

## Haemostatic Changes during Pregnancy and Puerperium in Kano, North-Western Nigeria

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### Abstract

**Aim:** Normal pregnancy is associated with haemostatic changes which have been linked to a complex physiological adaptation but these changes return to that of non-pregnant state at about 4 weeks of post-delivery. This study was undertaken to monitor the haemostatic changes during pregnancy and puerperium in North-Western Nigeria.

**Materials and methods:** Ten pregnant women, aged 17-40 years were monitored for haemostatic changes from the first trimester to 6 weeks after delivery between August 2010 and October 2011 at Aminu Kano Teaching Hospital, Kano. Blood samples collected for platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrin degradation products (FDP), fibrinogen level, d-dimer, protein C, factors VII and VIII activities were analysed using standard laboratory techniques.

**Results:** There were significantly lower values of platelet count, factor VIII concentration and protein C activity of  $275.5 \pm 4.14 \times 10^9/L$ ,  $93.2 \pm 31.6\%$  and  $56.7 \pm 13.4\%$  during pregnancy compared to  $378.5 \pm 74.0 \times 10^9/L$ ,  $122.5 \pm 3.0\%$  and  $97.1 \pm 14.6\%$  respectively, during puerperium. The values of PT, factor VII concentration, fibrinogen level, FDP and D-dimer concentrations during pregnancy and puerperium showed no significant differences ( $P > 0.05$ ). Factors VII and VIII concentrations increased significantly as gestation advanced ( $P < 0.05$ ).

**Conclusion:** The study concluded that changed values of platelet count, protein C and factor VIII concentrations during pregnancy, normalized at puerperal period while advanced gestation may pose a threat to pregnancy. It is recommended that protein C, factors VII and VIII concentrations be monitored during pregnancy to minimize thrombotic effect.

**Keywords:** D

### Introduction

Normal pregnancy is associated with extensive changes in haemostasis and these changes have been linked to a complex physiological adaptation, which ensures the rapid and effective control of bleeding from the placental site at the time of placental separation while allowing the expansion of the maternal and foetal circulations at the uteroplacental interface during pregnancy [1-3]. However, most of these changes in blood coagulation and fibrinolysis create a state of hypercoagulability [4] which protects the pregnant women from haemorrhage during delivery but predisposes them to thromboembolism [5]. These changes in haemostatic system during pregnancy return to normal or non-pregnant state within 4-6 weeks after delivery [6].

It has been reported that the levels of coagulation factors II, V, X, XI, XII and protein C, APTT and PT remained largely unchanged during pregnancy, delivery and postpartum as they were within the non-pregnant reference intervals [7] while plasma antithrombin III level was observed to rise significantly after normal delivery of about 2

weeks post-partum [5]. However, fibrinogen has been found to increase during pregnancy but gets consumed together with other coagulation factors and platelets during delivery [6] while d-dimer level was reported to increase with each trimester and decrease during puerperium [8,9].

This study was undertaken to monitor the haemostatic changes during pregnancy and puerperium in Kano due to the paucity of information on this subject in Nigeria as the findings could be of help in the management of pregnant women who are usually prone to thromboembolism.

### Materials and Methods

The research was conducted between August 2010 and October 2011 on ten (10) pregnant women, aged 17-40 years, who attended antenatal clinic in Aminu Kano Teaching Hospital (AKTH), Kano after the ethical approval from the ethical committee of AKTH and written informed consent were obtained. The pregnant women were monitored for haemostatic changes from the first trimester to 6 weeks after delivery.

At each visit, 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 blood was put into EDTA container to the final concentration of 1.5 mg/ml. Blood samples in the citrated containers were centrifuged at 2500g for 15 minutes and the plasma separated into plastic containers to avoid activation of clotting factors in glass containers for manual analyses of prothrombin time (PT) and activated partial thromboplastin (APTT) 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 (catalogue numbers P5200-010 and P300-010, Germany) and clotting times determined using Cormay KG coagulometer manufactured in Poland.

