Original Article

Effects of Maternal Dyslipidemia on Maternal and Perinatal Outcomes in Enugu, Southeast Nigeria: A Prospective Cohort Study

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Abstract

Background: Maternal dyslipidemia is one of the consistent metabolic changes during pregnancy. There is a controversy as to whether maternal lipid disturbances in early pregnancy are associated with adverse maternal and perinatal outcome. **Aim:** To determine the effects of maternal dyslipidemia on maternal and perinatal outcomes. **Methods:** A prospective observational cohort study of eligible pregnant women attending antenatal clinic (ANC) at two tertiary hospitals in Southeast Nigeria. The attendees blood samples were collected for lipid profile analysis and those who met the criteria for dyslipidemia constituted the study (exposed) group, while those with normal lipid levels were the control (unexposed group). Both groups were followed up throughout pregnancy and in labor to determine the pregnancy and perinatal outcomes. **Results:** Compared with pregnant women with normal lipid profile, those with dyslipidemia were at higher risk of low birth weight (LBW) (RR: 9.40, CI 95%: 1.3-70.2, P = 0.005), intrauterine fetal death (IUFD) (RR: 5.98; 95% CI: 0.8-46.9; P = 0.04), still birth (RR: 6.84, CI 95%: 8.9-52.7, P = 0.03), and birth asphyxia (RR: 10.26, CI 95%:1.4-76.0, P = 0.003). **Conclusion:** Maternal dyslipidemia is associated with some adverse perinatal outcomes such as LBW, IUFD, still birth, and birth asphyxia. These findings would guide in the care of pregnant women with dyslipidemia.

Keywords: *Dyslipidemia, maternal and perinatal outcomes, pregnancy*

Introduction

Maternal dyslipidemia is one of the common metabolic changes that occur during pregnancy.[1] In normal pregnancy, there are increased metabolic requirements of the growing fetus which will lead to more of lipogenesis than lipolysis resulting in increased production of lipids. During pregnancy, plasma total cholesterol (TC) and triglycerides (TG) may increase by 25% to 50% and 150% to 300%, respectively.[1] From the 12th week of pregnancy, the concentration of lipid parameters which include total cholesterol (TC), TG, low-density lipoprotein–cholesterol (LDL-C), high-density lipoprotein–cholesterol (HDL-C), and phospholipid generally increase. This rise is sustained throughout the second and third trimesters.[2,3] In addition to the influence of pregnancy in inducing dyslipidemia, genetic predisposition and sedentary lifestyle with excessive dietary intake of saturated fats, cholesterol, alcohol overuse, and trans fats are contributory.[4] Other

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common secondary causes include diabetes mellitus, hypothyroidism, and chronic kidney disease.[3,4]

Maternal dyslipidemia may induce atherosclerosis in the utero-placenta spiral arteries and, when combined with hyper coagulation, may result in thrombosis and placental insufficiency with consequent fetal compromise including preterm delivery and low birth weight.[5] The frequency of preterm deliveries among women with dyslipidemia has been found to be almost twice that of the healthy reference group.[6] Similarly, pregnancy-induced dyslipidemia has been reported to increase morbidity of gestational diabetes mellitus (GDM) and preeclampsia.[5,6] At all trimesters, high TG concentration is associated with raised risk of gestational impaired glucose tolerance (IGT) and GDM.[7] Evidence has also shown a concentration-dependent positive association between maternal TG and increased risk for preeclampsia.[8]

Despite these findings, there are still some controversies regarding the relationship between maternal lipid abnormalities and certain maternal and perinatal outcomes. For instance, although a systematic review reported an association between elevations in triglycerides and development in GDM,[9] a more recent study did not observe any significant associations, suggesting a need for further study in this direction.[10] In addition, there is still persistent debate as to whether the maternal TG level has any correlation with neonatal birth weight.[10]

As these controversies exist, a high incidence of obesity as a proven risk factor for maternal dyslipidemia was reported in Enugu, Southeast Nigeria.[11] This study therefore aimed to determine the effects of maternal dyslipidemia on maternal and perinatal outcomes among pregnant women in Enugu, Southeast, Nigeria. It is expected that the findings from this study would guide the care of pregnant women with dyslipidemia.

