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Increased Risk and Severity of Pre-Eclampsia among Peri-Urban Women in Kinshasa Province, Democratic Republic of Congo: The Role of Nutritional Transition, Obesity and Dyslipidemia

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Abstract: This study assessed the risk and severity of pre-eclampsia associated with obesity and dyslipidemia in a peri-urban population of Kinshasa Province, Democratic Republic of Congo (DRC). This case control study recruited 200 participants with preeclampsia as cases and 150 age-matched pregnant women without preeclampsia as controls at the LOMO Medical Centre, Kinshasa. Waist circumference, systolic and diastolic blood pressure, carotid intima-media thickness, serum lipids, C-peptide and Homeostasis-Insulin Resistance Index (HOMA-IR) were measured. There was a significant positive correlation between preeclampsia severity and most markers of metabolic syndrome with biologic gradient. The means±SD for controls, participants with mild and severe pre-eclampsia, respectively were: BMI (kg/m^2) 22.2±5.5, 24.1±5.7 and 25.6±6.0, $p<0.0001$; Total cholesterol (mg/dL) 105.0±56.8, 153.6±63.1 and 173.3±60.1, $p<0.0001$; LDC (mg/dL) 107.3±3.4, 112.2±4.7 and 122.6±3.5, $p = 0.006$; TNF-α (ng/L)101.8±4.8, 103.1±6.6, 137.7±5.2 $p<0.0001$; HOMA-IR (mg/dL) 7.3±0.9, 8.3±1.1 and 11.3±0.7, $p<0.0001$. There was a negative correlation between pre-eclampsia severity and HDL (mean±SD mg/dL) controls: 41.5±3.2, mild pre-eclampsia: 42.4±4.7 and severe pre-eclampsia: 29.4±2.4, $p = 0.003$. High BMI increases the risk and severity of pre-eclampsia which may increase the risk of subsequent chronic cardio-metabolic diseases in the mothers. Contrary to other studies, LDL was elevated among pre-eclampsia women in the study population.

Key words: Cardiovascular diseases, dyslipidaemia, obesity, pre-eclampsia, Democratic Republic of Congo, population

INTRODUCTION

Globally about 2.3 billion adults are overweight (BMI>25 kg/m^2) while 700 million are obese (BMI>30 kg/m^2) (Puoane *et al*., 2008). This is attributed to changes in dietary contents thatfavour high energy low fiber, processed foods; sedentary life styles and socio-economic developments such as rapid urbanization coupled with globalization (Puoane *et al*., 2008; Muaka *et al*., 2016). These social changes have been associated with an increased incidence of non-communicable diseases such as Type 2 Diabetes Mellitus (T2DM), cancers and cardiovascular diseases. Obesity is one of the established and modifiable determinants of pre-eclampsia.

In addition, pre-eclampsia is now known to be an independent risk factor for future cardiovascular disease in the mother (Chen *et al*., 2014; Bellamy *et al*., 2007); pre-eclampsia and metabolic syndrome in her progeny born from pre-eclamptic gestations (Tenhola *et al*., 2003; Vatten *et al*., 2003). High body mass index is not only associated with hypertensive diseases but also with increased risk of cancer (Laaksonen *et al*., 2004; Heikkila *et al*., 2009; Kruijsdijk *et al*., 2009). Hence, women presenting with hypertensive diseases in pregnancy with underlying obesity are likely to be predisposed to higher risk of various non-communicable diseases, severe morbidity and early mortality than non-obese females in the same age range. This study aimed to assess the risk and severity of pre-eclampsia associated with obesity and

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dyslipidemia in a peri-urban population of Kinshasa Province, DRC characterized by rapid urbanization (Muaka *et al*., 2016).

MATERIALS AND METHODS

Study setting: This case control study took place in 2008. The cases were participants with pre-eclampsia. The controls were age-matched pregnant women without preeclampsia. All participants were managed at the Maternity Unit of Lomo Medical Centre, Kinshasa, DRC.

Ethical consideration: The ethical approval for this study was granted by the institutional review board of Kinshasa University Medical School, DRC. Each participant gave written informed consent after receiving information on the purpose and process of the study. Each participant was managed in accordance with the Helsinki Declaration.

Sample size: During the study period, about 2100 antenatal women patients were monitored (eligible population). Two hundred of the women who developed pre-eclampsia were consecutively recruited into the study as cases. These were matched for age with 200 controls who delivered at term without developing pre-eclampsia. All cases and 150 controls who gave informed consent and had complete data were included in the current study.

