

Haemorheological adaptation during pregnancy in a Latin American population

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Abstract: *Objective:* To investigate haemorheological changes during pregnancy in a Latin American population and compare to previously published data from Caucasian populations. *Design:* Cross-sectional study. *Population:* 75 pregnant women at 10–36 wk of gestation and 17 non-pregnant female controls in Lima, Peru. All the women and their ancestors for three generations were born and lived at sea level.

Methods: Viscosity, haematocrit and plasma fibrinogen, albumin and total protein concentrations were determined in blood samples obtained after an overnight period of fasting. *Results:* At 10 wk of gestation, total protein concentration and plasma viscosity were above non-pregnant levels by about 15% and subsequently decreased linearly with gestation. Fibrinogen concentration was increased in the first trimester; it then decreased to a nadir at about 20 wk and subsequently increased.

Albumin concentration decreased linearly with gestation. Haematocrit decreased from pre-pregnancy levels at 10 wk to a nadir at about 26 wk. Blood viscosity increased in the first trimester and then decreased with gestation to a nadir at about 26 wk. *Conclusion:* In the first trimester of pregnancy blood and plasma viscosity are increased and they subsequently fall with advancing gestation. Plasma viscosity reflects the changes in total protein concentration, and blood viscosity is dependent on the interplay of changes in plasma viscosity and haematocrit.

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Normal pregnancy is characterised by a reduction in peripheral resistance in order to increase blood flow and facilitate the supply of oxygen and nutrients to the peripheral tissues. This decrease in resistance is achieved by both peripheral vasodilatation and reduction in blood viscosity. The latter is accomplished mainly by the increase in plasma volume that compensates for the increasing mass of the red cells and several plasma proteins (1).

In normal pregnancy plasma volume increases with gestation to about 40% above pre-pregnancy levels at 30 wk followed by a small decrease at term. Red cell mass increases linearly with gestation to about 25% above pre-pregnancy levels at term (2–4). Consequently, haematocrit decreases with gestation, reaching a nadir of about 15% below pre-pregnancy levels at 30 wk (4–6). Similarly, total

serum protein concentration decreases during pregnancy, mainly due to haemodilution (4). Plasma fibrinogen, the production of which is thought to be stimulated by progesterone (7), increases throughout pregnancy (5, 8–10). Blood viscosity, which in high-shear stress is dependent on the interplay of the changes in plasma viscosity and haematocrit, decreases with gestation (5, 11–13). However, there is controversy as to the changes in plasma viscosity, with some studies reporting no change with gestation (11, 14), some reporting an increase (12, 13), some a decrease (1) and others an initial increase followed either by no significant changes (15) or by a subsequent decrease (5).

The importance of the changes of blood viscosity in normal pregnancy has been highlighted by several studies that demonstrated an increase in

adverse pregnancy outcome with increasing haemoglobin levels (and thus whole-blood viscosity) (16–18) and a strong correlation between the prevalence of pre-eclampsia and plasma volume restriction and haemorheological disorders (19–24).

The prevalence of pre-eclampsia has been shown to vary between different ethnicities and racial groups (25–29). Plasma viscosity also has considerable geographical variations in the general population, and these correlate with regional differences in coronary heart disease (30, 31).

Most of the existing data on haemorheological changes in pregnancy are derived from studies performed in Caucasians living in developed countries, and it is uncertain if they are applicable to other populations. This study examines the changes in haemorheological factors and related parameters during pregnancy in a Latin American population, with a known higher prevalence of hypertensive disorders during pregnancy (32).

Materials and methods

This was a cross-sectional study of 75 pregnant women at between 10 and 36 wk of gestation and 17 non-pregnant female controls in Lima, Peru. The pregnant women were attending for routine antenatal care in the Instituto Materno-Perinatal in Lima, Peru. Only Mestizos (a mixture between native Quechuas and Spanish) and only women who were permanently resident for three generations at sea level were examined. All subjects were healthy non-smokers and were not taking any medication apart from ferrous sulphate and folic acid. None of the controls was taking hormonal contraception. None of the pregnancies was complicated by pre-eclampsia or intrauterine growth restriction. Gestation was calculated from the maternal last menstrual period and was confirmed by ultrasound biometry. The ethics committee of the Peruvian Ministry of Health gave approval for the study. All women gave written consent after reading the information leaflet.

