

## Altered Haemostatic Values During Pregnancy in North–West Nigeria: Do Maternal Age and Parity Play Any Role?

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### Abstract

**Background:** Normal pregnancy has been associated with alteration of the haemostatic system which has been linked to increased risk of thromboembolism. The study determined the haemostatic parameters in pregnant women in Kano, North-West Nigeria.

**Materials and Methods:** One hundred and fifty pregnant women, aged 17-40 years and 100 age-matched non-pregnant women were enrolled for the study between August 2010 and October 2011 in Aminu Kano Teaching Hospital, Kano. Blood samples collected were analysed for prothrombin time (PT) and partial thromboplastin time with kaolin (PTTK) using Diagen reagents and platelet count using manual method while factors VII and VIII activities were determined according to manufacturers' instructions of TECO kits and Cormay KG coagulometer.

**Results:** There were significantly lower value of platelet count and higher value of factor VIII activity of  $(248.2 \pm 78.8) \times 10^9/L$  and  $110.7 \pm 46.6\%$  in pregnant women compared to  $(289.4 \pm 68.7) \times 10^9/L$  and  $96.8 \pm 38.2\%$  respectively, in non-pregnant women ( $P < 0.05$ ) while the values of PT, INR, PTTK and factor VII activity in pregnant and non-pregnant women showed no significant differences ( $P > 0.05$ ). Gestation period showed significant effects on PTTK and factor VII activity during pregnancy ( $P < 0.05$ ) but had no effects on platelet count, PT and factor VIII activity while insignificant increased values of factors VII and VIII activities, and increased parity were observed at the age-group 35-40 years.

**Conclusion:** Changes in the haemostatic parameters in pregnancy are associated with reduced platelet count and increased factor VIII activity. Advanced maternal age, increased gestational age and parity may be risk factors for thrombosis. It is recommended that factors VII and VIII assays be included in routine antenatal tests.

**Keywords:** Altered; Haemostatic values; Pregnancy; North-West Nigeria

### Introduction

Haemostasis is a complex interaction between the vessel wall and components of blood which prevents excessive blood loss after vascular damage while maintaining a viable circulation by preventing thromboembolic conditions [1]. It is regulated by vascular wall, platelets and coagulation cascade by a set of processes to maintain blood in a fluid, clot-free state and to induce a rapid and localised haemostatic plug at the site of vascular injury [2,3].

Pregnancy is recognised as a hypercoagulable state that protects women from potentially catastrophic haemorrhage during placentation and the post-partum period [4]. Normal pregnancy has been associated with alteration of the haemostatic system which has been linked to increased risk of thromboembolic complications [5,6]. The incidence of venous thromboembolism (VTE) during pregnancy has been estimated to be approximately 1 per 1000 deliveries and this has been found to be 5.5-6 times higher than the general female population of child-bearing age [7].

During normal pregnancy, increased levels of coagulation factors XIII, XII, X, VIII and VII have been reported by earlier authors [8-13] while physiologically reduced coagulation factor XI has been documented probably to counter-balance the increases in other coagulation factors [14] but the reports of factor II (prothrombin) remains inconclusive [10-13].

However, subsequent study has shown that the levels of coagulation factors II, V, X, XI, XII and antithrombin, protein C, Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT) remained largely unchanged during pregnancy, delivery and post-partum as they have been observed to be within the non-pregnant reference intervals [15].

Conflicting reports on PT have been documented in Nigeria as prolonged PT was observed by some authors [16,17] reduced PT was reported by Durotoye et al. [18] while other study showed no significant difference [19]. Similar divergent views have been expressed on APTT during pregnancy as reduced APTT was documented by earlier authors [4,20] and other researchers reported prolonged APTT [17,21] while other study showed no significant difference [19].

Pregnancy has been associated with reduced platelet count [22-25] but Buseri et al. [17] reported increase in platelet count while other researchers reported no significant difference or change in platelet count [4,16,26].

This study in Kano, North-Western Nigeria was necessitated by the scanty information available in this region and conflicting reports on haemostatic parameters in pregnant women who are prone to haemorrhage and thromboembolism.

## Materials and Methods

This study was conducted on 150 pregnant women who attended ante-natal clinic in Aminu Kano Teaching Hospital (AKTH), Kano and 100 non-pregnant women (controls) from AKTH and Kano metropolis, aged 17-40 years, after the approval from ethnical Committee of Aminu Kano Teaching Hospital, Kano between August, 2010 and October, 2011. Pregnant and non-pregnant women with histories of recurrent miscarriages, liver disease, renal disease, diabetes and hypertension and non-pregnant women who are on oral contraceptives were excluded from the study. Informed consent was obtained from all the subjects.

