Research

Cord Blood Lipid Profile of Term and Preterm Newborns in a Tertiary Hospital in South East Nigeria: Relationship with Gestational Age and Birth Weight

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Abstract

Background: Early-onset atherosclerosis is a marker of future cardiovascular diseases. However, indicators of early dyslipidemia for primary prevention are generally lacking in sub-Saharan Africa. This study aimed at describing the cord blood lipid profile among apparently healthy newborns in a tertiary hospital in Southeast Nigeria, and its relationship with gestational age and birth weight.

Methods: Cross-sectional study of 167 consecutively recruited apparently well newborns in a tertiary hospital whose cord blood lipid profile parameters (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL – C), low-density lipoprotein cholesterol (LDL – C) and very low-density lipoprotein cholesterol (VLDL – C)) were assessed using an autoanalyzer (BiOLis 24i). Lipid variables were presented with descriptive statistics whereas their relationship with gestational age and birth weight was highlighted using Spearman's rank correlation analysis. Dunnett's T3 Post Hoc analysis was used for pairwise comparisons.

Results: The 167 newborns recruited included 15 (9%) moderate preterm, 46 (27.5%) late preterm and 106 (63.5%) term babies of which 79 (47.3%) were males and 88 (52.7%) were females. The number of recruited SGA, AGA and LGA were respectively 13 (7.8%), 142 (85%), 12 (7.2%). Mode of delivery was majorly vaginal delivery (69.5%) while the rest (30.5%) was by caesarean section. The median values (in mg/dL) of TC, TG, HDL – C, LDL – C and VLDL – C were 60.0, 30.5, 29.0, 25.8 and 6.1 respectively, all within the normal international ranges. Triglycerides and VLDL-C had a moderate positive correlation with gestational age ($r_s = 0.4$; $p < 0.001$) and were significantly higher in small-for-gestational-age newborns. Total cholesterol, HDL – C, and LDL-C had a weak negative correlation with gestational age and birth weight (spearman $r_s < -0.3$). Birth weight, gestational age, and paternal age were the common predictors of lipid profile variability.

Conclusion: The finding of a significant relationship between lipid variables with gestational age and birth weight underscores the need to clinically interpret these given the relationship. The relationship with paternal age is another interesting finding which needs to be replicated and the mechanism(s) elucidated.

Keywords: Cord blood lipid profile, Gestational age, Birth weight, Nigeria

Introduction

The assessment of cord blood lipid profile has been of interest to many researchers recently following evidence of the early onset of atherosclerosis that leads to cardiovascular disease (CVD), which is a major cause of morbidity and mortality worldwide.[1] Lipids are hydrophobic substances that are vital in the physiology of hormones and fat-soluble vitamins. They are important in adipose tissue accretion for heat production in foetuses, and in lung and brain

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development.[2] However, when its metabolism is abnormal, dyslipidemia results. The possibility that further environmental and behavioural modifications in children born with dyslipidemia may hasten the evolution of CVD in adult life evokes the need for early assessment.[3] It has also become needful to assess the relationship that cord blood lipid profile may have with both gestational age and birth weight since prematurity and low birth weight are both prevalent in sub-Saharan Africa,[4] and are reported to trigger diseases of foetal origin like atherosclerotic coronary heart disease.[5]

Dyslipidemia has been described as high blood levels of low-density lipoprotein – cholesterol (LDL - C) and triglycerides (TG) (>90th percentile for age and gender) and/or low levels of high-density lipoprotein – cholesterol (HDL - C) (<10th percentile for age and gender).[2] This is seldom a clinical problem in childhood, but accumulated exposure can silently lead to atherosclerosis progressing to adulthood.[6] A programmed permanent alteration of foetal physiology and metabolism which aids adaptation to intrauterine stress or malnutrition was suggested to trigger the foetal onset of adult diseases like coronary artery disease (CAD) and metabolic syndrome.[5] As early as three years of age, myocardial infarction in a child with homozygous familial hyperlipidemia has been reported with death being common in adolescence.[7]

The intrauterine lipid metabolism can be assessed with umbilical cord venous blood drawn at birth.[8] It spares the newborn from the trauma of venepunctures[9] which can alter measured lipid levels.[10] The following lipid fractions are assayed in the evaluation of dyslipidemia: total cholesterol (TC), triglyceride (TG), High-density lipoprotein cholesterol (HDL - C), low-density lipoprotein cholesterol (LDL – C), very low-density lipoprotein-cholesterol (VLDL - C), intermediate-density lipoprotein - cholesterol (IDL - C), lipoprotein-a, apolipoprotein A - I (Apo A - I) and apolipoprotein B (Apo B).