Materials and Methods

This study was a prospective observational cohort study of eligible pregnant women attending antenatal clinic at the university of Nigeria teaching hospital (UNTH) Ituku-Ozalla and Enugu state university teaching hospital (ESUTH) Parklane, Enugu. The recruitment was made consecutively at the point of booking during antenatal visits between January 2021 and August 2021.

The UNTH is located about 21 kilometers from Enugu (the capital of Enugu State), along Enugu-Port Harcourt express way, while the ESUTH is located at the Government Reserved Area (GRA), in the center of the state capital. The Departments of Obstetrics and Gynecology of both institutions receive good patronage from within Enugu and environs, and they record a total of about 4,000–4,500 deliveries annually. The newborn special care units (NBSCU) of the two hospitals are located very close to the labor wards. The antenatal clinics and wards including the labor ward served as points for data collection in this study.

Sample size determination

The sample size (n) was determined using the formula for prospective cohort analytical study.[12]

$$n = \frac{1}{(1-F)} \times \frac{2 \times (Z_\alpha + Z_\beta)^2 \times P(1-P)}{(P_0 - P_1)^2}$$

Using the proportion of preterm birth of 16.8% from previous study in Lagos,[13] the study was designed to detect a 5% increase in the incidence at 5% level of significance and 80% power. The calculated minimum sample size was 50 for each arm including a 10% attrition rate. However, a sample size of 60 per each arm was used for the study. Inclusion criteria were pregnant women < 20 weeks gestation with known last menstrual period (LMP), confirmed with 1st trimester ultrasound scan who voluntarily gave their consent to participate in the study. The exclusion criteria included multiple pregnancy, diabetes mellitus, hypertensive disease, thyroid disease before pregnancy, and conception via assisted reproductive technique.

Study procedure and data collection

After ethical clearance and written informed consent, the relevant history was obtained as routinely done in the antenatal clinics of the study institutions. General and obstetric examinations were performed. After an overnight fast of 8–12 hours and under aseptic conditions, 5 ml of venous blood was collected from the ante-cubital vein of the recruited women into a labeled plain bottle and taken to Chemical Pathology Laboratory of the UNTH Ituku-Ozalla, Enugu, for lipid profile analysis. The pregnant women who met with criteria for dyslipidemia were consecutively identified and formed the study (exposed) group, while those with normal lipid parameters were in the control (unexposed) group. Both groups were matched for age, gestational age (GA), and parity and were followed up throughout pregnancy and labor. All participants had routine antenatal care with routine examination, fasting blood sugar, and urinalysis measurements carried at each visit.

Information on delivery mode, gestational age at delivery, gender, and birth weight were obtained. APGAR scores were recorded on delivery of the recruited patients and scores recorded at 1 minute and 5 minutes from the time of birth. An APGAR score of less than seven (7) at the fifth minute was regarded as birth asphyxia.

The phone numbers and home addresses of the participants were collected with their consent. This helped in the follow-up for those who ended up not delivering at UNTH Ituku-Ozalla, Enugu, or ESUTH Parklane, Enugu.

Study outcomes

The main outcome measures were the incidence of adverse maternal outcomes including preeclampsia, gestational diabetes, and the incidence of adverse perinatal outcomes including intrauterine fetal death (IUFD) still birth, preterm births, birth asphyxia, low birthweight (LBW), and macrosomia.

The blood samples collected were allowed to clot and then centrifuged at 3000 rpm for 5 minutes. The serum was stored in a freezer at –20^{0}C, and the analysis was performed in batches within 1 week of sample collection. All the lipid measurements were performed on an automated biochemical analyzer (Abbot Architect C16000, Abbott Laboratories, USA).