6 ml of venous blood sample was collected from each subject and 4.5 ml of the blood was mixed with 0.5 ml of 32.0 g/L trisodium citrate solution while the remaining 1.5 ml of the blood was put into EDTA container to the final concentration of 1.5 mg/ml. Blood samples in the citrated containers were centrifuged at 2,500 g for 15 minutes and the

plasma separated into plastic containers for manual analyses of prothrombin time (PT) and Partial Thromboplastin Time with Kaolin (PTTK) using procedures of Diagen reagents manufactured by Oxon, UK while factors VII and VIII activities were determined according to the instructions of the TECO kits with catalogue numbers of P5200-010 and P300-010 respectively, manufactured in Germany and Clotting times determined using Cormay KG coagulometer manufactured in Poland. EDTA blood sample was used for manual platelet count determination [27].

## Statistical Analysis

The mean values and standard deviations determined and the differences between the values were assessed using student's t-test and one-way analysis of variance. P-values of less than 0.05 were considered significant.

## Results

Table 1 shows haemostatic values in pregnant and non-pregnant women. Pregnant women had significantly lower mean value of platelet count ( $248.2 \pm 78.8$ )  $\times 10^9/L$  compared to the value ( $289.4 \pm 68.7$ )  $\times 10^9/L$  in the control subjects and significantly higher value of factor VIII activity ( $110.7 \pm 46.6\%$ ) compared to the value ( $96.8 \pm 38.2\%$ ) for non-pregnant subjects ( $P < 0.05$ ) while the values of PT, INR, PTTK, and factor VII activity in pregnant and non-pregnant women showed no statistically significant differences ( $P > 0.05$ ).

Parameter	Non-pregnant women (controls)	Pregnant women	P-value
Number of subjects	100	150	
Platelet count ( $\times 10^9/L$ )	$289.4 \pm 68.7$	$248.2 \pm 78.8$	$< 0.05$
PT (seconds)	$15.1 \pm 1.2$	$14.9 \pm 1.6$	$> 0.05$
International Normalized Ratio (INR)	$1.11 \pm 0.1$	$1.09 \pm 0.16$	$> 0.05$
PTTK (seconds)	$47.46 \pm 5.6$	$47.47 \pm 8.1$	$> 0.05$
Factor VII activity (%)	$89.3 \pm 39.0$	$96.0 \pm 36.6$	$> 0.05$
Factor VIII activity (%)	$96.8 \pm 38.2$	$110.7 \pm 46.6$	$< 0.05$

**Table 1:** Haemostatic values in pregnant and non-pregnant women.

Changes in haemostatic parameters with gestation period (trimester) are summarised in Table 2. Differences in the fluctuated PTTK values ( $50.8 \pm 6.7$  seconds,  $44.1 \pm 7.2$  seconds and  $49.9 \pm 8.1$  seconds) and factor VII activities ( $72.0 \pm 21.7\%$ ,  $107.2 \pm 41.5\%$  and

$94.1 \pm 31.0\%$ ) with regard to first, second and third trimesters respectively, showed significance ( $P < 0.05$ ) while the values of platelet count, PT, INR and factor VIII activity with regard to first, second and third trimesters showed no significant differences ( $P > 0.05$ ).

Parameter	1st Trimester	2nd Trimester	3rd Trimester	P-value
Number of subjects	24	66	60	
Platelet count ( $\times 10^9/L$ )	$249.1 \pm 75.0$	$239.8 \pm 87.8$	$257.0 \pm 69.0$	$> 0.05$
PT (seconds)	$15.1 \pm 0.99$	$14.9 \pm 2.2$	$14.7 \pm 0.99$	$> 0.05$
International Normalized Ratio (INR)	$1.11 \pm 0.1$	$1.09 \pm 0.22$	$1.07 \pm 0.1$	$> 0.05$
PTTK (seconds)	$50.8 \pm 6.7$	$44.1 \pm 7.2$	$49.9 \pm 8.1$	$< 0.05$
Factor VII activity (%)	$72.0 \pm 21.7$	$107.2 \pm 41.5$	$94.1 \pm 31.0$	$< 0.05$

Factor VIII activity (%)	102.4 ± 47.1	112.1 ± 48.2	112.6 ± 46.2	>0.05
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**Table 2:** Changes in haemostatic parameters with gestation period (trimester).

Table 3 indicates the effect of maternal age on haemostatic parameters. The different values of platelet count, PT, INR, PTTK, factors VII and VIII activities with regard to age groups 17-22 years, 23-28 years, 29-34 years and 35-40 years of pregnant women respectively, showed no significance (P>0.05). However, age group 35-40 years showed the highest values of factors VII and VIII activities of 111.9 ± 39.8% and 127.6 ± 52.5% respectively.