According to international reference values, the mean cord blood level of TC is 68mg/dL and is known to rise rapidly to a level about twice that by the end of neonatal life.[2] Mean cord blood levels of other parameters which include TG, HDL – C, and LDL - C are 34mg/dL, 35mg/dL, and 29mg/dL respectively.[2] The safe level of LDL - C typically in newborns ranges from 20–40 mg/dL above which level, the risk of atherosclerotic events is markedly higher.[11] In Africa, Gomina *et al*[12] in Benin Republic reported mean values (in mg/dL) of TC, TG, HDL-C, and LDL-C as 68, 39, 29, and 31 respectively among term babies. These approximate the international reference values.[2] Boersma *et al*[13] in Tanzania reported higher mean values of TC and TG in small for gestational age (SGA) babies.

In Nigeria, earlier studies[14-16] involved few lipid fractions in the cord blood of term neonates, with TC being the consistent lipid studied. Taylor *et al*[16] and Ibeziako *et al*[14] in the South West reported a mean TC of 77.75mg/dL and 71.43mg/dl respectively, but Okoro *et al*[15] in the South East reported a mean TC of 104.79mg/dL. Hence, mean values of TC varied widely between babies in southwest and South East Nigeria. Umar *et al*[17] in 2017 reported mean cord blood TC of 72.3mg/dl, HDL - C of 27.1mg/dL, LDL - C of 39.4mg/dL, and TG of 22mg/dL in term babies in Northern Nigeria, while Ayoola *et al*[18] in 2012 in the South West, reported mean cord blood TC of 63.8mg/dl, HDL - C of 25.5mg/dL, LDL - C of 27.1mg/dL and TG of 70mg/dL in term babies. So far, there is paucity of data on lipid profile of preterm newborns especially in Nigeria.

With increasing death among CVD high-risk groups in developing countries,[19,20] the rationale for this study in our environment derives from the strength of genetic and environmental influences on serum lipid levels[2] in each population, and the need to assess dyslipidemia and changes in lipid transport from early life. By correlating lipid profiles with gestational age and birth weight, this study has helped to assess the influence of these factors. The findings of this study would serve as a baseline for subsequent longitudinal studies to assess the need for and extent of CVD preventive measures for high-risk newborns suitable in our environment. This study remains a contribution to the ongoing debate[2] on neonatal lipid screening programs in this environment.

Methods

Study Design and Setting: This was a cross-sectional study carried out at the Labour Ward, Maternity Theatre, and Special Research Laboratory of the Federal Medical Centre, Umuahia. The hospital is a tertiary institution in Abia State in South-Eastern Nigeria. It provides specialized care to patients and is a centre both for primary and secondary tiers of health care services in the State and seven neighbouring southern states.

Study duration: The study was conducted over a period of 16 months when the sample size was complete.

Study Population: Out of 2,102 live babies delivered during the period of study, 167 apparently healthy newborns via caesarean section (69.5%) and vaginal delivery (30.5%) who met the inclusion criteria were studied, and they included 106 term (gestational age up to 37 completed weeks) newborns, 46 late preterm (from

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34 weeks to less than 37 completed weeks of gestational age), 15 moderate preterm (which included babies between 32 and 34 completed weeks of gestational age, although 2 babies born at 31 weeks gestational age who could not stand alone in another category were allowed here).

Sampling Technique: Participants were recruited consecutively as the mothers presented in labour and based on the inclusion criteria after obtaining well-informed written consent. Enrollment into the study was continued until at least, the minimum sample size was achieved.