Total cholesterol (TC) was assayed with the cholesterol oxidase–phenol aminophenozone method. This involved using the serum in enzymatic reaction to hydrolyze cholesterol esters and oxidize the 3-OH group of cholesterol. One of the reactions by products H_2O_2 was then measured quantitatively in a perioxidase catalyzed reaction that produced a color. The color intensity was proportional to cholesterol concentration. This was measured with a spectrophotometer at 500 nm. Triglyceride (TG) was assayed using the glycerol-3-phosphate oxidase–phenol amino phenozone method which also involved enzymatic coupled reactions in which triglycerides were hydrolyzed to produce glycerol. Glycerol was then oxidized using glycerol oxidase and H_2O_2, one of the reaction products was measured as described above for cholesterol. High-density lipoprotein–cholesterol (HDL-C) assay involved reacting specimen with blocking reagent that renders them nonreactive with the enzymatic cholesterol reagent under conditions of assay. Absorbance was measured at 600 nm. Low-density lipoprotein–cholesterol (LDL-C) was calculated using the formula: LDL-C = Total Chol - (HDL-C) - TG/5 in mg/dl.

Definitions of variables

Dyslipidemia was diagnosed according to the criteria set by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) and classified into four phenotypes: hypercholesterolemia as serum total cholesterol (TC) ≥ 5.39 mmol/L, hypertriglyceridemia as serum triglyceride (TG) ≥ 1.92 mmol/L, hypo-HDL-cholesterolemia as serumHDL-C ≤ 1.06 mmol/L, and hyper-LDL-cholesterolemia as serum LDL-C ≥ 3.24 mmol/L.[14]

Preeclampsia was defined as blood pressure (BP) of ≥140/90 mmHg recorded on 2 occasions and at 4 hours interval with ≥2+ of protein in urine, while pregnancy-induced hypertension (PIH) was defined as occurrence of BP of ≥ 140/90 mmHg without proteinuria after 20 weeks gestation.[15] Gestational diabetes mellitus (GDM) was defined as occurrence of fasting blood glucose (FBG) of ≥ 7 mmol/l on 2 separate tests.[16] Preterm birth was defined as birth of new born less than 37 completed weeks of gestation. Neonates were defined as small for gestation age (SGA) if their birth weights fell below the 10th percentile for gestational age and as large for gestational age (LGA) if their birth weights exceeded the 90th percentile for gestational age.[17] Birth asphyxia was defined as APGAR scores of < 7 at 5 minutes of delivery.[18]

Ethical consideration

The ethical approval for the study was obtained from the Ethics Committee of UNTH Ituku/Ozalla, Enugu (NHREC/05/01/2008 B-FWA00002458-IRB 0002323), on 4 July, 2018, and supported by ESUTH Parklane, Enugu (ESUTHP/CMAC/RA/034/Vol. 10/55.8), on 17 October, 2018, and the study was conducted in compliance with 1964 Helsinki Declaration on human studies (revised in 2013). To ensure confidentiality, the identities of the participants were represented with codes and not their names.

Data analysis

Data analysis was both descriptive and inferential using IBM Statistical Package for Social Sciences (IBM Corp. Released 2019. IBMSPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) for Windows. Continuous variables were compared using the Student *t* test, while the discrete variables were compared using Fisher's exact or Chi-square test as applicable. Relationships were expressed using relative risks (RR) at 95% confidence interval. A *P* value of <0.05 was considered to be statistically significant.

Results

The first 60 consecutive women with dyslipidemia (Group A) were matched with appropriate 60 controls (Group B) selected from the 85 women without dyslipidemia. Both groups were followed up until delivery. Five women in group A and 13 women in group B were lost to follow-up as they did not deliver in the study institutions. Thus, 55 (Group A) and 47 (Group B) women's data were analyzed [Figure 1].

The mean age of the 102 participants was 30.6 ± 5.2 years (range: 21–42 years). The mean GA at booking was 17.4 ± 3.0 weeks (range: 10–20 weeks). The