Parameter	17-22 years	23-28 years	29-34 years	35-40 years	P-value
Number of subjects	24	67	48	11	
Platelet count (X10 <sup>9</sup> /L)	244.1 ± 86.2	253.2 ± 76.4	248.3 ± 78.6	239.2 ± 93.2	>0.05
PT (seconds)	14.9 ± 2.0	14.9 ± 1.3	14.7 ± 2.0	15.2 ± 1.1	>0.05
International Normalized Ratio (INR)	1.09 ± 0.19	1.09 ± 0.13	1.07 ± 0.2	1.12 ± 0.12	>0.05
PTTK (seconds)	46.1 ± 7.9	47.6 ± 7.4	48.6 ± 8.9	44.1 ± 8.5	>0.05
Factor VII Activity	100.1 ± 37.9	95.0 ± 34.6	93.0 ± 39.4	111.9 ± 39.8	>0.05
Factor VIII activity (%)	100.4 ± 44.3	114.6 ± 46.6	105.9 ± 45.7	127.6 ± 52.5	>0.05

**Table 3:** Effect of maternal age on haemostatic parameters.

Table 4 shows the parity influence on haemostatic parameters. The fluctuated and different values of platelet count, PT, INR, PTTK, factors VII and VIII activities with regard to parity of 0-3 showed no significance (P<0.05). Increased parity showed the high values of factor VII activity (100.0 ± 38.7%) and factor VIII activity (112.2 ± 47.5%).

Parameter	0 parity	1-2 parity	≥ 3 parity	P-value
Number of subjects	42	51	57	
Platelet count (X10 <sup>9</sup> /L)	251.1 ± 88.1	242.9 ± 77.6	250.7 ± 73.6	>0.05
PT (seconds)	14.9 ± 1.87	14.9 ± 1.70	14.8 ± 1.35	>0.05
International Normalized Ratio (INR)	1.09 ± 0.18	1.09 ± 0.18	1.08 ± 0.14	>0.05
PTTK (seconds)	46.3 ± 7.3	46.5 ± 7.3	49.4 ± 9.0	>0.05
Factor VII Activity	93.6 ± 36.8	94.5 ± 35.0	100.0 ± 38.7	>0.05
Factor VIII activity (%)	106.9 ± 46.0	112.2 ± 46.3	112.2 ± 47.5	>0.05

**Table 4:** Parity influence on haemostatic parameters in pregnant women.

## Discussion

In normal pregnancy, marked increase in the procoagulant activity in the maternal blood is characterized by elevation of factors VII, X, VIII, fibrinogen and Von-Willebrand factor [28]. However, scanty information and conflicting reports from earlier authors on haemostatic parameters during pregnancy [16-20] necessitated this study in Northern Nigeria.

This study has shown significantly lower value of platelet count during pregnancy compared to the control subjects. This is in line with some authors [23-25] but other researchers reported no significant difference between pregnant and non-pregnant women [4,16,26]. The divergent views may be associated with improper sample collection, techniques employed and variation in sample sizes among other factors. However, reduced platelet count in pregnancy has been linked to haemodilution and accelerated platelet consumption [29,30].

There was no significant change in prothrombin time (PT) in normal pregnant women compared to the control subjects in this study. This finding is consistent with the previous authors [15,19,31] but disagrees with the prolonged PT reported by other authors [16,17] and the reduced PT documented by Durotoye et al.[18]. However, variation of PT results may be associated with poor storage of plasma samples and reagents, improper sample collection and methodology employed.

The study has revealed that PTTK showed no significant difference in pregnant women compared to the control subjects. This finding agrees with earlier researchers [19,31] but disagrees with prolonged reports from previous studies [17,21] and reduced APTT report documented by Hellgren [4] and Della et al. [20]. Inconsistent PTTK results by various authors may be linked to poor storage of plasma samples and reagents, improper sample collection and techniques employed.

Factor VII activity in pregnant women is yet to be documented in Nigeria. This study has further revealed insignificant increase in factor VII activity during pregnancy which is in line with the earlier reports [10,15]. However, elevated factors VII and VIII activities, von-Willebrand factor and fibrinogen during pregnancy have been associated with thrombophilia [32].

This study has demonstrated significantly higher factor VIII activity during pregnancy. This finding has further confirmed previous reports [10,15,17]. However, elevated factor VIII activity has been associated with recurrent early pregnancy loss [33].

The study has further demonstrated that maternal age and parity had no significant effects on haemostatic parameters during pregnancy and these agree with the earlier reports [17,18] but the elevated values of factors VII and VIII and activities observed in pregnant women with advanced maternal age and increased parity may put pregnant women at risks for thrombosis.

This study has further shown that gestation period had no significant effects on platelet count, PT, INR and factor VIII activity which further confirmed earlier reports [15,25,31] while significant

effects were observed on PTTK and factor VII activity. However, factor VII activity fluctuated significantly during pregnancy.

In conclusion, changes in the haemostatic parameters during pregnancy in this study are associated with reduced platelet count and increased factor VIII activity. However, advanced maternal age, increased gestational age and parity may be risk factors for thrombosis during pregnancy. It is recommended that platelet count, factors VII and VIII assays be part of routine antenatal tests to avoid complications during pregnancy.

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