In computing the required sample size for the study, the findings of an Iran study by Tohman *et al*[21] were used for the following reasons: Firstly, the population sampled in their study is `essentially similar to that of the index study. Secondly, the two study settings share similar socioeconomic attributes (i.e., low and middle-income countries). The study reported a mean Total Cholesterol of 85.64mg/dL with a Standard Deviation, S of 35.55mg/dL. Based on their reported mean and standard deviation of total cholesterol, we computed the required sample size by using these figures to substitute in the Suresh *et al*[22] formula for the mean (Z^2S^2/d^2) and arrived at 167 as the minimum sample size after adjusting for the expected population in the study period.

Selection criteria

Inclusion criteria: Participants were included if they were apparently well newborns (irrespective of gestational ages), delivered in the study setting and their parents/caregivers gave written informed consent.

Exclusion criteria: Excluded newborns with 5th minute APGAR scores <7,[20] with congenital abnormalities, or any major illness at birth requiring admission, and those born to mothers with endocrine and metabolic diseases (e.g., diabetes mellitus, thyroid diseases), hypertension, chronic ailments (like chronic kidney disease and retroviral disease), established fetal distress, rupture of membrane >24 hours, chorioamnionitis or mothers taking lipid-altering medications,[23,24] were excluded. Those with a family history of dyslipidemia were also excluded.

Ethical Considerations: Ethical clearance was duly obtained from the institution's Health Research Ethics Committee (HREC) with the number: FMC/QEH/G.596/Vol.10/461. This was renewed accordingly to cover the period of the study. Informed written consent was obtained from the parents/caregivers. Since cord blood consent policies are varied and involve 3 phases (pre-natal, pre-labour, and post-collection phases),[25] consent from each mother was obtained at any or all of these phases, but preferably in the more generally accepted prenatal phase. In any phase of consent collection, the study was explained to the parents/caregivers, and reassurance was given on the safety of the procedure. They were reassured that they were not under any obligation to give consent and hence could opt out at any time including the post-collection phase.

Data collection: Data collected included the results of the lipid profile assay for each newborn, sociodemographic information obtained from parents/caregivers, relevant obstetric history, and the examination of the newborns.

Information from mothers and their case notes were obtained. These included gestational age and sex of baby at birth; the age, educational level, and occupations of both parents; marital status of mother; maternal ailments and intake of lipid-altering drugs in pregnancy, family history of dyslipidemia; mode of delivery; the presence of obvious neonatal illness or congenital anomaly; place of origin and tribe. The socioeconomic status of each baby was assessed using the Oyedeji classification as modified by Ezenwosu et al.[26]

A thorough physical examination of each baby was done to exclude any gross deformity, pallor, cyanosis, edema, fever, and other abnormalities, guided by the Newborn & Infant Physical Examination (NIPE) paper form by Royal Berkshire NHS Foundation Trust.[27]

SECA® digital electronic baby scale manufactured by GmbH & co. Kg (made in Germany; Model:757 7021094) which measures to the nearest 5 grams was used to measure each baby's weight at birth. The digital scale was placed on a table. First, only a clean paper was placed on it to avoid direct contact with the baby's body, and it read 0.000kg initially. Then each baby (without clothing) was gently lowered into it, ensuring the baby was not holding on to anything outside the scale. The examiner's hand was made to hover close to the baby's chest without touching the chest to guard against the baby slipping off the scale. After weighing and taking note of the weight, each child was dressed up and handed over to the mother safely.

Gestational age was estimated (in the last completed weeks) from the date of the last normal menstrual period by Naegele's rule, 1st semester ultrasound[28] and, or by examination using the new Ballard chart.[29]

Head circumference (HC) was measured by wrapping a non-stretchable tape snugly around the head across the

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most prominent part of the forehead (glabella) and the occipital prominence at the back of the head, such that the widest circumference of each baby's head was measured. This was repeated 3 times and the average measurement to the nearest of 0.1cm was recorded.
The 5th minute APGAR scores were assigned using the APGAR chart.

