ORIGINAL RESEARCH REPORT

Circulating levels of plasma lipids and cardiovascular risk in Nigerian women with severe preeclampsia

Ifeoma C. Udenze, Babasola O. Okusanya[1], Oyetunji O. Soriyan, Iwuchukwu O. Ajie, Ephraim U. Egbuagha

Departments of Clinical Pathology and [1]Obstetrics and Gynaecology, College of Medicine, University of Lagos, Lagos, Nigeria

ABSTRACT

Background and Objectives: Preeclampsia has been associated with disorders of lipid metabolism. In the general population, dyslipidemia has been identified as a cause of endothelial damage and cardiovascular disease. Few studies have evaluated these relationships in Nigerian women with preeclampsia. This study aims to determine the level of plasma lipids in severe preeclampsia and assess the relationship between dyslipidemia, organ damage, and C-reactive protein (CRP) in Nigerian women with severe preeclampsia. **Materials and Methods:** This was a case-control study conducted on 50 women with severe preeclampsia and 50 with normal pregnancy matched for gestational age. The women were included from the antenatal clinic of the Lagos University Teaching Hospital, Lagos, Lagos State, Nigeria. Informed consent was obtained and sociodemographic and clinical data were obtained using a questionnaire. Blood was collected from the women after an overnight (10-12 h) fast for biochemical analysis. Employing the IBM SPSS statistical software, comparisons of the continuous variables and categorical variables were done using the Student's *t*-test and Chi-square test, respectively. Correlation analysis was used to determine the associations between the variables. Statistical significance was set at $P < 0.05$. **Results:** The levels of high-density lipoprotein (HDL) cholesterol were significantly lower ($P < 0.0003$) and the levels of triglyceride (TG), low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC) were significantly higher in women with severe preeclampsia compared to the controls ($P < 0.0005$, $P < 0.007$, $P < 0.009$, respectively). The HDL/LDL ratio was significantly lower and CRP was significantly higher in severe preeclampsia ($P < 0.0001$ and $P < 0.0002$, respectively). The lipid profile parameters showed a significant association with the markers of organ dysfunction. TG showed a statistically significant correlation with uric acid, creatinine, alkaline phosphatase (ALP), systolic blood pressure (SBP), and diastolic blood pressure (DBP). HDL showed a statistically significant correlation with uric acid, ALP, aspartate aminotransferase (AST), SBP, and DBP. While TC showed a statistically significant correlation with SBP and DBP, TG, in addition, had a statistically significant correlation with CRP in women with severe preeclampsia. **Conclusion:** Severe preeclampsia is associated with dyslipidemia, which has been linked to organ damage and an increased cardiovascular risk in Nigerian women. Although dyslipidemia resolves with each pregnancy, risk of cardiovascular disease in the future remains. Thus, continuous monitoring of Nigerian women with a history of severe preeclampsia is suggested.

Key words: Cardiovascular risk, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, plasma lipids, pregnancy, severe preeclampsia, total cholesterol, triglyceride

Address for correspondence:
Dr. Ifeoma C. Udenze,
Department of Clinical Pathology,
College of Medicine, University
of Lagos, Lagos, Nigeria.
E-mail: kristyudenze@ymail.com

Access this article online

Quick Response Code:

Website: www.jcsjournal.org

DOI: 10.4103/2408-7408.179680

INTRODUCTION

Preeclampsia is a pregnancy-specific, hypertensive disorder with multisystem involvement. It is usually associated with raised blood pressure and proteinuria. Preeclampsia affects 5-10% of all pregnancies, with significant maternal and perinatal mortality and morbidity.[1-3] The prevalence of preecclampsia in Nigeria is about 5.6%.[4]

According to the National High Blood Pressure Education Program Working Group[5] and the International Society for the Study of Hypertension in Pregnancy,[6] preeclampsia is defined as the onset after 20 weeks gestation of proteinuria (≥300 mg/24 h or ≥100 mg/L, equivalent to ≥2+ on dipstix urinaysis) on at least two random urine samples at least 4-6 h apart but not more than 7 days apart, and systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg measured using an appropriately sized cuff repeatable at least 4-6 h apart but not more than 7 days apart and a remission of these symptoms by 6 weeks postpartum.[5,6]

Despite extensive investigation, important pathophysiological aspects of preeclampsia remain elusive.[7] Widespread endothelial dysfunction affecting multiple systems has been implicated in the pathophysiology of preeclampsia.[7] Dyslipidemia is one of the strong predictors of cardiovascular disease causing endothelial damage and loss of vasomotor function and may contribute to the endothelial lesions and organ damage observed in preeclampsia.[8-10] The association of altered lipid profile and essential hypertension is well-documented[11] but the role of dyslipidemia in the pathophysiology of preeclampsia is still being investigated. A recent systematic review has linked preeclampsia with increased future risk of cardiovascular disease.[12]

Many studies have reported altered lipid patterns in preeclampsia,[13-15] including a few in Nigerian women[16,17] but the association between incident preeclampsia and cardiovascular risk in Nigerian women with preeclampsia has not been reported.