Protein C and antithrombin III activities were assayed according to instructions of TEChrom kits (reference numbers C1100-012 and C1000-010, Germany) and the clotting times determined using Cormay KG coagulometer while plasma fibrinogen concentration was determined using modified Clauss method (catalogue number 050-500, Poland). D-dimer and FDP were determined using latex agglutination kits of catalogue numbers 150-700 and 00541 respectively manufactured from PZ, Poland and Diagnostica Stago, France respectively while manual platelet count was determined from EDTA blood sample using haemocytometer.

### Statistical Analysis

The mean values and standard deviations of the parameters in pregnancy and puerperium were assessed using Student's t-test while the differences with regard to trimester periods and puerperium were analysed using one-way analysis of variance (ANOVA). P values of  $\leq 0.05$  were considered statistically significant.

### Results

Haemostatic changes during pregnancy and puerperium as shown in Table 1. There were significantly lower values of platelet count, factor VIII concentration and protein C activity of  $(275.5 \pm 41.4) \times 10^9/L$ ,  $93.2 \pm 31.6\%$  and  $56.7 \pm 13.4\%$  respectively during pregnancy compared to  $(378.5 \pm 74.0) \times 10^9/L$ ,  $122.5 \pm 3.0\%$  and  $97.1 \pm 14.6\%$  respectively, in puerperium while significantly higher values of APTT and antithrombin III concentration of  $47.2 \pm 4.0$  seconds and  $85.7 \pm$

$4.7\%$  respectively were observed during pregnancy compared to  $44.0 \pm 1.4$  seconds and  $82.0 \pm 2.12\%$  respectively, in puerperium. The values of PT and factor VII concentration during pregnancy and puerperium showed no significant differences ( $P > 0.05$ ).

Parameter	Pregnancy (n=10)	Puerperium (n=10)	P-value
Platelet count (10 <sup>9</sup> /L)	275.5 ± 41.4	378.5 ± 74.0	<0.05
Prothrombin time (seconds)	14.9 ± 1.14	14.5 ± 0.71	>0.05
APTT (seconds)	47.2 ± 4.0	44.0 ± 1.4	<0.05
Factor VII (%)	118.5 ± 31.8	122.5 ± 3.53	>0.05
Factor VIII (%)	93.2 ± 31.6	122.5 ± 3.53	<0.05
Protein C (%)	56.7 ± 13.4	97.1 ± 14.6	<0.05
Antithrombin III (%)	85.7 ± 4.7	82.0 ± 2.12	<0.05

**Table 1:** Haemostatic changes in pregnancy and puerperium.

Table 2 reveals changes in haemostatic parameters with gestation and during puerperium. The values of platelet count of  $(289.6 \pm 19.9) \times 10^9/L$ ,  $(267.0 \pm 68.6) \times 10^9/L$  and  $(270.0 \pm 35.8) \times 10^9/L$  for the first, second and third trimesters respectively, fluctuated and showed no statistically significant differences ( $P > 0.05$ ) but when compared to platelet count of  $(378.5 \pm 74.0) \times 10^9/L$  during puerperium, showed significant differences ( $P < 0.05$ ).

The values of factor VII activities ( $88.4 \pm 27.5$ ,  $122.0 \pm 39.6\%$  and  $145.0 \pm 28.3\%$ ), factor VIII activities ( $77.6 \pm 18.5\%$ ,  $93.0 \pm 4.24\%$  and  $109.0 \pm 72.1\%$ ), protein C activities ( $48.9 \pm 16.9\%$ ,  $58.0 \pm 18.3\%$  and  $63.3 \pm 5.09\%$ ) for the first, second and third trimesters respectively, showed statistically significant differences ( $P < 0.05$ ) while the values of PT, APTT and antithrombin III for first, second and third trimesters and puerperium showed no statistically significant differences ( $P > 0.05$ ).