Laboratory methods

Specimen collection and storage: After cleaning the placental end of the umbilical cord with alcohol swabs to avoid contamination with maternal blood, two to four millilitres of umbilical cord venous blood were drawn directly from the umbilical vein which is easily identified by its flabby collapsible wall and wider lumen compared to the two adjacent thick-walled arteries. Each drawn blood sample was emptied gently into a well labelled plain specimen bottle with the following cautious steps taken to avoid haemolysis of the red blood cells which could cause positive interference in the total cholesterol result: Drawn samples were emptied into specimen bottles only after detaching the needle from the syringe; vigorous shaking of samples was avoided; the centrifuge was balanced to avoid undue vibrations during spinning of samples which was done at 3000 revolutions per minute for 15 minutes.[30] The separated sera were stored promptly in the refrigerator at a temperature of -20 degrees Celsius and analysed within 2 weeks.[17]
The lipid profile values were determined using an autoanalyser, (BiOLis 24i manufactured by Tokyo Boeki medisys inc.). All quality control measures were instituted throughout the processing of the samples by a certified chemical pathologist.

Formular-derivable values: VLDL-C and LDL-C were calculated with Friedewald's formular[31] which states that VLDL-C = TG/5, while LDL-C = TC – HDL-C – TG/5. This formular applies to lipid fractions measured in mg/dL which is the unit of measurement of the spectrophotometer in the research facility.
Quality control: Quality Control (QC) sera were run daily. Laboratory tests on subjects' specimens were done only when QC were passed QC sera were used for precision studies to determine within and between run coefficients of variation (CV).

Data Analysis

Data were analysed using the International Business Machine Statistical Package for Social Sciences (IBM-SPSS) statistics software version 20
First, data were scrutinized for incorrectly filled information and cleaned. Thereafter, the normality of the distribution of data was assessed using Kolmogorov - Smirnov and Shapiro-Wilk tests. It was found that all the lipid parameters were not normally distributed. The results were summarized using the descriptive statistics of median and interquartile range. The correlation between lipid variables (TC, TG, HDL-C, LDL-C, and VLDL-C), gestational age and birth weight were analyzed using Spearman's rank correlation, The associations between lipid parameters and gestational age (categorised as premature, near-term and term) and birth weight (categorised as LBW, NBW and macrosomia) were tested using Kruskal - Wallis test. Multivariate analyses using step-wise multiple linear regressions were used to assess the predictors of the risk of atherogenesis using various lipid indices as the dependent variable. The predictors assessed included the mother's age, father's age, mother's parity, gestational age, birth weight, gender of the newborn, head circumference, mode of delivery, mother's booking status and socio-economic class. All tests of significance were two-tailed at the 5% level of significance and confidence interval estimation of 95% (with a p-value set at < 0.05).

Results

A total of 184 newborns were recruited consecutively, among which there were 10 lysed cord blood samples, 3 samples that had analytical errors at the laboratory and 4 serum samples lost to unfavourable storage temperature due to interrupted power supply. However, a total of 167 subjects were studied of which majority 106 (63.5%) were full-term neonates as seen in **Table 1.** The median gestational age of the newborns was 36 weeks, with an inter quartile range of 3.25. The male to female ratio of 1:1.1 was observed. Mean age of the fathers was about 38 weeks while that of the mothers was about 31 weeks. On Oyedeji's socioeconomic class assessment, 64.1% were of the upper socioeconomic class (class I and II), while 32.3% were of middle class (class III).

Table 1: Socio-demographic characteristics of the study participants (n =167)

Variables	Frequency (%)
Gestational age sub – groups:	
Moderate preterm	15 (9.0%)
Late preterm	46 (27.5 %
Term	106 (63.5%)
Gestational age –adjusted birth weight groups:	
SGA	13 (7.8%)

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Variables	Frequency (%)
AGA	142 (85%)
LGA	12 (7.2%)
Gender:	
Male	79(47.3)
Female	88(52.7)
Ethnicity:	
Igbo	163(97.6)
Others	4 (2.4)

SD=Standard deviation,
IQR= Inter quartile range
SGA: Small for gestational age,
AGA: Appropriate for gestational age,
LGA: Large for gestational age

The summary of the descriptive analysis of the lipid profile among the participants (Table 2) shows that the mean values of the lipid parameters approximated the international reference mean values.[2]

Table 2: Cord blood lipid profile of the study participants (n =167)