Definitions: Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy (Tranquilli *et al*., 2014). Pre-eclampsia is characterised by the new onset of hypertension (>140 mmHg systolic or >90 mmHg diastolic) after 20 weeks gestation with proteinuria (spot urine protein/creatinine >30 mg/mmol or >300 mg/day or 2+ on dipstick testing); other maternal organ dysfunction: renal insufficiency (creatinine >90 umol/L; 1.02 mg/dL); liver involvement (elevated transaminases at least twice upper limit of normal±right upper quadrant or epigastric abdominal pain), neurological complications (such as eclampsia, altered mental status, blindness, stroke, hyperreflexia, severe headaches and persistent visual scotomata), haematological complications (thrombocytopenia-platelet count below 150,000/dL, DIC, haemolysis) and utero placental dysfunction (foetal growth restriction, abrupt placentae or IUFD). Severe pre-eclampsia is gestational hypertension (>160 mmHg systolic or >110 mmHg diastolic with or without systemic organ involvement. Eclampsia is hypertension (>140 mmHg systolic or >90 mmHg diastolic) after 20 weeks gestation with convulsions.

Clinical examination and laboratory methods: All participants were examined after fasting for at least 8 h and disclosure identity in terms of sex and age. Trained nurses measured height, weight, Waist Circumference (WC), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) according to standardized procedures. The certified sonographer (codified as BLM) examined the carotid artery B-mode ultrasound imaging using a Bio Sound Phase (Bio sound Inc., Indianopolis, USA), a device equipped with an annular array probe of 7.5 MHz. Carotid Intima-Media Thickness (cIMT) was measured at near and far wall interfaces of internal and external carotid arteries.

Blood (total, serum and plasma) samples were assayed immediately to measure concentrations of High Density Cholesterol (HDL), total cholesterol, triglycerides, Low Density Lipoprotein (LDL), oxidized Low Density Lipoprotein (oxLDL), C-peptide and glucose. Homeostasis-Insulin Resistance Index (HOMA-IR) was calculated using fasting glucose and insulin. The Hach DR/2010 was ideal for both field and mobile laboratory use since it is portable, operating from either battery or line power.

Statistical analysis: Proportions (percentages) of categorical variables were compared using chi square test while means of continuous variables were compared using Student's t-test or ANOVA. A p-value of <0.05 was considered as statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS) for windows Version 23.0 (SPSS Inc.) Chicago, Il, USA.

RESULTS AND DISCUSSION

The mean chronological and gestational ages of the study participants is shown in Table 1. The BMI, serum levels of total cholesterol, triglycerides, LDL, oxidized LDL, VLDL, HOMA-IR and uric acid increased significantly with the severity of pre-eclampsia. Waist and hip circumference were significantly different between all cases and controls with no clinically significant difference between mild and severe cases of pre-eclampsia/ eclampsia. Similarly, cIMT was higher among cases than normal pregnant women with similar mean values for mild

Table 1: Mean chronological and gestational age at recruitment

Variables	Controls	All cases of pre-eclampsia	Mild pre-eclampsia	Severe pre-eclampsia
Mean age (years)	33.5±5.2[a]	32.4±6.0	32.7±6.3[c]	32.3±6.3
Mean gestation age (WOA)	37.7±4.0[b]	31±7.9	27.1±6.5[d]	32.4±7.9

[a]p = 0.072 all cases and controls; [b]p<0.0001 all cases and controls; [c]p = 0.184 mild and severe preeclampsia; [d]p<0.0001 mild and severe preeclampsia

Table 2: Variation of metabolic syndrome markers with the severity of hypertensive disease in pregnancy

Biomarkers	Normal pregnancy (Mean±SD)	Mild preeclampsia (Mean±SD)	Severe preeclampsia/eclampsia (Mean±SD)	p-values
Body mass index (kg/m^2)	22.2±5.5	24.1±5.7	25.6±6.0	<0.0001
Waist circumference (cm)	76.7±10.0	76.4±10.5	83.7±12.9	<0.0001
Hip circumference (cm)	90.2±13.1	90.5±17.7	94.5±16.5	0.0270
Total cholesterol (mg/dL)	105.0±56.8	153.6±63.1	173.3±60.1	<0.0001
Triglycerides (mg/dL)	110.3±4.8	128.8±7.9	149.4±4.7	<0.0001
LDC-C (mg/dL)	107.3±3.4	112.2±4.7	122.6±3.5	0.0060
Oxidised LDL (iU/L)	106. 6±7.9	133.4±10.8	158.3±6.0	<0.0001
VLDL (mg/dL)	18.1±9.7	20.8±11	27.1±12.4	<0.0001
HDL-C (mg/dL)	41.5±3.2	42.4±4.7	29.4±2.4	0.0030
HOMA-IR (mg/dL)	7.3±0.9	8.3±1.1	11.3±0.7	<0.0001
cIMT (mm)	0.50±0.03	0.70±0.05	0.70±0.03	<0.0001
TNF α (ng/L)	101.8±4.8	103.1±6.6	137.7±5.2	<0.0001
IL-6 (U/mL)	268.7±13.5	207.1±19.3	359.8±10.9	<0.0001