Parameter P-value	First trimester (n=10)	Second trimester (n=10)	Third trimester (n=10)	Puerperium (n=10)
Platelet count (10 <sup>9</sup> /L) <0.05	289.6 ± 19.9	267.0 ± 68.6	270.0 ± 35.8	378.5 ± 74
PT (seconds) >0.05	15.2 ± 1.30	14.5 ± 0.71	15.0 ± 1.41	14.5 ± 0.71
APTT (seconds) >0.05	47.5 ± 4.93	48.5 ± 3.54	45.5 ± 3.5	44.0 ± 1.4
Factor VII (%) <0.05	88.4 ± 27.5	122.0 ± 39.6	145.0 ± 28.3	122.5 ± 3.53
Factor VIII (%) <0.05	77.6 ± 18.5	93.0 ± 4.24	109.0 ± 72.1	122.5 ± 3.0
Protein C (%) <0.05	48.9 ± 16.9	58.0 ± 18.3	63.3 ± 5.09	97.1 ± 14.6
Antithrombin III (%) >0.05	82.8 ± 7.56	88.9 ± 2.47	85.3 ± 4.1	82.0 ± 2.12

**Table 2:** Changes in haemostatic parameters with gestation and during puerperium.

Fibrinolytic changes during pregnancy and puerperium are summarized in Table 3. The values of fibrinogen concentration, fibrin

degradation products (FDP) and D-dimer during pregnancy and puerperium showed no statistically significant differences ( $P > 0.05$ ).

Parameter	Pregnancy (n=10)	Puerperium (n=10)	P-value
Fibrinogen concentration (g/L)	2.71 ± 0.34	2.40 ± 0.85 >0.05	>0.05
FDP (µg/L)	1.48 ± 0.75	1.25 ± 0.18	>0.05
D-dimer (µg/L)	0.15 ± 0.2	0.11 ± 0.18	>0.05

**Table 3:** Fibrinolytic changes in pregnancy and puerperium.

Table 4 represents changes in fibrinolytic parameters with gestation and during puerperium. Differences in the values of fibrinogen concentration, FDP and D-dimer with regard to first, second and third trimesters and puerperium showed no significance ( $P>0.05$ ).

Parameter	First trimester	Second trimester	Third trimester	Puerperium	P-value
Fibrinogen Concentration (g/L)	2.82 ± 0.3	2.65 ± 0.26	2.67 ± 0.4	2.4 ± 0.85	>0.05
FDP (µg/L)	1.13 ± 0.18	2.19 ± 1.9	1.13 ± 0.18	1.25 ± 0.18	>0.05
D-dimer (µg/L)	0.11 ± 0.18	0.23 ± 0.25	0.11 ± 0.18	0.11 ± 0.18	>0.05

**Table 4:** Changes in fibrinolytic parameters with gestation and during puerperium.

## Discussion

Haemostatic changes during pregnancy, delivery and puerperium have been linked to many haemostatic complications, morbidity of both mother and foetus [1,2,6,10]. However, the information on the monitoring of haemostatic and fibrinolytic parameters during pregnancy and to about six weeks after normal childbirth (puerperium) in Nigeria has been scanty which therefore necessitated this study as the findings could give a clue on haemostatic and fibrinolytic changes during pregnancy and puerperium in Kano, North-Western Nigeria.

In this study, significantly lower and fluctuations of platelet counts have been observed during pregnancy compared to the puerperium. These findings are in agreement with earlier reports [5,11-13]. Thrombocytopenia has been associated with haemodilution and accelerated platelet consumption during pregnancy [13-15] while increased platelet count during puerperium could be associated with consumption of platelets and blood coagulation factors during delivery [6].

This study further revealed that PT values fluctuated during the periods of pregnancy and puerperium and these observations are in line with some of the authors [7,16] but disagree with the findings of other authors who showed decreased PT results during pregnancy [17-19]. Different values of PT by various authors may be associated with the sensitivities of the reagents and techniques employed. However, variability in PT results from different researchers have been traced to the differing sensitivities of the thromboplastin reagents used, concentration of citrate anticoagulant and method of analysis [20]. It is advisable to interpret PT result with caution especially if international normalized ratio (INR) that resolves interlaboratory variation of PT

results through the incorporation of sensitivity of the thromboplastin is not employed [20].