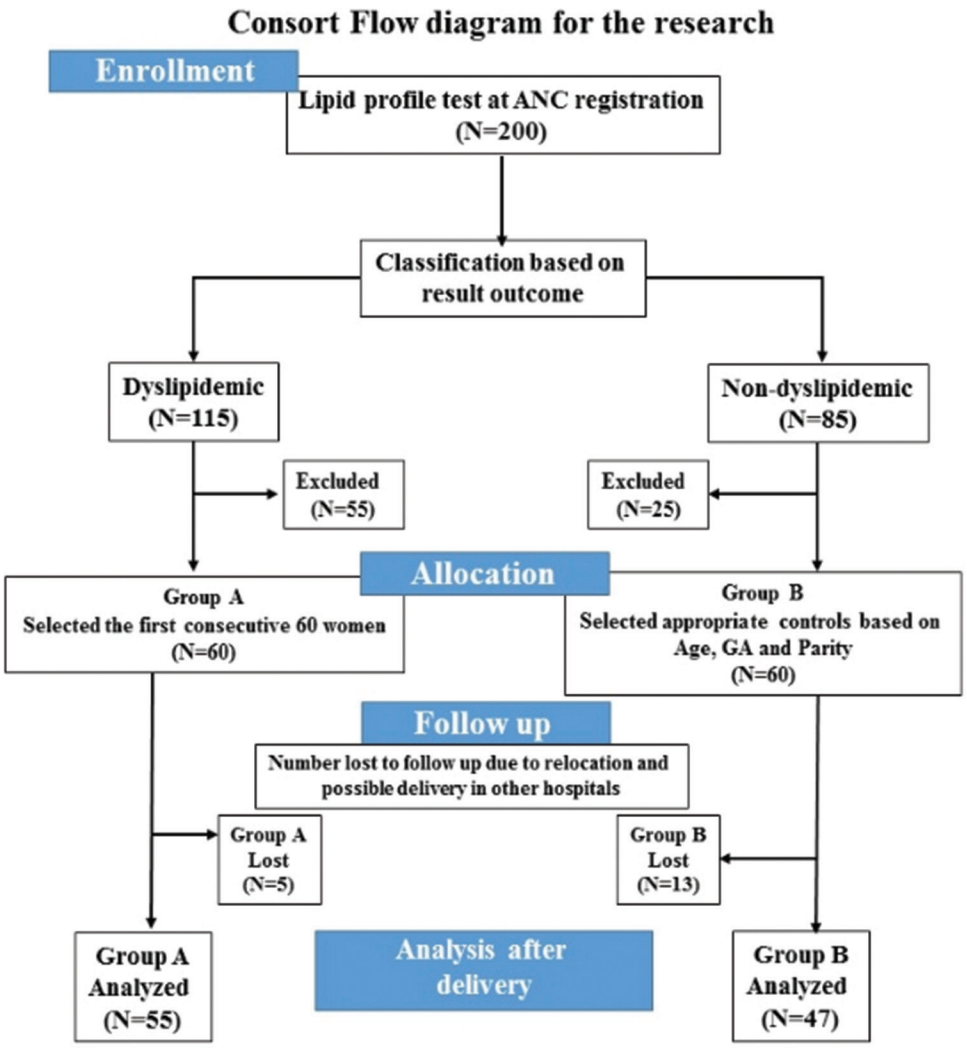

Figure 1: Consort flow diagram for the research

Table 1: Sociodemographic characteristics of the participants

Sociodemographic factors	Values	Dyslipidemia (*n*=102)		*P*
		Yes [Group A] (*n*=55)	No [Group B] (*n*=47)	
Age Mean (SD)		30.4 (5.4)	29.8 (5.3)	
Age group	<26 years	7 (12.7%)	14 (29.8%)	0.127
	26 to 30 years	19 (34.5%)	11 (23.4%)	
	31 to 35 years	16 (29.1%)	15 (31.9%)	
	> 35 years	13 (23.6%)	7 (14.9%)	
Parity	Nulliparous	5 (9.1%)	10 (21.3%)	0.184
	Primiparous	21 (38.2%)	21 (44.7%)	
	Multiparous	25 (45.5%)	14 (29.8%)	
	Grand Multiparous	4 (7.3%)	2 (4.3%)	
Mean GA at Registration (SD)		17.3 (2.6)	17.6 (2.3)	
GA at registration	<17 weeks	15 (27.3%)	15 (31.9%)	0.501
	17 to 18 weeks	20 (36.4%)	20 (42.6%)	
	19 to 20 weeks	20 (36.4%)	12 (25.5%)	
Education	Secondary	19 (34.5%)	14 (29.8%)	0.609
	Tertiary	36 (65.5%)	33 (70.2%)	

baseline characteristics including age, parity, and gestational age at booking were similar in both groups [Table 1].