As of now, there is no effective prophylactic therapy for preeclampsia and delivery of the baby remains the only definitive treatment. Some researchers have proposed the use of statins in the prevention of preeclampsia.[11,18] This is because its beneficial effects extend beyond lipid-lowering and involve endothelial function modification, immunoinflammatory responses modulation, and prevention of thrombus formation.[11,19] It is important, therefore, that the interplay between dyslipidemia and preeclampsia be understood as identification of such relationships will better direct interventional and therapeutic strategies for the management of preeclampsia and its consequences.

This study aims to compare the level of plasma lipids in women with severe preeclampsia with levels in normal pregnancy and determines the relationship, if any, between dyslipidemia, organ damage, and C-reactive protein (CRP) in Nigerian women with severe preeclampsia.

MATERIALS AND METHODS

During the period from July 2012 to August 2013, 50 gestational age-matched pregnant women attending the antenatal clinic at the Lagos University Teaching Hospital, Lagos, Lagos State, Nigeria who were diagnosed with severe preeclampsia and 50 pregnant women without hypertension or proteinuria as controls who were in their third trimesters of pregnancy were consecutively recruited for this study.

Severe preeclampsia was defined as SBP ≥160 mmHg and/or DBP ≥110 mmHg, and ≥2+ of proteinuria. Pregnancy was dated from the last menstrual period and confirmed by clinical examination or ultrasonography.

Pregnant women with multiple gestation, diabetes, and sickle cell disease were excluded from the study. The Health Research Ethics Committee of the hospital approved the study protocol. Written informed consent was obtained from the participants. Clinical and demographic information including age, ethnicity, level of education, marital status, medical history, and history of index and previous pregnancies of the women were obtained using a structured questionnaire.

Venous blood was collected from the women after an overnight fast (between 10-12 h). The total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), creatinine, urea, and uric acid were estimated from lithium heparin plasma using reagents from Biolabo laboratories (02160, Maizy, Picardy, France). Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were estimated from lithium heparin plasma using reagents from Randox Laboratories Limited (Antrim, Ireland, UK, BT29 4QY). Spectrophotometric methods were employed for the biochemical analysis on a semiautomatic biochemistry analyzer BS3000P (SINNOWA Medical Science and Technology Co. Ltd., Nanjing, Jiangsu Province, China, 211135). Plasma levels of CRP were determined from ethylenediaminetetraacetic acid (EDTA) plasma using reagents from BioVendor R and D (62100 Brno, Czech Republic) by an enzyme-linked immunoassay technique on Acurex Plate Read (Acurex Diagnostics, Ohio, CO, USA, 419-872-4775).

Statistical analysis

The data were analysed using the IBM (Sun Microsystems, USA) SPSS version 19.0 package. Independent Student's *t*-test, Chi-square test, and Pearson's correlation were employed for the analysis. Statistical significance was set at $P < 0.05$.

RESULTS

The women were in their third trimesters of pregnancy with a mean gestational age of 31.0 ± 3.8 weeks. The women also did not differ in their mean chronological age. The mean

age of the women with preeclampsia was 31.9 ± 6.3 years and it was 32.3 ± 5.8 years for the normotensive women ($P = 0.82$). Both groups of women were also similar in some sociodemographic characteristics.

Table 1 compares the sociodemographic and clinical characteristics of the women with severe preeclampsia and those of the normotensive controls.

Table 2 shows the laboratory parameters of the women with severe preeclampsia and controls.

All the lipid parameters were significantly elevated in the women with severe preeclampsia. Some of the markers of renal (creatinine, uric acid) and liver (AST, ALP, GGT) injuries as well as CRP were also significantly elevated in severe preeclampsia.

Table 3 shows Pearson's correlation coefficient of the association of the lipid parameters with the markers of organ dysfunction in severe preeclampsia.

The lipid parameters showed a significant correlation with the markers of organ dysfunction.

