African Journal of Medicine and Medical Sciences

Editor: O.A. Ladipo
Assistant Editors:
B.O. Osotimehin and A.O. Uwaifo

Volume 18
1989

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BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Melbourne

Afr. J. Med. med. Sci. (1989) **18**, 89–93.

The fibrinolytic enzyme system in pregnancy in Nigerians

I. AKINSETE* AND P. O. UYANWAH†

**Departments of Haematology & Blood Transfusion, and †Obstetrics & Gynaecology, College of Medicine, University of Lagos, Lagos, Nigeria*

Summary

Results of a detailed study of the fibrinolytic enzyme system in pregnant and non-pregnant Nigerians are reported.

It was observed that plasma plasminogen, α_1-antitrypsin, and α_2-macroglobulin were significantly increased in pregnancy ($P < 0.001$) in comparison with the non-pregnant state. Fibrinogen was also increased but at a level of $P < 0.01$. A prolonged euglobulin clot lysis time was also observed ($P < 0.001$). There was no significant difference in the mean values of platelet count in the two groups.

These findings indicate that Nigerian women in pregnancy show physiological changes in haemostasis identical to those reported in Caucasians [5,7].

Résumé

Les résultats d'une étude détaillée portant sur le système enzymatique de nature fibrinolytique des Nigérianes en état de grossesse et de ceux qui ne le sont pas sont présentés.

Nous avons remarqué que la quantité du plasma plasminogen, α_1-antitrypsin, et celle du α_2-macroglobulin ont considérablement augmenté pendant la grossesse ($P < 0.0001$). La fibrinogène a également augmenté mais à un niveau de $P < 0.001$. Une durée prolongée du caillot lyse euglobulin a été constatée ($P < 0.001$). Il n'y avait pas de différence importante dans les valeurs moyennes de la numération des plaquettes sanguinaires dans les deux groupes.

Ces découvertes indiquent que les Nigérianes enceintes manifestent les mêmes changements physiologiques en haemostase tels que nous les avons présentés [5,7].

Correspondence: Dr I. Akinsete, Department of Haematology & Blood Transfusion, College of Medicine, University of Lagos, PMB 12003, Lagos, Nigeria.

Introduction

Several studies have reported significantly greater plasma fibrinolytic activity in age-matched black Africans when compared with their European counterparts [1–4]. In normal pregnancy, however, both groups have been shown to have reduced activity [5–8].

This study was undertaken to find out if changes in fibrinolytic activity reported in pregnancy, in black Africans and in Europeans, occur in Nigerians.

Subjects and methods

Sixty-five healthy pregnant women, aged 20–40 years, attending the antenatal clinic at the Lagos University Teaching Hospital, were randomly selected. Each of the women selected had an uneventful pregnancy, and was certain of the date of her last menses. Uterine size was consistent with the period of amenorrhoea.

Blood samples

Blood was obtained from all subjects between 09.30 h and 12.30 h each day of the test. Twenty millilitres of blood were drawn into a plastic syringe by careful venepuncture from an antecubital vein using minimal stasis. Ten millilitres of whole blood were transferred into a plastic tube where 3.8% sodium citrate was added in the ratio of nine volumes of whole blood to one volume of sodium citrate. Five millilitres were delivered into a standard plastic sequestrene bottle for estimation of platelet count, and 5 ml

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into a plain plastic tube for estimation of α_1-antitrypsin (α_1-AT) and α_2-macroglobulin (α_2-MG). The tubes, except the sequestrene, were stored at 4°C for less than 10 min, and that containing citrate was spun at 3000 *g* for 10 min at 4°C. Thereafter the supernatant plasma was removed and euglobulin clot lysis time (ELT) performed within 25 min of collection of the blood. Plasma samples for estimation of plasminogen were processed until the pH was neutralized [9,10], they were stored at −20°C for subsequent bulk assay within 4 weeks. Clotted samples were spun for 10 min at 3000 *g* at 4°C, and cell-free samples were transferred into plastic containers and stored at −20°C for subsequent bulk assay within 4 weeks. Fibrinogen was assayed by the clot weight method [11], α_2-MG and α_1-AT were assayed by quantitative single radial immunodiffusion of serum, using commercially prepared plates and standardized reference sera [12]. Platelet count was carried out according to the method of Dacie & Lewis [13].

