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Lipid Profile Changes In Pregnancies Complicated With Hypertensive Disease: A Matched Case Control Study.

Shadrack Muindu Mweu[1], Alfred Osoti[2], Joseph J.N. Ngeranwa[3], Christine B. Sekadde kigondu[4], Wilfred Gatua[5], Joseph Kangethe Mburu[5]

[1](Department of Applied Science, The Kabete National Polytechnic, Kenya)
[2] (Department of Obstetrics and Gynaecology, University of Nairobi, Kenya)
[3](Department of Biochemistry and Biotechnology, Kenyatta University, Kenya)
[4](Department of Human Pathology, University of Nairobi, Kenya)
[5](Department of Laboratory Medicine, Kenyatta National Hospital, Kenya)
Corresponding Author: Shadrack Muindu Mweu

***Abstract*:** *Metabolism of lipids is altered during pregnancy to cater for the increased demand for fats to support the growth and development of the fetus. Hypertensive disease in pregnancy (HDP) is a major cause of morbidity for both mother and fetus. This study was aimed at determining the lipid profile changes in hypertensive pregnancies which could be used as a biomarker for HDP. This case control study comprised of 85 women with hypertensive disease in pregnancy (cases) and an equal number of matching controls. We compared the third trimester lipid profile in hypertensive and normal pregnancies. Fasting blood samples were analysed for total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) using enzymatic and spectrophotometric methods in an autoanalyzer. The serum low density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald's formula. Statistical analysis was done using student's t-test for continous variables and chi-square test for categorical values. Compared to normotensive controls, hypertensive cases had statistically significantly higher levels of TC (6.80±2.28 versus 5.22±0.59), TG (2.59±0.86 versus 2.21±0.47) and LDL-C (3.97±2.17 versus 2.65±0.63) ($p<0.05$), however there was no statistically significant differences in HDL-C between the hypertensive cases (1.66±0.66) and control (1.53±0.30) groups ($p = 0.11$). Hypertensive disease in pregnancy is associated with deranged lipid profile in the third trimester of pregnancy. Fasting lipid profile test may be a biomarker for onset and progression of HDP. Additional studies should evaluate the post-partum and long term effects of the changes in lipid profile.*

Keywords: *Lipid profile, hypertension, third trimester, pregnancy.*

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I. Introduction

Hypertensive disease in pregnancy (HDP) is a major cause of morbidity for both mother and fetus in developing countries. Hypertension is a common medical problem that affects 20-30% of the adult population and complicates more than 5%-8% of all pregnancies worldwide [1,2]. Metabolism of lipids is altered during pregnancy to cater for the increased demand for fats to support the growth and development of the fetus. It is known that high levels of many steroids occur as pregnancy advances. The circulating steroids are derived from cholesterol and therefore lipid metabolism is very intriguing as cholesterol is a major factor in the development of atherosclerosis [3]. As gestation advances, changes in circulating hormone levels affect lipid metabolism which in normotensive pregnancies is marked by the increase in serum levels of total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) [4,5]. The role of lipid metabolism in the pathophysiology of HDP has not been described in the Kenyan population. The uteroplacental blood flow system has been the focus of the patho-physiology of the disease due to the consistent abnormalities of the placentae and uteroplacental vascular interface. The disease mostly occurs in primigravidas with immature uterine vasculature [6]. The vascular changes which characterize the disease may be related to abnormal lipid metabolism during pregnancy. During the management of this disease clinicians are mainly concerned about the elevated blood pressure and the harmful effects on both the mother and the fetus. In most cases the neonate bears the burden of the disease because premature deliveries are performed to preserve the health of the mother. Lipid levels can be controlled and if found to alleviate the hypertension this can be used as an intervention method to delay delivery and prolong fetal gestation thus lower neonatal morbidity and mortality.

II. Methods

The study was carried out at the department of reproductive health, Kenyatta National Hospital. The study design was matched case control with an equal number of cases and controls. The controls were matched according to the maternal age, gestational age and parity of the cases. A total 170 pregnant women were enrolled in the study grouped into two categories: 85 pregnant hypertensive women (cases) and 85 normal pregnant women (controls). The cases were chosen from among patients admitted in the antenatal ward and those presenting for ante-natal care while the controls were recruited from among pregnant women who attended the ANC clinic at KNH during the study period. The serum LDL-C level was calculated using the Friedewald's formula. The study was approved by Kenyatta National Hospital – University of Nairobi (KNH-UoN) ethical research committee (Protocol number P53/02/2015). Cases were included if they were; hypertensive pregnant in the third trimester, aged 18-45 years without history of concomitant chronic diseases such as diabetes mellitus, renal disease and HIV/AIDS. Age >45 years were also excluded because pregnancy in those age groups is considered unsafe since the incidence of miscarriage and ectopic pregnancies goes up substantially with age [7]. The control group comprised of consenting healthy pregnant women who had a BP ≤140/90 mmHg and no cormobid conditions such as diabetes mellitus, renal disease and HIV/AIDS. From each hypertensive case and healthy control, 4 ml of fasting blood samples were collected by venipuncture from an arm vein, allowed to clot and analysed for TC, TG and HDL-C using enzymatic and spectrophotometric methods using an automated biochemistry analyzer (Human Diagnostics, Germany). The serum LDL-C level was calculated using the Friedewald's formula. Data was entered into excel spread sheet and imported into SPSS version 20 for analysis. Results were presented as mean ± SD and t-test was used to means between the cases and control groups for continuous variables. The odds of developing HDP for the cases and controls was compared using odds ratio and chi-square test to determine the level of significance. In all cases a P value of <0.05 was considered statistically significant.