The mean values of the various lipid parameters among the women with dyslipidemia compared with those,

Table 2: Distribution of lipid parameters among the two groups

Lipid Profile	Mean (SD)		*P*
	Presence of Dyslipidemia *n*=55	Absence of Dyslipidemia *n*=47	
Total Cholesterol TC (mmol/l)	5.4±0.42	4.20±0.65	<0.001
Triglyceride TG (mmol/l)	1.8±0.44	1.29±0.52	0.014
Low Density Lipoprotein LDL (mmol/l)	3.8±0.62	2.62±0.53	0. 042
High Density Lipoprotein LDL (mmol/l)	1.10±0.42	1.42±0.30	0.013

Table 3: Association between dyslipidemia and maternal outcomes

Maternal outcomes	Dyslipidemia		*P*	Risk ratio		
	Yes (%) (*n*=55)	No (%) (*n*=47)		RR	95% C.I	
					Lower	Upper
Gestational diabetes (GDM)						
Yes (%)	3 (5.5%)	2 (4.3%)	0.780	1.282	0.224	7.349
No (%)	52 (94.5%)	45 (95.7%)				
PIH/Preeclampsia						
Yes (%)	11 (20.0%)	4 (8.5%)	0.102	2.305	0.801	6.893
No (%)	44 (80.0%)	43 (91.5%)				
Mode of delivery						
C.S (%)	20 (36.4%)	12 (25.5%)	0.240	1.424	0.781	2.596
S.V.D (%)	35 (63.6%)	35 (74.5%)				

Gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), intrauterine fetal death (IUFD), cesarean section (CS), spontaneous vaginal delivery (SVD)

Table 4: Association between dyslipidemia and neonatal outcomes

Neonatal outcomes	Dyslipidemia		*P*	Risk ratio		
	Yes (%) (*n*=55)	No (%) (*n*=47)		RR	95% C.I	
					Lower	Upper
Preterm						
Yes (%)	7 (12.7%)	3 (6.4%)	0.283	1.99	0.546	7.282
No (%)	48 (87.3%)	44 (93.6%)				
IUFD						
Yes (%)	7 (12.5%)	1 (2.1%)	0.044	5.98	0.76	46.887
No (%)	48 (87.3%)	46 (97.9%)				
Still birth						
Yes (%)	8 (14.5%)	1 (2.1%)	0.028	6.836	0.887	52.685
No (%)	47 (85.5%)	46 (97.9%)				
Birth Asphyxia						
Yes (%)	12 (21.8%)	1 (2.1%)	0.003	10.255	1.384	75.961
No (%)	43 (78.2%)	46 (97.9%)				
Low birth weight (LBW)						
Yes (%)	11 (20.0%)	1 (2.1%)	0.005	9.400	1.260	70.138
No (%)	44 (80.0%)	46 (97.9%)				
Macrosomia						
Yes (%)	9 (16.4%)	10 (21.3%)	0.525	0.769	0.341	1.732
No (%)	46 (83.6%)	37 (78.7%)				

among the group with normal lipid values, are as follows: total cholesterol, TC (5.4 ± 0.42 vs 4.20 ± 0.65 $P < 0.001$); triglyceride, TG (1.8 ± 0.44 vs 1.29 ± 0.52 $P = 0.014$); low-density lipoprotein, LDL (3.8 ± 0.62 vs 2.62 ± 0.53, $P = 0.042$); and high-density lipoprotein, HDL (1.10, ±0.42 vs 1.42 ± 0.30, $P = 0.082$), respectively [Table 2].

The incidence rates of GDM, preeclampsia, and caesarean delivery were not significantly different between the two groups [Table 3].

The incidence of LBW was significantly higher among mothers with dyslipidemia than the controls (20% vs 2.1%, RR: 9.40, CI 95%: 1.3-70.2, $P = 0.005$). In

addition, the incidences of IUFD, still births, and birth asphyxia were significantly higher among mothers with dyslipidemia than the controls (RR = 5.98; 95% CI: 0.8-46.9; *P* = 0.04; RR: 6.84, CI 95%: 8.9-52.7, *P* = 0.03; RR: 10.26, CI 95%: 1.4-76.0, *P* = 0.003, respectively). On the other hand, the incidence rates of preterm delivery and neonatal macrosomia were not different between the two groups [Table 4].