Results

The values for the different components of the fibrinolytic enzyme system are expressed as mean ± standard deviation. For each parameter assessed, a statistical comparison was made between the means in the non-pregnant and the pregnant females using Student's *t*-test (Table 1). All the parameters; plasma plasminogen, ELT, α_1-AT, and α_2-MG, were significantly increased during pregnancy ($P < 0.001$). Fibrinogen was also significantly increased, but at a level of $P < 0.01$. There was, however, no significant difference in the values of platelet count in the two groups.

The results of all the parameters measured were further analysed in the pregnant group during the periods 8–15 weeks, 16–23 weeks, 24–31 weeks, 32 weeks to term and 6 weeks after parturition.

It was found that the plasma fibrinogen level was slightly increased in early pregnancy at a level of 331 ± 60.5 mg/dl compared to a level of 317 ± 50.7 mg/dl in the non-pregnant group (Table 1). The level increased with the length of gestation to 416 ± 60.1 mg/dl at term. Six weeks post-partum the fibrinogen level was 250 ± 88.7 mg/dl. Plasminogen levels were significantly higher in early pregnancy at 5.2 ± 1.1 casein units/ml compared to 3.5 ± 1.0 casein units/ml ($P < 0.001$) in non-pregnant females. However, plasminogen levels did not rise much with increasing gestation (Table 2). Six weeks post-partum the plasminogen level was still 4.6 ± 2.3 casein units/ml.

The ELT increased steeply from 221.5 ± 30.1 min at early pregnancy to 261.0 ± 32.7 min at term. Six weeks post-partum it was down to 158.4 ± 27.2 min compared to 179.9 ± 21.8 min in the non-pregnant group. The α_1-AT concentration rose steeply with gestation and the highest concentration of 517 ± 66.7 mg/dl was found at term, compared to 214 ± 25.8 mg/dl

Table 1. Mean levels of haemostatic parameters in non-pregnant and pregnant Nigerians

Haemostatic parameter	Non-pregnant (n = 28)	Pregnant (n = 65)	Statistical comparison
Fibrinogen (mg/dl)	317 ± 50.7	400 ± 65.0	$P < 0.01$
Plasminogen (casein unit/ml)	3.5 ± 1.0	5.2 ± 1.1	$P < 0.001$
ELT (min)	179.9 ± 27.4	257.8 ± 32.8	$P < 0.001$
α_1-antitrypsin (mg/dl)	279 ± 90	430.0 ± 96.0	$P < 0.001$
α_2-macroglobulin (mg/dl)	288 ± 59.0	349 ± 56.0	$P < 0.001$
Platelet count (× 10^9/l)	201.4 ± 49.1	201.0 ± 57.6	n.s.*
Age (years)	32.7 ± 6.4	30.5 ± 6.4	

*n.s. = Not significant.

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Table 2. Mean levels of haemostatic parameters at different stages of pregnancy in Nigerians

Gestation	Age	Fibrinogen (mg/dl)	Plasminogen (casein unit/ml)	Platelet count ($\times 10^9$/l)	ELT (min)	α_1-antitrypsin (mg/dl)	α_2-macro-globulin (mg/dl)
8–15 weeks, (n = 28)	28.1 ± 5.0	331 ± 60.5	5.2 ± 1.1	199 ± 61.0	221.5 ± 30.1	373 ± 82.8	350 ± 59.6
16-23 weeks (n = 12)	28.3 ± 4.8	340 ± 67.5	5.7 ± 1.0	200 ± 76.0	252.7 ± 43.4	411 ± 62.0	365 ± 75.8
24–31 weeks (n = 12)	26.7 ± 5.5	382 ± 68.5	5.7 ± 0.6	187 ± 47.0	260.4 ± 43.4	481 ± 69.4	364 ± 75.8
32–term (n = 11)	25.4 ± 4.5	416 ± 60.1	5.8 ± 1.2	207 ± 67.0	261.0 ± 32.7	517 ± 66.7	361 ± 47.3
6 weeks post-partum (n = 9)	28.5 ± 4.6	250 ± 88.7	4.6 ± 2.3	221 ± 49.0	158.4 ± 27.2	214 ± 25.8	322 ± 52.2

6 weeks post-partum (Table 2). The α_2-MG concentration also increased in pregnancy from 350 ± 59.6 mg/dl in early pregnancy to a level of 361 ± 47.3 mg/dl at term. Six weeks post-partum the concentration fell to 322 ± 52.2 mg/dl. There was no rise in platelet count during pregnancy, nor was there a difference in the mean values found 6 weeks post-partum.

