increased prothrombin time values among pregnant women. The increase in the second trimester could be as a result of physiological changes for the fact that prothrombin time values were not significant in the first and third trimesters. Activated partial thromboplastin time recorded statistically significant increase in the first, second and third trimesters when compared with the control group. This might be attributed to the physiological changes in the maternal haemostatic system arising from the concentration of foetal haemoglobin in the maternal circulation. It is also not clear if antenatal drugs have significant effect on activated partial thromboplastin time. It is concluded that activated partial thromboplastin time should be interpreted with caution during pregnancy.

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