DISCUSSION

This study reports significantly increased levels of the lipid profile parameters, LDL, TG, and TC and significantly decreased HDL levels in the group with severe preeclampsia compared to the controls. This is similar to the findings of studies conducted by many authors.[13-15] Das *et al.*[20] reported a difference in the TG values alone in women with preeclampsia compared to the normotensive controls. In the study by Das *et al*., the heat test, a nonspecific test, was used to determine proteinuria. It is possible that some of the women may have been misclassified by that procedure. The study by Demir *et al.*[21] reported a difference only in HDL of the lipid profile parameters in women with preeclampsia compared to the controls but the study did not discriminate between the mild and severe forms of the disease.

Normal pregnancy is associated with increase in TG, TC, and HDL.[22,23] In the first trimester, there is an increased deposition and hypertrophy of the maternal fat stores with an increased expression of insulin receptors such that glucose is available to meet the metabolic demand of the growing fetus. Increased maternal insulin and increased progesterone lead to lipogenesis with increased production of lipids, which are then transported across the placenta and metabolized for the normal growth and development of the fetus.[22] However, these changes are generally non-atherogenic and return to prepregnancy levels following delivery. Women with preeclampsia

Table 1: Sociodemographic and clinical characteristics of the study participants

Characteristics	Severe PET, *n*=50 (%), mean±SD#	Controls, *n*=50 (%), mean±SD	*P*
Age (years)	31.90±6.34	32.33±5.88	0.82
SBP (mmHg)	170.2±22.71	110.90±15.74	<0.0001*
DBP (mmHg)	100.90±37.74	71.38±6.37	<0.0001*
BMI? (kg/m²)	29.12±4.69	26.97±4.91	0.093
Ethnic group	25 (50)	22 (44)	0.33
Igbo	23 (46)	22 (44)	
Yoruba	2 (4)	6 (12)	0.078
Others	50 (100)	47 (94)	
Marital status	0 (0)	3 (6)	0.69
Married	30 (60)	28 (56)	0.84
Single	20 (40)	22 (44)	0.46
Parity	30.95±3.79	31.23±4.77	0.0009*
Primipara	5 (10)	3 (6)	
Multipara	45 (90)	47 (94)	
Gestational age at delivery (weeks)	10 (20)	0 (0)	
History of chronic hypertension	40 (80)	50 (100)	
History of preeclampsia			

*Statistically significant, #SD=Standard deviation, ?BMI=Body mass index, PET=Preeclampsia, SBP=Systolic blood pressure, DBP=Diastolic blood pressure

Table 2: Laboratory parameters of women with severe preeclampsia and the controls

Parameter	Severe preeclampsia (mean±SD)	Controls (mean±SD)	*P*
HDL (mmol/L)	0.89±0.33	1.39±0.44	0.0003*
TG (mmol/L)	1.82±0.33	1.36±0.43	0.0005*
TC (mmol/L)	6.07±1.81	4.75±0.94	0.009*
LDL (mmol/L)	4.34±1.60	2.74±0.90	0.0007*
LDL/HDL ratio	5.36±1.23	3.22±1.09	0.03*
Creatinine (µmol/L)	175.11±137.88	60.97±15.20	0.0013*
Uric acid (µmol/L)	448.83±104.73	215.05±44.75	<0.0001*
Urea (µmol/L)	3.95±2.84	3.74±7.57	0.91
ALT (U/L)	14.51±19.27	14.27±2.84	0.96
AST (U/L)	43.85±27.36	4.08±1.29	<0.0001*
ALP (U/L)	248.96±112.29	146.81±6.08	<0.0001*
GGT (U/L)	31.63±33.73	8.23±2.71	0.005*
CRP (Mg/L)	44.98±37.50	6.97±13.06	0.0002*

*Statistically significant. HDL=High-density lipoprotein, TG=Triglyceride, TC=Total cholesterol, LDL=Low-density lipoprotein, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ALP=Alkaline phosphatase, GGT=Gamma-glutamyl transferase, CRP=C-reactive protein

Table 3: Correlation of markers of organ dysfunction and CRP with lipid parameters in severe preeclampsia

Parameter	TG	HDL	TC
Uric acid	0.326*	−0.617*	0.201
Creatinine	0.407*	−0.083	0.237
ALP	0.413*	−0.497*	0.212
AST	0.243	−0.477*	0.272
GGT	0.234	−0.279	0.135
SBP	0.496*	−0.400*	0.527*
DBP	0.370*	−0.371*	0.536*
CRP	0.401*	−0.298	0.072

*Statistically significant *P*<0.05. AST=Aspartate aminotransferase, ALP=Alkaline phosphatase, GGT=Gamma-glutamyl transferase, CRP=C-reactive protein, SBP=Systolic blood pressure, DBP=Diastolic blood pressure

display additional alterations in their blood lipids. There is limited data demonstrating the effect of elevated blood pressure on lipid levels but the interplay of hypertension and dyslipidemia[11] suggests that the new onset hypertension of preeclampsia leads to further increases in the atherogenic lipids with a decrease in the cardioprotective HDL cholesterol.