Blood samples were obtained from the antecubital vein at between 8 and 10 am after an overnight period of fasting for 10–14 h. Blood was immediately transferred to tubes containing EDTA, shaken, and placed on ice. Within 2 h, samples were centrifuged at 3000 rpm for 10 min, plasma was frozen at minus 20 °C and the samples were transported to London on dry ice (−78.5 °C). Maternal haematocrit was determined by the microhaematocrit method (33), fibrinogen by a thrombin clotting technique (34), total protein by the Biuret method (35) and albumin by the Bromocresol green method (36) (Sigma Diagnostic Reagents, Poole,

UK). Plasma globulin concentration was estimated by subtracting the fibrinogen and albumin concentrations from the total protein concentration.

Plasma viscosity was measured with a rotational viscometer (Contraves LS 30, 1+1 bob and cup, Zurich, Switzerland) at 37 °C. High shear rate whole-blood viscosity was calculated from the haematocrit and plasma viscosity: $\log(\text{blood viscosity}) = \log(\text{plasma viscosity}) + \text{constant} \times \text{haematocrit}$. This can be extended to give a general relationship to cover simultaneous changes in haematocrit and plasma viscosity: $V_h = V_p (V_{45}/V_p)^{h/45}$, where V_h is the viscosity of blood with a haematocrit of $h\%$ and plasma viscosity of V_p , and V_{45} is the viscosity of blood with a haematocrit of 45% and plasma viscosity of V_p (37). When standard values are substituted for V_{45} and V_p , the viscosity at high shear rate of any blood sample can be estimated if its plasma viscosity and haematocrit are known. In this study we have used values of 4.7 mPa s and 1.34 mPa s for V_{45} and V_p ; respectively. These are averaged values for a healthy adult population (38). Hence, the final expression used for the calculation of blood viscosity was: $V_h = V_p (4.7/1.34)^{h/45}$, where V_h is the calculated high shear rate blood viscosity for each subject at her native haematocrit (h) and plasma viscosity (V_p).

Statistical analysis

The Kolmogoroff–Smirnov test was used to assess the normality of the distribution of the data and univariate regression analysis was used to examine the effect of gestational age on blood viscosity, plasma viscosity, haematocrit, albumin, fibrinogen, globulin and total protein. Non-linear effects of the gestational age were investigated by including a quadratic term in the regression equation. Multiple regression analysis was used to examine the relationships between plasma viscosity at 37 °C and gestational age, albumin, plasma fibrinogen and globulin concentration. The differences between non-pregnant controls and pregnant women were investigated with the unpaired *t*-test.

For the univariate regression analysis the regression equation (y = the dependent variable, x = gestational age), the *R*-square (R^2) and *p* values of the regression model are provided. For the *t*-test results the means of the two populations, the degrees of freedom (*df*), the *t*-test statistic (*t*) and the *p* values are provided.

Results

Haematocrit decreased with gestation to a nadir at about 26 wk ($y = 0.0162x^2 - 0.84x + 45.87$, $R^2 = 0.18$, $p < 0.001$; Fig. 1). The mean value in early

