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Association between Plasma Triglyceride and Haemorheological Variables in Nigerian Primigravidae and Multigravidae

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Abstract: Abnormal haemorheology has been shown to be in almost all conditions associated with accelerated atherosclerotic cardiovascular disorders. The aim of this study is to test the hypothesis that high concentration of plasma Triglyceride (TG) predicts altered hemorheological variables in normal pregnancy. Sixty pregnant women attending antenatal clinic of the University of Ilorin Teaching Hospital at 14-36 weeks of gestation (aged 21-36 years) were recruited after giving informed consent to participate in the study. They consisted of 28 primigravidae and 32 multigravidae. Twenty-four healthy non-pregnant women of similar age and socioeconomical status were also recruited. The study showed that fasting plasma Triglyceride (TG) increased significantly in primigravidae and multigravidae. There was a positive correlation between plasma TG level and blood viscosity ($r = 0.36$, $p<0.01$). TG also correlated positively with haematocrit ($r = 0.48$, $p<0.001$), haemoglobin concentration ($r = 0.43$, $p<0.001$) and white blood cell count ($r = 0.38$, $p<0.01$) in the pregnant group as a whole. In primigravidae, there was a correlation between TG and blood viscosity ($r = 0.63$, $p<0.001$), hematocrit ($r = 0.88$, $p<0.001$), haemoglobin concentration ($r = 0.85$, $p<0.001$), white blood cell count ($r = 0.40$, $p<0.05$) and total serum protein ($r = 0.37$, $p<0.05$). However, there was an insignificant correlation between TG and the haemorheological variables in multigravidae. The study suggests that plasma TG concentration in primigravidae is strongly associated with blood viscosity and its main determinant, haematocrit as well as white blood cell count and haemoglobin concentration, but the association is lost in multigravidae. Therefore, TG could be considered as an important potential indicator of altered blood rheology in primigravidae, but not in multigravidae.

Key words: Pregnancy, triglyceride, haemorheology, primigravidae, multigravidae

INTRODUCTION

Pregnancy has been associated with increased Triglyceride concentration (TG) and insulin resistance (Cong *et al*.,1994; Kautzky-Willer *et al*., 1993; Smolarzyk *et al*., 2001; Herrera, 2002). It is becoming interestingly clear that hypertriglyceridemia is an important risk factor for insulin resistance-related cardiovascular disorders (Ginsberg, 1997). It is therefore, important to identify and understand factors that are related to increase in TG concentration during pregnancy. Though, maternal plasma TG has been reported to have a beneficial impact on normal foetal development (Herrera, 2002).

The casual role for TG in the aetiology of atherosclerotic cardiovascular disease is still not fully understood, because TG-containing lipoproteins are larger and unlikely to enter the arterial wall (Stender and Zilversmit, 1981; Hokanson and Austin, 1996). However, data have shown that serum TG may contribute significantly to blood rheology (Lowe, 1994; Woodward *et al*., 1999; Rosenson *et al*., 2001). Hence, plasma TG may contribute to atherosclerotic cardiovascular disorders by increasing blood viscosity and/or its determinants. Moreover, increase in white blood cells in the microcirculation may perpetuate ischemia and the white blood cell count has been associated with increase incidence of cardiovascular disease (Ernst *et al*., 1987; Danesh *et al*., 1998).

Surprisingly, it is unclear whether there is a relationship between plasma TG and haemorheological indices in normal pregnancy, which could be relevant in predicting TG-related cardiovascular risk factors during pregnancy. We hypothesized that changes in fasting

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plasma TG may be an important indicator for altered haemorheology during pregnancy. To test this hypothesis, we evaluated the association between fasting plasma concentration of TG and haemorheological variables in primigravidae and multigravidae.

MATERIALS AND METHODS

Sixty pregnant women attending antenatal clinic of the University of Ilorin Teaching Hospital at 14-36 weeks of gestation (aged 21-36 years) were recruited after giving informed consent to participate in the study. They consisted of 28 primigravidae and 32 multigravidae. The study was conducted in accordance with the Declaration of Helsinki. Twenty-four healthy non-pregnant women of similar age and socioeconomical status who were mainly staff of the University of Ilorin were also recruited. Recruitment into the study included women who were sure of their last menstrual dates. Patients with risk factors for gestational diabetes, diabetes mellitus, hypertension, cardiac, renal, cholestasis, obstetric complications such as pre-eclampsia and polyhydramnios or smokers were excluded. Non-pregnant subjects who were on any medication including oral or injectable contraceptives were also excluded from the study.