Divergent views have been expressed by various authors on APTT results during pregnancy and postpartum period as Szecsi et al. [7] and Jeremiah et al. [16] observed no significant differences during pregnancy, postpartum period and non-pregnant state but Saha et al. [21] reported decreased APTT result in pregnancy compared to the period of puerperium while Avwioro et al. [22] reported increased APTT result during pregnancy. This study has shown significantly higher APTT result during pregnancy most especially in the second trimester compared to the puerperium. Divergent reports made by the researchers may be due to different sensitivities of APTT reagents, poor end-point detection by analyst and poor storage of plasma or delay in running the samples as the heat-labile factors may be affected. However, different APTT results have been associated with sensitivities of APTT reagents used and methods of analysis [20].

The study has further shown increasing factor VII levels as the pregnancy advanced but decreased during the puerperium. These findings are in agreement with previous reports [7,23]. However, increased factor VII activity and plasma fibrinogen level have been associated with risks of thrombosis [24,25].

This study has shown that factor VIII concentration increased significantly with advanced gestation which agrees with earlier reports [23] while the significantly higher factor VIII activity during puerperium compared to pregnancy period is in contrary to the findings of some authors [23,26] who reported that factor VIII activity returned to non-pregnant level by 5-8 weeks postpartum or during puerperium. Different values of factor VIII levels during pregnancy and puerperium amongst various researchers may be attributed to the techniques used, sample sizes and poor storage or delay in running the samples. However, Dossenbach-Glaninger et al. [27] linked recurrent early pregnancy loss to elevated factor VIII level.

This study has further revealed significantly lower protein C activity throughout the period of pregnancy compared to the puerperium and this is consistent with the findings of some authors [28,29] but this is in contrary with the findings of Said [30] that reported unchanged protein C values during pregnancy, delivery and postpartum period. However, protein C deficiency has been associated with venous thromboembolism [31,32]. Antithrombin III fluctuated significantly during pregnancy in this study but reduced during puerperium. This finding is in line with earlier report [33] but conflicts with the findings of Choi and Pai [23] and Szecsi et al. [7] who documented no significant change in antithrombin III levels during pregnancy and puerperium. However, mild variation of antithrombin III concentrations reported by various authors during pregnancy and puerperium could be associated with different types of reagents used, techniques employed and sample sizes considered.

There were no significant differences in the values of fibrinogen, fibrin degradation products and d-dimer during pregnancy compared to the puerperium in this study. Fibrinogen concentrations fluctuated during the trimester periods but reduced at the puerperal period in this study, but the differences showed no significance. These findings disagree with the reports of Fletcher et al. [34] and Reger et al. [35] who documented progressive increase in fibrinogen levels during pregnancy. However, raised fibrinogen level during pregnancy has been associated with increased fibrinogen synthesis due to its utilization in the utero-placental circulation or hormonal changes [36].

This study further showed that concentrations of fibrin degradation products and d-dimer during pregnancy showed no significant changes compared to puerperium. Elevated values of FDP and d-dimer during pregnancy in this study are in line with earlier authors [2,23,37,38] and these raised values have been attributed to increased fibrinolysis following fibrin formation [37,39,40].

In conclusion, significant haemostatic changes during pregnancy and puerperium are associated with platelet count, APTT, factor VIII, protein C and antithrombin III concentrations, however, the changed values of platelet count, APTT, protein C and factor VIII concentrations during pregnancy, normalized at the puerperal period while advanced gestation may pose a threat to pregnancy. It is recommended that protein C, factors VII and VIII concentrations be monitored during pregnancy to minimize thrombotic effect.

## Addendum

M. Imoru designed and conducted the research while statistical analysis was carried out by M. Imoru and O.I. Ajayi but M. Imoru wrote the manuscript and had primary responsibility for the final content. O.I. Ajayi made critical comments on the manuscript while both authors read and approved the final manuscript.

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