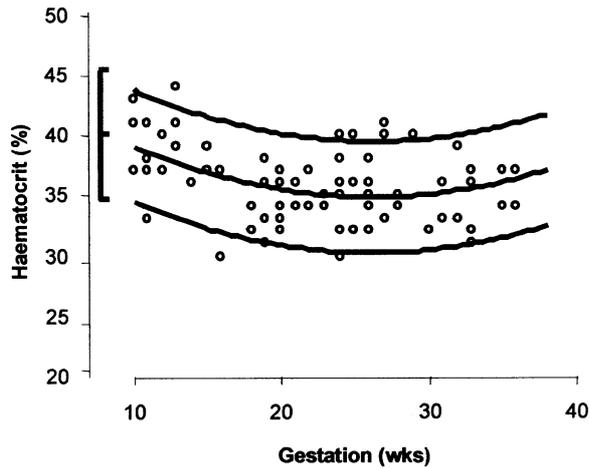


Fig. 1. Haematocrit changes with gestation, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

pregnancy (10–15 wk) was not significantly different from non-pregnant controls (38.9% versus 39.9%; $df=30$, $t=-1.01$, $p=0.3$). Plasma fibrinogen concentration increased significantly with gestation ($y=0.0061x^2-0.23x+5.76$, $R^2=0.12$, $p<0.001$; Fig. 2). The mean value in early pregnancy (10–15 wk) was significantly higher than non-pregnant controls by about 70% (3.94 g/L versus 2.26 g/L; $df=30$, $t=3.97$, $p<0.001$). Plasma viscosity at 37°C decreased significantly with gestation to pre-pregnancy levels at term ($y=-0.0038x+1.357$, $r=0.28$, $p=0.001$, Fig. 3). In early pregnancy (10–15 wk) the mean level was significantly higher than in non-pregnant controls by about 15% (1.34 mPa s versus 1.18 mPa s, $df=30$, $t=5.85$, $p<0.0001$). Albumin decreased linearly with gestation to values about 20% lower than in non-pregnant controls ($y=-0.4726x+45.827$, $r=0.54$, $p<0.0001$,

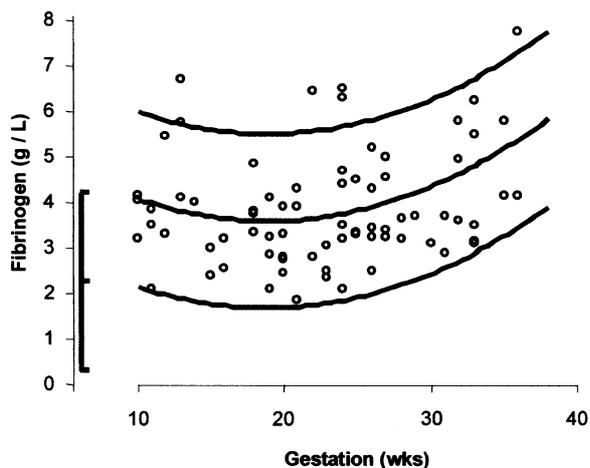


Fig. 2. Fibrinogen changes with gestation, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

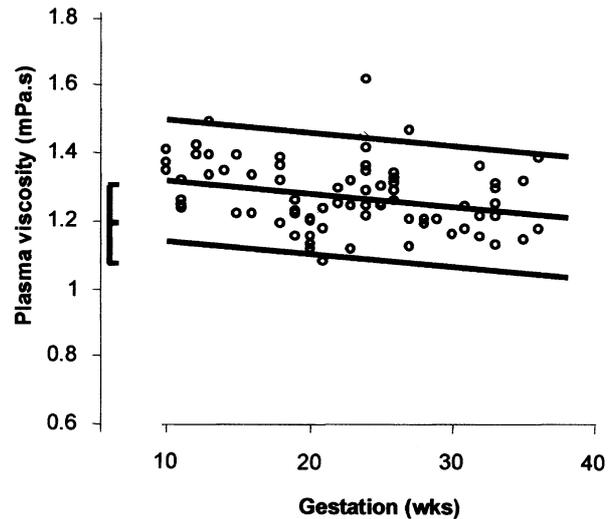


Fig. 3. Plasma viscosity changes with gestation at 37°C, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