Discussion

This study showed that dyslipidemia in pregnancy increases the risk of low birth weight (LBW). In fact, mothers with dyslipidemia were 9.4 times more likely to have babies with LBW than the controls (RR = 9.40; CI 95%: 1.3-2.1; *P* = 0.005). The observed higher incidence of LBW in the mothers with dyslipidemia is similar to findings from other related studies.[19,20] Dyslipidemia in early pregnancy may cause structural and functional alterations in placenta as a result of lipid deposition in the placenta.[21] Considering the fundamental effect of dyslipidemia in adult, it may be possible that this might result in atherosclerotic placental changes resulting in reduction in maternal blood flow and nutrient supply to the fetus with consequent interference in fetal growth and resultant low birth weight.[22] Triglyceride levels have been found to correlate negatively with fetal birth weight, and concentration of triglycerides in the third trimester has been reported to be a strong predictor of birth weight.[23] This is in agreement with our study which showed significantly higher low birth weight among the infants delivered to women with dyslipidemia in which triglyceride was significantly high. Similarly, this study indicated a significantly high incidence of birth asphyxia and intrauterine fetal death among women with dyslipidemia compared with women without dyslipidemia. This is similar to findings from other related studies that indicated significantly higher birth asphyxia and intrauterine fetal death among women with dyslipidemia compared to those with normal lipid levels[19,20] which might be related to poor placental perfusion caused by dyslipidemia-induced atherosis.

Though not significant, the risk of having preterm birth in women with dyslipidemia was higher than those with normal lipid profile (RR = 1.99; CI 95%: 0.55-7.28; *P* = 0.283), and this is in agreement with a previously related study.[24] Maternal obesity and hypertensive disease which are known risk factors for preterm liveries[25] were found to be higher among the women with dyslipidemia in our study, and this may have been contributory. Moreover, there is an established link between maternal dyslipidemia and raised tumor necrosis factor alpha (TNFα) and other inflammatory changes which have been implicated in preterm delivery.[26]

In our study, although the incidence of GDM was higher among women with dyslipidemia, the difference was not significant. This is similar to the report by Ryckman *et al*.[27] which in a meta-analysis found no significant association between maternal dyslipidemia and GDM during pregnancy. On the contrary, Jin *et al*.[28] in a study in 2016 reported a significant association between maternal dyslipidemia and GDM. In another related study, high TG concentrations were found to be associated with raised risk for gestational impaired glucose tolerance (GIGT) and GDM.[28,29] These conflicting results could potentially be explained by differences in the trimester of pregnancy studied, and/or the condition of glycemic control, and race/ethnicity. However, the real causes are not yet known.[29]

There was no significant association between development of PIH or preeclampsia between the two groups which is also in agreement with other previous related studies.[29,30]

The lipid profiles were measured in the second trimester at a mean gestational age of 17.4 weeks. Even though the lipid profile in pregnancy is not significantly altered in the first half of pregnancy,[2] a prepregnancy or first trimester measurement would have been more reliable in determining women with prepregnancy dyslipidemia. More so, a repeat lipid assay should have been done at the 3rd trimester to know if more women became dyslipidemic after their initial screening. In addition, socioeconomic factors and inadequate physical activity may affect the lipid profile of women during pregnancy, and there was no clear information on nutrition and physical activity of the participants during pregnancy.

Conclusion

Pregnant women with dyslipidemia have significantly increased risk of adverse perinatal outcomes such as LBW, IUFD, stillbirth, and birth asphyxia. These findings would guide in the care of pregnant women with dyslipidemia.

Authors' contributions

CED and EOU were involved in the study conceptualization. CEO, PUA, EOU, HUE, PON, MIE, GUE, KEE, AOU, PCE, and CSA were involved in the study design and data acquisition/collection. CEO, PUA, EOU, HUE, PON, MIE, GUE, KEE, AOU, PCE, and CSA were involved in the data analysis, interpretation of findings, writing the paper for intellectual content, and approving the final paper for publication.

Research data availability

The research data for this manuscript is available upon request to the corresponding author.

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Conflicts of interest

There are no conflicts of interest.

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