All tests were done in the morning from 09: 00 h, after an overnight fast of a minimum of 12 h. After a 20 min rest in sitting position, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were determined using a standard mercury sphygmomanometer. The systolic first phase and diastolic fifth phase were used in each occasion. Subject weight and height were recorded without shoes.

Blood handling: Venous blood was collected without stasis. Blood was anticoagulated with dry dipotassium EDTA (1.5 mg mL^{-1}). Plasma or serum was separated from the whole blood by centrifugation for 10 min at 3000 rpm. All samples were refrigerated at 4°C until time for analysis. Measurements of haemorheological and haematological variables were done within 24 h after venepuncture.

Lipids determination: Plasma was analysed for Total Cholesterol (TC), Triglyceride (TG) and High-Density Lipoprotein-Choleterol (HDL-C) using enzymatic colorimetric method with assay kits, supplied by Randox Laboratory Corporation (U.K.).

Haemorheological and haematological variables determination: Haematocrit (Hct), Haemoglobin concentration (Hb) and White Blood Cell Count (wbc) were determined by automated haematological analyzer SYSMEX KX-21 (SYSMEX Corporation, Japan) using whole blood. Plasma fibrinogen concentration was determined by the Clauss method using fibrinogen kit (Baxter Diagnostics Inc., Deerfield, Illinois) and serum protein by biuret method with kit supplied by Randox Laboratory Corporation (U.K) as in past studies (Woodward *et al*., 1999; Rosenson *et al*., 2001). Prior to viscosity determination, the blood and plasma samples were maintained at 37°C in an incubator (BISCA, Model Cella Thermostatica Ad-Aqua, BE-89, Italy). Whole blood viscosity and plasma viscosity were measured by capillary viscometry at 37°C. Relative Blood Viscosity (RBV) and Relative Plasma Viscosity (RPV) were determined as in previous studies (Famodu, 1998; Famodu *et al*., 1998).

Statistical analysis: Values are given as means±SEM. The SPSS® statistical software (SPSS, Chicago, IL, USA) for Windows was used for data analyses. Comparison between groups was carried out using Analysis of Variance (ANOVA) followed by Bonferroni. Relationship between plasma TG and selected variables was done using Pearson's correlation tests. $P<0.05$ was taken as statistically significant.

RESULTS

Table 1 summarizes clinical characteristics including biochemical data of primigravidae, multigravidae and non-pregnant women. There were no significant differences in maternal age and height among the studied groups. Gestational age of the primigravidae was similar to that of the multigravidae. SBP, DBP and HDL-cholesterol were significantly lower in both pregnant groups than in non-pregnant subjects while plasma TG, TC levels were significantly higher in both primigravidae and multigravidae subjects than in non-pregnant subjects. TC/HDL-cholesterol (an atherogenic index) was significantly higher in primigravidae than in the multigravidae and non-pregnant subjects.

Both primigravidae and multigravidae had significantly lower Hct and RBV than non-pregnant women. On the other hand, RPV, plasma fibrinogen was significantly higher in both pregnant groups than in non-pregnant subjects (Table 2).

Pearson correlation coefficient [r] for fasting plasma TG and haemorheological variables are shown in Table 3. There was significant positive relationship of fasting plasma TG with Hct ($r = 0.48$, $p<0.001$), Hb ($r = 0.43$, $p<0.001$), RBV ($r = 0.36$, $p<0.01$) and wbc ($r = 0.38$, $p<0.01$) in the pregnant group as a whole. There was a significant positive relationship of fasting plasma TG with Hct ($r = 0.88$, $p<0.001$), Hb ($r = 0.85$, $p<0.001$), serum

Table 1: Characteristic of non-pregnant (I), primigravidae (II) and multigravidae (III)