Fig. 4). The mean value in early pregnancy (10–15 wk) was not significantly different from non-pregnant controls (41.6 g/L versus 43 g/L, $df=30$, $t=-0.87$, $p=0.3$). Total protein decreased significantly with gestation to about 10% below non-pregnant levels at term ($y=-0.06x+7.62$, $r=0.48$, $p<0.0001$, Fig. 5). In early pregnancy (10–15 wk) the mean level was significantly higher than in non-pregnant controls by about 15% (72.6 g/L versus 62.3 g/L, $df=30$, $t=4.11$, $p<0.0001$). Plasma globulin concentration decreased with gestation but this change did not reach statistical significance ($y=-0.1716x+27.411$, $r=0.21$, $p=0.08$, Fig. 6). In early pregnancy (10–15 wk) plasma globulin levels were significantly higher compared to non-pregnant controls by about 70% (27 g/L

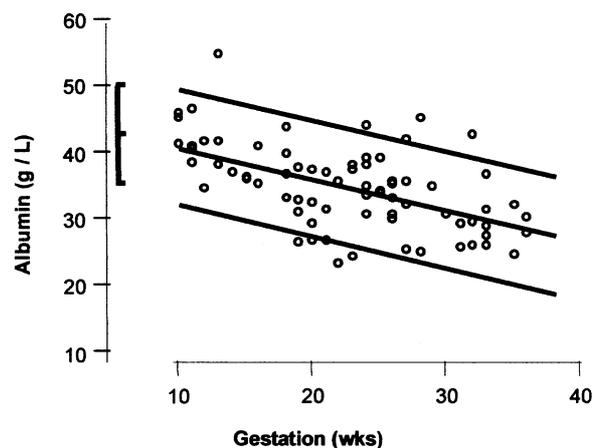


Fig. 4. Albumin changes with gestation, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

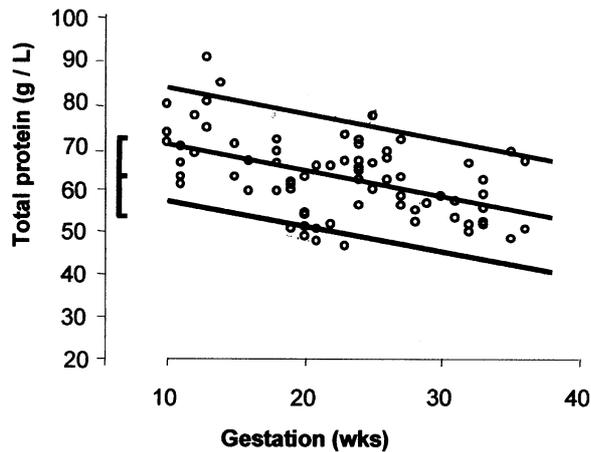


Fig. 5. Total protein changes with gestation, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

versus 16 g/L, $df=30$, $t=4.51$, $p<0.0001$). Blood viscosity at 37°C decreased significantly with gestation to a nadir at about 26 wk ($y=0.0022x^2 - 0.13x + 5.1$, $R^2=0.23$, $p<0.0001$, Fig. 7). The mean value in early pregnancy (10–15 wk) was significantly higher than non-pregnant controls by about 10% (3.99 mPa s versus 3.63 mPa s; $df=30$, $t=2.22$, $p=0.03$).

Backward stepwise multiple regression analysis demonstrated that plasma viscosity is significantly and independently related to albumin, plasma fibrinogen and globulin concentration (plasma viscosity = $0.72 + 0.008 \times \text{albumin} + 0.024 \times \text{fibrinogen} + 0.007 \times \text{globulins}$, $R^2=0.61$, $p<0.0001$).

Discussion

The results of this study demonstrated that haemorheological changes during the course of pregnancy in a Latin American population were similar to those reported previously in Caucasian populations. Thus, in pregnancy haematocrit decreases by about 15%, albumin concentration decreases by 20%, while fibrinogen and globulin concentrations increase by about 100% and 70%, respectively. During the first trimester plasma viscosity, total protein concentration and blood viscosity increase by about 15%, 15% and 10%, respectively, and decrease thereafter towards pre-pregnancy levels at term. These findings are consistent with those of previous studies, and the pattern of change with gestation in plasma viscosity confirms the results of Buchan (5) and contradicts those of Eastham *et al.* (15), Dintenfass *et al.* (39), Heilmann *et al.* (1) and Inglis *et al.* (12).