III. Results

Cases and controls were matched on maternal age, parity and gestational age. The mean maternal age of the study participants was 29.22±5.5 years (Table 1). When categorised by age groups 16.7%, 35.6%, 29.4% and 12.8% of the participants were in the age brackets <25 ,25-30, 30-35 and >35 years respectively. The mean systolic and diastolic blood pressure of the cases was 166.96 ± 17.91 and 103.91 ± 12.10 mmHg respectively while the controls had a mean systolic and diastolic blood pressure of 115.93 ± 13.24 and 74.52 ± 8.8 mmHg respectively. The differences in mean systolic and diastolic blood pressure values between cases and controls were statistically significant (p values 0.024 and 0.014 respectively). All the participants were in the third trimester where third trimester which was defined as >26 weeks of gestational age (GA). Because participants were matched on GA, for both cases and controls, 54.1% of the participants were above 36 weeks, while 8.2% and 37.6% were at 27-31 weeks and 31-35 gestational weeks respectively.

Table: 1 Socio- demographic and clinical characteristics of the study population

Parameters		**Cases Mean (SD) Or Number(%)**	**Controls Mean (SD) Or Number(%)**	**P value**
Maternal age (years)		29.22 ± 5.51	29.11 ± 5.3	1.000
Blood pressure (mmHg)	Systolic	166.96 ± 17.91	115.93 ± 13.24	0.024*
	Diastolic	103.91 ± 12.10	74.52 ± 8.8	0.014*
Gestational Age (weeks)	< 31	07 (8.2%)	07 (8.2%)	1.000
	31-35	32 (37.6%)	32 (37.6%)	
	36-40	46 (54.1%)	46 (54.1%)	
Parity	Para 0+0	19 (22.3%)	19 (22.3%)	1.000
	Para 1+0	26 (30.5%)	26 (30.5%)	
	Para 2+0	21 (24.7%)	21 (24.7%)	
	Para 3+0	13 (15.3%)	13 (15.3%)	
	Para 4+0	06 (7.0%)	06 (7.0%)	

The lipid profiles comprising serum levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were compared between hypertensive and normotensive women (Table 2). The mean TC level in cases was 6.80 ±2.28 mmol/l compared to 5.22 ±0.59 mmol/l in controls, while TG level was 2.59 ±0.86 mmol/l in cases and was 2.21 ±0.47mmol/l in normotensive controls. Similarly, hypertensive women had a mean HDL-C level of 1.66 ±0.66 mmol/l compared to normotensive controls of 1.53 ±0.30 mmol/l. Finally the mean LDL-C level for hypertensive cases

was 3.97 ±2.17 mmol/l compared to 2.65 ±0.63 mmol/l for normotensive controls. Three of the four parameters TC, TG and LDL-C were statistically significantly different between hypertensive cases and normotensive controls ($p<0.005$). In contrast there was no statistically significant difference for HDL-C between the hypertensive and control groups ($p = 0.11$). The mean value of the ratio of TC to HDL-C in the hypertensive group was 4.52 ±2.21 and 3.50 ±0.68 hypertensive and normotensive control groups respectively and was statistically significant ($p <0.05$).

Table 2. Comparison of lipid profile of hypertensive group and controls

Parameter	**Hypertension in pregnancy (Cases)**	**Normotensive (Controls)**	**p-value**
TC	MEAN ±SD	MEAN ±SD	< 0.001*
	6.80 ±2.28	5.22 ±0.59	
TG	2.59 ±0.86	2.21 ±0.47	**0.001***
HDL-C	1.66 ±0.66	1.53 ±0.30	0.114
LDL-C	3.97 ±2.17	2.65 ±0.63	**<0.001***
Ratio (TC:HDL)	4.52 ±2.21	3.50 ±0.68	**<0.001***

SD =standard deviation, *p<0.05 represents statistically significant values.