	I	II	III
Characteristic	(n = 24)	(n = 28)	(n = 32)
Maternal age (yrs)	26.8±2.8	28.0±1.0	29.8±2.1
Gestational age (wks)	-	20.2±2.0	23.3±1.4
Body weight (kg)	58.2±3.4	67.8±3.3*	70.5±2.5*
Height (m)	1.60±0.08	1.59±0.03	1.57±0.05
SBP (mmHg)	117.3±2.2	102.3±2.7*	107.2±1.9*
DBP (mmHg)	80.3±2.5	66.3±2.7*	65.2±1.8*
Plasma TG (mmol L^{-1})	0.80±0.05	1.41±0.11*	1.52±0.08*
Plasma TC (mmol L^{-1})	3.8±0.2	4.4±0.2*	4.7±0.2*
Plasma HDL-C (mmol L^{-1})	1.47±0.05	0.69±0.03*#	1.00±0.09*
TC/HDL-C ratio	2.30±0.20	4.28±0.18*	2.86±0.30

Values are expressed as means±SEM. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, TG: Triglyceride, TC: Total Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, HDL-C: High Density Lipoprotein Cholesterol *p<0.05 compared with non-pregnant: # p<0.05 compared with multigravidae

Table 2: Selected hemorheological and haematological variables in non-pregnant (I), primigravidae (II) and multigravidae (III)

	I	II	III
Variables	(n= 22)	(n = 30)	(n = 32)
Hct (%)	38.8±0.3	33.4±0.8*	34.8±0.5*
TSP (g L^{-1})	68.9±1.8	63.6±3.3	62.8±2.2
Fibrinogen (g L^{-1})	2.8±0.5	3.6±0.2*	3.7±0.3*
RPV	1.75±0.10	2.41±0.10*	2.35±0.06*
RBV	6.9±0.4	4.4±0.1*	4.5±0.2*
Hb (g d L^{-1})	12.6±0.3	11.5±0.2	11.6±0.2
rbc ($\times 10^{12}$ L^{-1})	4.4±0.3	3.8±0.4	3.9±0.3
wbc ($\times 10^{9}$ L^{-1})	5.4±0.4	7.7±0.9*	7.1±0.3*

Values are expressed as means±SEM. Hct: Hematocrit, Hg: Hemoglobin TSP: Total Serum Protein, RPV: Relative Plasma Viscosity, RBV: Relative Blood Viscosity, WBC: White Blood Cell Count, RBC: White Blood Cell Count, *p<0.05 compared with non-pregnant

Table 3: Pearson's correlation coefficient (r) between selected hemorheological or hematological variables and fasting plasma triglyceride in non-pregnant (I), primigravidae (II) and multigravidae (III)

	I	II	III	II+III
Hb (gdL^{-1})	0.16	0.85***	0.29	0.43***
Hct (%)	0.22	0.88***	0.34	0.48***
TSP (gL^{-1})	0.11	0.37*	0.28	0.24
Fibrinogen (gL^{-1})	0.19	0.12	0.18	0.20
RPV	0.44*	0.11	0.27	0.19
RBV	0.25	0.63***	0.04	0.35**
wbc($\times 10^{9}L^{-1}$)	0.30	0.40**	0.32	0.38**

Hct: Hematocrit, Hg: Hemoglobin TSP: Total Serum Protein, RPV: Relative Plasma Viscosity, RBV: Relative Blood Viscosity, wbc: White Blood Cell Count, *p<0.05, **p<0.01 and ***p<0.001

protein concentration (r = 0.37, p<0.05), RBV (r = 0.63, p<0.001) and wbc (r = 0.40, p<0.05) in the primigravidae.

In the non-pregnant, fasting plasma TG correlated significantly only with RPV (r = 0.43, p<0.05). However, in the multigravidae, there was a weak correlation between fasting plasma TG and selected haemorheological and haematological variables.

DISCUSSION

The data of the present study demonstrated that normal pregnancy resulted in increase fasting TG concentration and decreased HDL-Cholesterol in both primigravidae and multigravidae. The total cholesterol/HDL-Cholesterol as an atherogenic index was found to be significantly higher in primigravidae than in the multigravidae and non-pregnant subjects. More so, fasting plasma levels of HDL-Cholesterol in primigravidae was also found to be significantly lower than that in the multigravidae. These results seem to suggest that alteration in fasting plasma lipids may be of pathological significant more in primigravidae than in multigravidae.