LDL-C = Low Density Lipoprotein; oxidized LDL = oxidized Low Density Lipoprotein; VLDL = Very Low Density Lipoprotein; HDL-C = High Density Lipoprotein; HOMA-IR = Homeostasis-Insulin Resistance Index; cIMT = Carotid Intima-Media Thickness (cIMT)

and severe cases of pre-eclampsia/eclampsia. HDL which is usually protective against cardiovascular diseases, showed marked reduction along the gradient of pre-eclampsia severity (Table 2).

The current study established an increased risk of pre-eclampsia severity among women along a concentration gradient of biomarkers of metabolic syndrome. This is consistent with previous research which showed not only increased risk but also more severe manifestation of pre-eclampsia among women with obesity (Sharami *et al*., 2012; Wetzka *et al*., 1999; Ware-Jauregui *et al*., 1999; Hubel *et al*., 1996). This is not surprising as the study was conducted in peri-urban district of Kinshasa Province, DRC, characterized by rapid urbanization and nutritional transition (Puoane *et al*., 2008; Muaka *et al*., 2016). Of concern, however, is the finding that most cases were women in the upper range of normal BMI and lower range of overweight categories (mean BMI 24.1-25.6 kg/m^2).

Although, the aetiology and pathophysiology of pre-eclampsia is not yet fully understood, the underlying factors that increase the risk of pre-eclampsia include non-modifiable factors such as age, previous history of pre-eclampsia, multifetal pregnancy, primi-gravida and modifiable factors such obesity (Magdaleno *et al*., 2012).

The current study clearly demonstrated the increased risk of pre-eclampsia even among women considered to have normal BMI but in the upper range of normal with severe pre-eclampsia among those who were overweight or obese. This is consistent with other studies that observed similar association (Bodnar *et al*., 2007; Catov *et al*., 2007).

Pre-pregnancy maternal obesity and dyslipidemia are associated with increased risk of pre-eclampsia (Romundstad *et al*., 2010). In the current study, the structural manifestations of obesity were the elevated BMI, waist and hip circumference which varied positively with severity of pre-eclampsia. These too correlated with features of dyslipidemia such elevated total cholesterol, low density cholesterol, oxidized LDL, very low density LDL and reduced serum high density Lipoprotein whose derangement also increased with the severity of pre-eclampsia.

Increased waist circumference among women with pre-eclampsia is a feature of central/visceral obesity and white adipose tissue. TNF-α and IL-6 also lead to increased insulin resistance, another known risk factor for endothelial dysfunction and atherosclerosis (Grimble, 2002; Conrad *et al*., 1998; Kupferminc *et al*., 1994). In the current study, women with severe pre-eclampsia who also had the highest mean BMI had significantly higher mean levels of TNF-α, IL-6 and HOMA-IR than normotensive women and women with mild pre-eclampsia ($p<0.0001$). This is in agreement with the theories that implicate pre-pregnancy low grade inflammation, insulin resistance and endothelial cell dysfunction in the aetiopathogenesis of pre-eclampsia.

Insulin resistance leads to elevated production of mitochondrial superoxide (O_2) radicals (Lazo-de-la-Vega-Monroy and Fernandez-Mejia, 2013). The superoxide (O_2) radicals react with Nitric oxide (N_O) produced by the endothelium, reducing serum N_O concentration causing vasoconstriction but also producing the more potent peroxynitrite (ONOO) radicals (Kumar and Clark, 2002). Both O_2 and ONOO radicals oxidise fatty acids, lipoproteins and phospholipids, a process termed lipid peroxidation forming lipid peroxides. These lipid peroxides cause severe damage to plasma membranes and are also capable of diffusing to other cells, causing vascular permeability and inflammation by binding to oxidized low density lipoprotein (LOX) receptors with resultant apoptosis and endothelial activation (Kumar and Clark, 2002).