A practical problem with this study was the fact that there was no viscometric apparatus available in

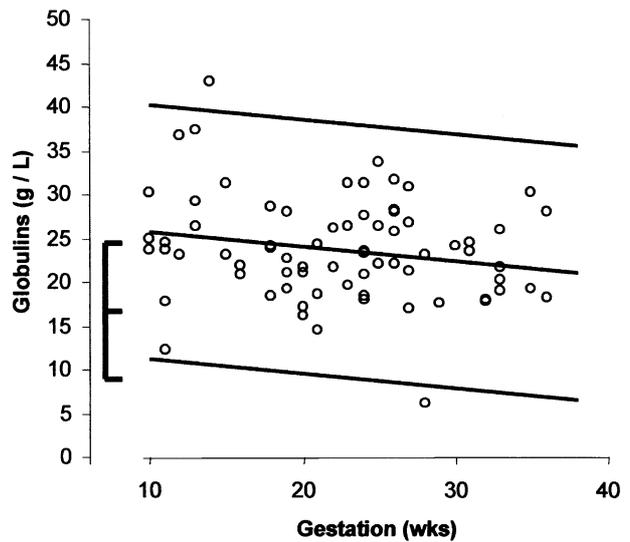


Fig. 6. Plasma globulin concentration changes with gestation, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

Peru. This was the reason that the viscosity of whole-blood has had to be determined by calculation. It also meant that the plasma samples had to be stored deep frozen and transported to the UK for plasma viscosity measurement. There is very little literature on the effects of freezing on plasma viscosity. Indeed the only paper that specifically addresses this problem from an experimental point of view is that of Mantzavinos *et al.* (40). They showed that flash freezing of plasma samples did not significantly effect their viscosity values. Rampling, in an unpublished study of plasma samples frozen for up to one month, also found

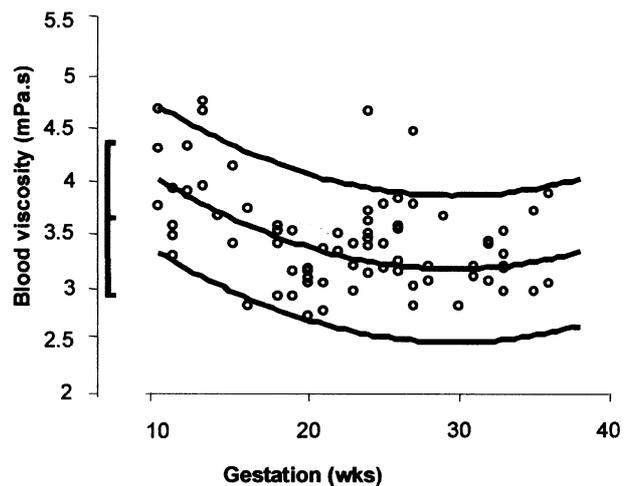


Fig. 7. Blood viscosity changes with gestation at 37°C, illustrating individual values and the regression lines of the 50th, 95th and 5th centiles. The vertical line on the left illustrates the 50th, 95th and 5th centiles of the non-pregnant controls.

no changes in viscosity. In spite of this relative lack of published data, it is widely accepted amongst haemorheologists that freezing has no effect on plasma viscosity (41–43). Hence we are convinced that the plasma data presented here are robust.

The increase in plasma viscosity to above pre-pregnancy levels observed from as early as 10 wk is likely to be due to the increased level of fibrinogen and globulins. The subsequent reduction of about 10–15% with gestation, despite the further 20–30% increase in plasma fibrinogen concentration, is likely to be the consequence of the 20% reduction in albumin. The increase in plasma fibrinogen concentration from at least 10 wk of gestation, compared to non-pregnant controls, may be a consequence of the increasing progesterone levels. Thus, fibrinogen is increased during the luteal phase of the menstrual cycle and the levels are higher in women taking strongly progestogenic oral contraceptive pills (7).