This study have shown that fasting plasma levels of TG is positively correlated with relative blood viscosity, haematocrit, haemoglobin and white blood cell count in healthy pregnant women. In contrast, plasma viscosity and it determinants (plasma fibrinogen and serum protein concentrations) are not significantly associated with plasma TG. Elevated fasting plasma TG, plasma viscosity and blood viscosity have been reported to be associated with increased incidence of cardiovascular disease in non-pregnant (Lowe, 1994; Hokanson and Austin, 1996; Criqui and Golomb, 1998; Woodward *et al*., 1999; Rosenson *et al*., 2001; Livingstone and Collison, 2002) and in pregnant subjects (Cong *et al*., 1994; Bollini *et al*., 2003). The finding that fasting plasma TG related positively to relative blood viscosity and its main determinant, haematocrit as well as haemoglobin and white blood cell count in the pregnant women may at least in part, be attributed to direct effects of TG carrier lipoproteins (Woodward *et al*., 1999; Rosenson *et al*., 2001). The association of plasma TG with relative blood viscosity could be attributed to the association of plasma TG with haematocrit and white blood cell count (Lowe, 1994; Hokanson and Austin, 1996; Criqui and Golomb, 1998; Woodward *et al*., 1999; Rosenson *et al*., 2001; Bollini *et al*., 2003). The weak relationship found between plasma TG and relative plasma viscosity, plasma fibrinogen and serum protein suggests that the increases in plasma viscosity and fibrinogen concentration in these pregnant subjects is unlikely to be TG-mediated.

One of the principal consequences of high circulating concentrations of sex steroids is an increase in plasma TG that occurs by oestrogen-induced stimulation of hepatic synthesis of triglyceride-rich lipoproteins (VLDL) and inhibition of hepatic and adipose tissue TG lipase activity (Applebaum-Bowden *et al*., 1989; PEPI Trial, 1995; Livingstone and Collison, 2002). Increased plasma TG level has been reported to be an independent risk factor

of cardiovascular disease (Hokanson and Austin, 1996; Criqui and Golomb, 1998; De Man *et al*., 2000; Tooke and Hannemann, 2002; Ginsberg, 1997). Hence, increase in plasma TG may negate the beneficial impact of TG on normal foetal development because elevated plasma TG is associated with altered blood rheology (Brunzell, 1989; Rosenson *et al*., 2001). These relationships between fasting plasma TG and markers of blood rheology were weak in multigravidae and non-pregnant women. The disparity between the primigravidae and multigravidae concerning the relationship between plasma TG and the blood rheological variables may be relevant to suggest that fasting plasma TG may be a strong predictor of altered blood rheology-related cardiovascular disorders more in primigravidae than in multigravidae. This study could imply that monitoring of plasma TG may be necessary in pregnancy, especially in primigravidae.

Given that fasting plasma TG, haematocrit and white blood cell count have been implicated in hyperviscosity syndrome, as in pre-eclampsia (Woodward *et al*., 1999). The significant positive relationship of plasma TG with haematocrit, white blood cell count or blood viscosity found in this study may explain the pathophysiological role of increased fasting plasma TG in pregnancy-induced hypertension (Cong *et al*., 1994). The maternal age, gestational age or socioeconomical status (assessed by the level of education) could not explain the differences observed in these subjects. The fact that the study was conducted in the morning after a 12 h overnight fasting further ruled out the possibility that diet or physical activity influences our observations in this study. Furthermore, decreased haematocrit without any change in haemoglobin concentration and red blood cell count reflects haemodilution in these subjects, suggesting that increase in fasting plasma TG level was not due to haemoconcentration or contraction of plasma volume. Hence, increased fasting plasma TG in the pregnant women appears to be due to the influence of high circulating levels of ovarian steroid hormones. Although, plasma level of these hormones were not determined in the present study, but evidence exist that high plasma levels of these sex steroids during normal pregnancy are associated with hypertriglyceridemia (Smolarzyk *et al*., 2001; Herrera, 2002; Livingstone and Collison, 2002). It is biologically conceivable that elevated plasma TG might promote cardiovascular disease, possibly by increased blood viscosity, haematocrit and white blood cell count (Lowe, 1994). However, the associations between plasma TG and these variables may be a cause or consequence (Lowe, 1994). Hence, the causal role of plasma TG can only be confirmed by large randomized trials of TG-lowering agents.

CONCLUSION

These results have demonstrated that plasma TG significantly related to blood viscosity; haematocrit and white blood cell count in normal pregnancy. The study suggests that fasting plasma levels of TG could predict blood viscosity, haematocrit, haemoglobin concentration and white blood cell count in primigravidae, but the association is likely to be lost with successive pregnancy.

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