Endothelial activation, apart from predisposing to pre-eclampsia will lead to systemic endothelial

dysfunction and increased intima thickness which heralds atherosclerosis, a precursor of cardiovascular disease. Therefore, the elevated total cholesterol, LDL, VLDL and triglycerides and the diminished HDL (which serves to reduce peripheral VLDL and triglycerides) observed in the current study serve as a recipe for endothelial dysfunction and pre-eclampsia (Pritchard *et al*., 2002; Ngo *et al*., 1997).

However, obese women in DRC a country known to have iodine deficiency may be more prone to high levels of lipid peroxides during pregnancy since iodine, a potent antioxidant, reacts with lipids forming iodolipids which are less prone to oxidation by oxygen reactive species (Smyth, 2003; Omorogiuwa and Ozor, 2015). In a normal pregnancy, serum triglycerides increase 2 times above the pre-pregnancy levels and total cholesterol increases more than 50% by in the third trimester. These are expected to revert to normal within 6-10 weeks post partum (Phuse, 2012; Ogura *et al*., 2002). Although, a non-pregnant control group was absent in the current study, women with severe pre-eclampsia had a mean BMI >25 kg/m^2 and more severe derangement in all the biomarkers of metabolic syndrome. This is consistent with findings from other studies that also found excessive circulating maternal hypertriglyceridemia, more free fatty acids, reduced high density lipoprotein and increased concentrations of small LDL and oxidized LDL among women with pre-eclampsia (Qiu *et al*., 2006; Das *et al*., 2013).

In the current study, women who were overweight or obese not only tended to present with severe pre-eclampsia but also presented at a much later gestation age compared to women with mild pre-eclampsia (26.9 WOA for mild pre-eclampsia and 32.5 WOA for severe preeclampsia/eclampsia). Obesity, therefore, seems to predispose to severe pre-eclampsia later on in pregnancy, possibly by exacerbation of normal physiological lipid metabolism in the third trimester (Phuse, 2012; Ogura *et al*., 2002). This may be as a result of excessive LDL and VLDL substrates that are oxidized into lipid peroxides by O_2 and ONOO radicals (Kumar and Clark, 2002).

Unlike some who found no difference in the mean levels of LDL among pre-eclamptic and normotensive women, our study demonstrated elevated levels of LDL among pre-eclamptic women which increased with the severity of pre-eclampsia (Sharami *et al*., 2012; Bonetti *et al*., 2003). It has been proposed by some that LDL plays a critical role in the initiation of atherosclerosis by inhibition of endothelial NO synthase leading to oxidative endothelial damage, inflammation, secretion of growth factors and cytokines that lead to macrophage recruitment and smooth muscle proliferation (Pritchard *et al*., 2002; Ngo *et al*., 1997).

Indeed in the current study, patients with severe pre-eclampsia not only had the highest carotid intima thickness but also a higher BMI and more markedly deranged biomarkers of dyslipidemia. Furthermore, the increased carotid intima thickness, an early feature of atherosclerosis and cardiovascular disease (Kapur, 2015), may indicate the chronic low grade endothelial dysfunction associated with obesity which is made worse by the physiological changes of pregnancy. This may partially explain the higher risk of recurrent pre-eclampsia and cardiovascular disease that is usually higher in women who present with more severe pre-eclampsia (Chen *et al*., 2014). It is now known that the offspring of pre-eclampsia women, obese and diabetic women are at increased risk of metabolic syndrome or one or more of its constituent diseases such as hypertension, diabetes and cardiovascular diseases (Barker, 1997). This is thought to be a result of genetic and epigenetic changes and premature birth that is usually associated with these conditions.

Study strength: This study demonstrates the relationship between the structural and biochemical markers of obesity as well as the risk and severity of pre-eclampsia associated with derangement of these markers. This study seems to be the first to suggest that obesity increases the risk and severity of pre-eclampsia later in the second half of pregnancy. The non-inclusion of a non-pregnant control group is a limitation.

CONCLUSION

Contrary to other studies, this present study found elevated LDL among pre-eclampsia women. The study found significant increase in BMI, serum levels of total cholesterol, triglycerides, LDL, oxidized LDL, VLDL, HOMA-IR and uric acid with severity of pre-eclampsia. Additionally, the study reveal increased risk of pre-eclampsia even among women considered to have normal BMI but in the upper range of normal with severe pre-eclampsia among those who were overweight or obese. The study found patients with severe pre-eclampsia not only having the highest carotid intima thickness but also a higher BMI and more markedly deranged biomarkers of dyslipidemia. This study seems to be the first to suggest that obesity increases the risk and severity of pre-eclampsia later in the second half of pregnancy.

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