Using the clinical chemistry laboratory cut offs, parameters were categorized as normal or high using the following reference values; TC 0-5.7 mmol/l, TG 0.3-2.3 mmol/l, HDL-C 0.9-1.68 mmol/l, LDL-C 1.0-3.9 mmol/l and TC/HDL upto 5. Using these cut offs, proportions, odds and odds ratios (OR) of having elevated TC, TG, HDL-C, LDL-C and TC:HDL-C were obtained for cases compared to controls. The odds of developing hypertension in pregancy was highest for LDL-C> 3.9 mmol/l followed by TC>5.7 mmol/l and TG> 2.3 mmol/l. Women who had TC>5.7 mmol/l had 2.25 odds of developing hypertension in pregnancy (OR 0.226; 95% Confidence Interval (CI) 0.19 – 0.439 p <0.001) while those with TG> 2.3 mmol/l, LDL-C> 3.9 mmol/l and TC:HDL-C ratio >5.0 had 1.48 (OR 0.487; 95% CI 0.263-0.899 p 0.021), 33.0 (OR 0.019; 95% CI 0.002 – 0.141 p <0.001) and 12.0 (0R 0.061; 95% CI 0.14-0.269 p <0.001) odds of developing hypertension in pregnancy respectively. Elevated HDL-C was associated with increased but not statistically significant odds of developing HDP (OR 0.67; CI 0.34 – 1.31 p 0.241).

Table: 3 Odds ratio of elevated lipid profile in hypertensive and normotensive women.

Parameter	Hypertension in pregnancy (Cases) (N/%)	Normotensive (Controls) (N/%)	Odds ratio	95% confidence interval		p-value
				Lower	Upper	
TC >5.7 mmol/l	54 (63.5%)	24 (28.2%)	0.226	0.118	0.431	< 0.001*
TG >2.3 mmol/l	46 (54.1%)	31 (36.4%)	0.487	0.263	0.899	0.021*
HDL-C >1.68mmol/l	29 (34.1%)	22 (25.8%)	0.674	0.348	1.306	0.241
LDL-C >3.9mmol/l	33 (38.8%)	1 (1.1%)	0.019	0.002	0.141	<0.001*
Ratio >5	24 (28.2%)	2 (2.35%)	0.061	0.14	0.269	<0.001*

*p<0.05 represents statistically significant odds ratio when odds of cases are compared to the odds of matching controls.

IV. Discussion

This case control study investigated the role of changes in lipid profile on the occurrence of hypertensive disease in pregnancy during the third trimester in subjects aged 19-40 years. Serum levels of total cholesterol (TC), triglycerides (TG) and low density lipoprotein cholesterol (LDL-C) were significantly higher in the hypertensive group compared to the normotensive control group while high density lipoprotein cholesterol (HDL-C) did not differ between the cases and controls. Similarly, when reference levels and laboratory cut offs were used, there was significant lower odds for TC> 5.7 mmol/l, TG> 2.3 mmol/l, LDL-C >3.9 mmol/l and TC:HDL-C ratio>5.0. These changes reflect the lipid profile pattern associated with hypertensive disease in pregnancy in the population studied. Findings of concurrently elevated TC, TG and

LDL-C in hypertensive pregnant women have been reported in India [8,9,10,11,12]. The increase in plasma levels of endogenous female sex hormones such as progesterone and the increased demand of fats by the fetus could be responsible for the elevation of TC. Elevation of TC is expected during the third trimester of normal pregnancies because this stage is characterized by increased breakdown of maternal lipids [13]. The findings of this study suggest that in hypertensive pregnancies survival of the fetus is promoted by increased breakdown rate of the maternal lipids. We observed significantly elevated LDL-C level in hypertensive women a finding previously reported in pregnant women at risk of developing pregnancy induced hypertension in Sudan [14]. This study did not find statistically significant difference in the serum levels of HDL-C between hypertensive and normotensive pregnant women. This similarity may be accounted for by the human placental lactogen (HPL) synthesized during pregnancy since it leads to insulin resistance which in turn decreases HDL-C synthesis. The mean serum level of HDL-C for both cases and controls were above the normal range cut off value. The increase in HDL-C could be responsible for exerting its protective effect from atherosclerosis. Low plasma level of HDL-C during pregnancy has been reported in Nigerian pregnant women [15]. The insulin resistance occasioned by HPL may be may be linked to the pathogenesis of HDP since it increases the accumulation of fats especially TG. Significantly increased levels of TG were observed in the hypertensive group suggesting that there could be increased synthesis of TG by the action of hepatic lipase in the liver during hypertensive than in normotensive pregnancies. Similar observation of TG elevation in HDP in different studies was attributed to a decrease in the activity of lipoprotein lipase which decreases catabolism at the adipose tissue level and whose net effect was an increase in circulating TG [16]. The circulating TG is likely to be deposited in the predisposed spiral arteries and contribute to endothelial dysfunction a known finding in pregnancies complicated by hypertensive disease [17]. Hypertriglyceridemia may also be caused by the hepatic failure associated with HDP because the failure to remove the products of hydrolysis from circulation by the liver leads to the accumulation of TG. In another study the increase in TG level was linked to the reduction in fetoplacental perfusion [18].

V. Conclusions

In conclusion, this study suggests that fasting lipid profile test should be considered as a screening test for HDP in addition to the testing of proteins in urine. Since this study was done during the third trimester, similar studies should be carried out in the first and second trimesters of pregnancy to establish the rate and severity of lipid profile changes early in gestation. Reference ranges should be established for the lipid profile parameters in each trimester and the findings made available to clinicians to be used in the management of HDP.

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