Insulin resistance has also been associated with preeclampsia.[23] Insulin resistance promotes a state of dyslipidemia. In insulin resistance, lipoprotein lipase is not fully activated. This causes decreased hydrolysis of TG in very low-density lipoprotein (VLDL) cholesterol with decreased VLDL degradation. The net effect is an increased VLDL level. In lipoprotein remodeling, the cholesteryl ester transfer protein is responsible for the transfer of TGs from VLDL to LDL and HDL in exchange for cholesteryl ester. The transfer of cholesteryl ester to the TG-rich VLDL makes it more atherogenic. A higher proportion of TG is transferred from the TG-rich VLDL to LDL and HDL. This makes them more susceptible to hepatic lipase and endothelial lipase. The hydrolysis of the TG-rich LDL produces a preponderance of small, dense LDL and HDL particles.[24] The smaller HDL particles are more avidly removed by the kidneys, leading to low HDL-cholesterol values.[24,25]

Preeclampsia has been associated with varying severity of organ damage, especially the liver, kidney, and the hematological and central nervous systems.[26] This study reports an increase in some markers of organ damage in women with severe preeclampsia compared to the controls. Plasma creatinine, uric acid, AST, ALT, and GGT were significantly elevated in severe preeclampsia. Other authors also stated similar findings in women with preeclampsia.[27,28] The widespread endothelial injury in preeclampsia caused by the release of various vasoactive factors by an ischemic placenta has been implicated in the pathogenesis of organ damage in preeclampsia.[7]

This study also reports a significant correlation between the lipid profile parameters and the markers of organ damage. TG and HDL correlated significantly with some markers of renal and liver damage as well as with hypertension while TC correlated with SBP and DBP alone. The study conducted by Lima *et al.*[15] showed a correlation between the higher levels of VLDL and proteinuria in women with preeclampsia. These findings suggest that dyslipidemia contributes to the endothelial dysfunction that underlies organ damage, which is associated with preeclampsia.

The LDL/HDL ratio is an index of cardiovascular risk,[29] with high values indicating high cardiovascular risk status. From this study, the women with severe preeclampsia had significantly higher LDL/HDL ratio compared to those with normotensive pregnancy. These abnormal lipid patterns were thought to be non-atherogenic as they resolved soon after delivery. Emerging evidence, however, suggests that women who have had preeclamptic pregnancies were at a greater risk of cardiovascular disease in the future than those who have had normotensive pregnancies.[12] It is possible that the endothelial lesions were incompletely resolved and predisposed these women to future cardiovascular events.[12] This study also showed that 20% of women with severe preeclampsia had had previous episodes of the disease in earlier pregnancies; the effect on the endothelium could be cumulative, hence resulting in an increase in future cardiovascular risks in these women.

In this study, CRP, which is an independent marker of inflammation and cardiovascular risk, was also significantly elevated in severe preeclampsia. Several previous studies have reported increased CRP in this group. Demir *et al.*[21] reported increased lipoprotein (a) levels in women with preeclampsia, another indication of increased cardiovascular risk in preeclampsia. This study further finds a significant correlation between CRP and TG in women with preeclampsia. Focal increase of apolipoprotein B (ApoB) containing lipoproteins in the intima of the blood vessels is the first stage in the series of events leading to atherosclerosis.

The sequestered lipoproteins become oxidized and the chemically modified lipids induce inflammation and cytokine release that results in the evolution of the fatty streak to the complex fibro-fatty atherosclerotic lesion.[30] The concurrent endothelial damage by placental factors and hypertension may likely serve to accelerate these events. Morphological features of endothelial lesions in preeclampsia have been found to be similar to those of atherosclerosis outside pregnancy,[31] showing that these women may be susceptible to cardiovascular disorders both during and after pregnancy.

CONCLUSION

Women with severe preeclampsia have increased atherogenic lipids: Triglyceride, low density lipoprotein cholesterol and total cholesterol and a decreased cardioprotective lipid high density lipoprotein cholesterol which are associated with organ damage and increased cardiovascular risk. Although these effects recede after pregnancy, studies have shown increased susceptibility of these women to future cardiovascular diseases. Continued and long-term follow-up of these women for the early detection of the cardiovascular disease is, therefore, suggested.

REFERENCES

1. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. J Hypertens 2010;28:1349-55.
2. Duley L. The global impact of pre-eclampsia and eclampsia.