Discussion

Reports from different parts of the world are in general agreement that the ELT is prolonged during pregnancy, indicating that the activity of the fibrinolytic enzyme system is lowered [5,14,15]. The only contrasting report [16] observed that the ELT was unaltered in pregnancy. It has been shown that this prolonged ELT is similar in both Europeans and Africans during pregnancy [1], and this is confirmed in the present study. This decreased fibrinolytic activity begins early in pregnancy, and immediately returns to normal values post-partum. We have also observed this prolonged ELT early in pregnancy, with a return to normal levels 6 weeks post-partum in Nigerians (Table 2), confirming the findings in African women in Kenya [7].

The plasminogen concentration has been reported to be higher in pregnancy [5,17]. In Kenya, an increase was noted at the tenth week of gestation [7]. Our result also confirms a rise at 8–15 weeks of gestation, the values remained significantly ($P < 0.001$) higher throughout pregnancy, and returned to normal 6 weeks post-partum (Table 2). An increasing concentration of plasminogen, concordant with the increase in plasma fibrinogen, has been reported [5]. However, this was not observed in the present study (Table 2). Other workers have also failed to find alterations in the concentration of plasminogen in pregnancy [15]. Different methods of assay of plasminogen may be responsible for these discrepancies [15].

The increase in plasma fibrinogen concentration has been reported by several workers [5,15,18]. In this study the rise begins early in pregnancy, and the mean value at term was 416 mg/dl in contrast to 317 mg/dl in the non-pregnant female ($P < 0.001$). Six weeks post-partum the fibrinogen concentration returned to normal non-pregnant levels (Table 2).

Alpha$_1$-AT was reported to be increased throughout pregnancy, and the increase was about 20% at 10 weeks gestation [19,20]. This study observed a level of 373 mg/dl during pregnancy compared to 279 mg/dl ($P < 0.001$) in non-pregnant females (Tables 1 and 2).

Alpha$_2$-MG has been shown to be only slightly increased in pregnancy [21]. The reported increase in α_2-MG remained constant up to the first week post-partum. The present findings also show a significant rise during pregnancy, which was still elevated 6 weeks post-partum (Table 2). Alpha$_2$-MG and α_1-AT provide the majority of the anti-plasmin activity of plasma. Alpha$_2$-MG reacts quickly as a competitive inhibitor of plasmin while α_1-AT reacts more slowly but more firmly with plasmin to produce an inactive complex. Which factor or factors cause the increase in these two anti-plasmins is not known. It has been suggested that the control may be hormonal and the increase in pregnancy may be a result of this [21].

Several reports, with a few exceptions, agree that platelet number is not altered during pregnancy in Europeans [6,19] while others reported a decrease in Africans [1,6]. This study does not show any difference in platelet count between non-pregnant and pregnant Nigerians (Table 1). Platelet count in symptom-free Nigerians has been reported to be lower than the internationally accepted normal range of 150–400 × 10^9/l [22], while Nigerian new-borns have counts which are similar to those of European new-borns, but higher than those of adult Nigerians [23]. The differences between platelet count in new-borns and symptom-free Nigerians, in both males and females, is due to chronic malarial infestation [22].

The mechanism responsible for the decreased fibrinolytic activity during pregnancy is unknown. It has been suggested that the decrease in fibrinolytic activity might be due partly to an increase in levels, perhaps originating in the placenta [14].

The relative freedom of Africans from complications of atheromatous disease is well documented [24,25], and evidence of enhanced fibrinolytic activity has been demonstrated in Africans [2,4]. It has been suggested that this may contribute to the lower prevalence of thromboembolic disorders in black Africans [2,3]. In pregnancy, increases in concentration

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of some coagulation factors and decreases in fibrinolytic activity have been considered to lead to a hypercoagulable state. This implies an increased capacity to form fibrin and an increased tendency to thrombosis, all these being physiological preparations for the requirements of labour.

This present study confirms that Nigerian women in pregnancy appear to show the same changes in the fibrinolytic enzyme system as those of their European and African counterparts, and that the same physiological preparation for labour occurs in haemostasis.

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(*Accepted* 19 *July* 1987)

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