Albumin concentration, in contrast to fibrinogen, decreases with gestation, and the levels at term are about 20% lower than in early pregnancy and in non-pregnant controls. The most likely explanation for this decreased concentration is that increased production in pregnancy is not sufficient to counteract the 40% expansion in plasma volume. However, plasma volume expansion reaches a plateau at about 30 wk (44, 45), whereas the decrease in albumin concentration with gestation continues to term. It is therefore possible that in the third trimester there is either a decrease in production of albumin by the mother or increased urinary excretion or catabolism. Intravascular albumin mass is not reduced in pregnancy; it either remains stable (46) or is increased (47). On the contrary, total protein and albumin urinary excretion is considerably increased in the third trimester, contributing to the continuing fall of the albumin concentration (48, 49). Studies have suggested a role for albumin as a source of placental and hence fetal amino acids, providing a reserve pool for nitrogen for the mother and the fetus (50, 51). Beaconsfield postulated that the placenta might be one of the sites of albumin degradation, providing the necessary substrate for the protein synthesis. Additionally, albumin synthesis appears to be stimulated by insulin (52) and decreased synthesis may be due to increasing insulin resistance with gestation (53).

Plasma globulins, which consist of numerous components, are the third fraction of the plasma proteins. The observed 70% increase in early pregnancy is likely to be due to oestrogen-stimulated hepatic protein synthesis. The change of the total plasma globulin concentration through-

out pregnancy reflects the sum of the individual changes of the different components. The plasma concentration of the immunoglobulins A, G and M decreases with gestation, with the most marked decrease in immunoglobulins G (about 30–40% lower at 28 wk than in the immediate postpartum period) (54). Contrary to immunoglobulins, pregnancy is associated with a marked increase in the concentration of hormone-binding proteins, complement component C₃ and globulins responsible for coagulation and fibrinolysis (54). The total circulating mass of ceruloplasmin increases by 150% by 28 wk (54).

These patterns of change with gestation in plasma fibrinogen, globulin and albumin concentrations are reflected in the observed changes in total protein concentration, with an initial increase in the first trimester, due to the rise in fibrinogen and globulin concentration, and a subsequent decrease to below pre-pregnancy levels at term, due to the reduction in albumin concentration.

The clinical significance of plasma viscosity levels in the non-pregnant population has been recently established, since increased plasma viscosity correlates with the incidence of coronary heart disease (31, 55). Furthermore, a large multinational study (Glasgow Multinational Monitoring of Trends and Determinants of Cardiovascular Disease) demonstrated that regional differences in plasma viscosity correlated with regional differences in coronary heart disease (30).

In pregnancy, there is substantial evidence that pre-eclampsia is associated with a constriction in plasma volume (20, 21, 56–58), and increased whole-blood (24, 59) and plasma viscosity (19). Differences in the prevalence of pre-eclampsia have been established between different racial groups in Europe (28) and between different ethnic and racial groups in the United States (27, 59). Furthermore, prospectively collected data by the World Health Organisation concerning populations of Southeast Asia have revealed that there are genuine differences in the incidence of hypertensive disorders of pregnancy in these populations and that these are not caused by underlying differences in baseline blood pressures (25).

Although data published by the World Health Organisation demonstrate a nearly four-fold increase in the prevalence of hypertensive disorders during pregnancy between the Established Market Economies and Latin American countries (32), the findings of this study indicate that changes in the haemorheological factors during the course of pregnancy in Lima are similar to those reported in Caucasian populations. These findings offer an insight in the adaptation during pregnancy of a

Latin American population at sea level and will form the basis for the study of the possible effect of high altitude, in the Andes, on plasma and blood viscosity.

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