Semin Perinatol 2009;33:130-7.
3. Igberase G, Ebeigbe P. Eclampsia: Ten-years of experience in a rural tertiary hospital in the Niger delta, Nigeria. J Obstet Gynaecol 2006;26:414-7.
4. Alphonsus NO, Okolo AA. Perinatal outcome in patients with Pre-eclampsia in Benin City, Nigeria. Trop J Obstet Gynaecol 2004;21:148-52.
5. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000;183:S1-22.
6. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX-XIV.
7. Reslan OM, Khalil RA. Molecular and vascular targets in the pathogenesis and management of the hypertension associated with preeclampsia. Cardiovasc Hematol Agents Med Chem 2010;8:204-26.
8. Wong ND, Lopez V, Tang S, Williams GR. Prevalence, treatment and control of combined hypertension and hypercholesterolemia in adults in the United States. Am J Cardiol 2006;98:204-8.
9. Anderson M, Castelli P, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA 1987;257:2176-80.
10. Nickenig G, Harrison DG. The AT (1)-type angiotensin receptor in oxidative stress and atherogenesis: Part I: Oxidative stress and atherogenesis. Circulation 2002;105:393-6.
11. Dalal JJ, Padmanabhan TN, Jain P, Patil S, Vasnawala H, Gulati A. LIPITENSION: Interplay between dyslipidemia and hypertension. Indian J Endocrinol Metab 2012;16:240-5.
12. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: Systematic review and meta-analysis. Eur J Epidemiol 2013;28:1-19.
13. Aziz R, Mahboob T. Pre-eclampsia and lipid profile. Pak J Med Sci 2007;5:751-4.
14. Phalak P, Tilak M. Study of lipid profile in pre-eclampsia. Indian J Basic Appl Med Res 2012:2:405-9.
15. Lima VJ, Andrade CR, Ruschi GE, Sass N. Serum lipid levels in pregnancies complicated by preeclampsia. Sao Paulo Med J 2011;129:73-6.
16. Irinyenikan TA, Arowojulo A, Olayemi O. Comparative study of serum lipids in normotensive and preeclamptic Nigerian women. Int J Med Biomed Res 2014;3:137-45.
17. Enaruna NO, Idemudia JO, Aikoriogie PI. Serum lipid profile and uric acid levels in preeclampsia in University of Benin Teaching Hospital. Niger Med J 2014;55:423-7.
18. Morton S, Thangaratinam S. Statins in pregnancy. Curr Opin Obstet Gynecol 2013;25:433-40.
19. Vlachadis N, Tsamadias, V, Economou E. Statins in pregnancy: Safety and perspectives of therapeutic applications. BJOG 2013;120:1439-40.
20. Das S, Char D, Sarkar S, Das P, Saha PK, Biswas S. Comparison of Lipid Profiles in Normal Pregnancy and in Pre-Eclampsia: A case control study. JDMS 2011;11:53-5.
21. Demir B, Demir S, Atamer Y, Guven S, Atamer A, Kocyigit Y, *et al*. Serum levels of lipids, lipoproteins and paraoxonase activity in pre-eclampsia. J Int Med Res 2011;39:1427-31.
22. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine 2002;19:43-55.
23. Roberts JM, Gammill H. Insulin resistance in preeclampsia. Hypertension 2006;47:341-2.
24. Ginsberg HN, Zhang YL, Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res 2005;36:232-40.
25. Krauss RM. Triglycerides and atherogenic lipoproteins: Rationale for lipid management. Am J Med 1998;105:58S-62.
26. ACOG Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002;99:159-67.
27. Munazza B, Raza N, Naureen A, Khan SA, Fatima F, Ayub M, *et al*. Liver function tests in preeclampsia. J Ayub Med Coll Abbottabad 2011;23:3-5.
28. Manjareeka M, Nanda S. Elevated levels of serum uric acid, creatinine or urea in preeclamptic women. Int J Med Sci Public Health 2013;2:43-7.
29. Lemieux I, Lamarche B, Couillard C, Pascot A, Cantin B, Bergeron J, *et al*. Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: The Quebec Cardiovascular Study. Arch Intern Med 2001;161:2685-92.
30. Girn HR, Orsi NM, Homer-Vanniasinkam S. An overview of cytokine interactions in atherosclerosis and implications for peripheral arterial disease. Vasc Med 2007;12:299-322.
31. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340:115-26.

How to cite this article: Udenze IC, Okusanya BO, Soriyan OO, Ajie IO, Egbuagha EU. Circulating levels of plasma lipids and cardiovascular risk in Nigerian women with severe preeclampsia. J Clin Sci 2016;13:72-6.

Source of Support: Nil, **Conflict of Interest:** None declared.