Variables	Present study Median (IQR)	Present study Mean ± SD	International reference values[+] Mean (5th & 95th percentiles)
TC (mg/dl)	60.00 (29.25)	66.61 ± 22.81	68 (42 & 103)
TG (mg/dl)	30.50 (21.00)	34.34 ± 23.50	34 (14 & 84)
HDL – C (mg/dl)	29.00 (13.25)	30. 32 ± 10.10	35 (13 & 60)
LDL-C (mg/dl)	25.80 (19.70)	29.76 ± 15.76	29 (17 & 50)
VLDL-C (mg/dl)	06.10 (4.20)	06.87 ± 04.70	**Not reported**

IQR=Inter – quartile range, [+]= International reference study[2],
SD=Standard deviation

The correlations between gestational age, birth weight and lipid variables (Table 3) show that LDL-C, HDL – C and TC had a weak negative correlation with both birth weight and gestational age at birth. On the other hand, TG and VLDL – C had a significantly moderate positive correlation with gestational age at birth (with Spearman's rank correlation coefficient (r_s) of 0.40 and p-value <0.001). However, TG and VLDL - C had an insignificant weak positive correlation with birth weight.

Table 3: Correlation of cord blood lipid profile values with gestational age and birth weight (n =167)

Lipid profile variables	Gestational age at birth	Birth weight
TC: r_s(p-value)	-0.23(0.003)	-0.26(0.001)
TG: r_s(p-value)	0.40(<0.001)	0.10(0.21)
HDL - C: r_s(p-value)	-0.23(0.002)	-0.18(0.02)
LDL-C: r_s(p-value)	-0.25(0.001)	-0.21(0.007)
VLDL-C: r_s(p-value)	0.40(<0.001)	0.10(0.20)

r_s=Spearman's rank correlation

With regard to lipid profile and gestational age sub-categories (Table 4), there was a significant association between all the subcategories of gestational ages at birth with each of the lipid profile parameters. While TG and VLDL- C were higher in term newborns, the reverse was the case with HDL – C, TC and LDL-C. Post - Hoc multiple pairwise comparisons between lipid profile sub-categories of gestational age showed that the difference in the TG levels was obvious between near-term and term (p = 0.03). For LDL-C, the significance was obvious between premature and near-term (p = 0.002) and premature and term (p <0.001). For VLDL-C, the difference was between near-term and term (p = 0.03); and for TC, the significance was between premature and term (p=0.01).

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Table 4: Relationship between cord blood lipid profile parameters and gestational age subcategories (n =167)

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Lipid parameter in mg/dL	Moderate preterm Median (IQR)	Late preterm Median (IQR)	Term Median (IQR)	*χ^2	p-value
TC	80.00 (49.00)	62.50 (29.25)	58.00 (18.00)	10.24	0.006
TG	25.00 (32.00)	23.50 (19.00)	36.50 (24.25)	17.73	<0.001
HDL-C	29.00 (25.00)	30.00 (11.75)	27.00 (10.25)	6.34	0.04
LDL-C	41.40 (36.40)	27.00 (20.30)	23.60 (13.70)	14.95	0.001
VLDL-C	5.00 (6.40)	4.70 (3.80)	7.30 (4.85)	17.92	<0.001

***χ^2=**Kruskal-Wallis Test

Low-birth-weight subcategories (**Table 5**) had significantly higher TC (p = 0.01) and LDL - C (p = 0.003).

Table 5: The relationship between cord blood lipid profile parameters and birth weight subcategories (n=167)

Variables	LBW Median (IQR)	NBW Median (IQR)	Macrosomia Median (IQR)	**χ^2	p-value
TG	26.00(30.75)	32.50(21.25)	33.00(24.50)	0.47	0.79
HDL-C	29.50(19.75)	29.00(6.15)	6.60(4.90)	5.81	0.06
LDL-C	34.30(35.00)	23.60(15.65)	25.40(10.60)	11.70	0.003
VLDL-C	5.20(6.15)	6.50(4.30)	6.60(4.90)	0.46	0.79
TC	79.00(40.00)	59.00(24.25)	51.00(13.50)	8.55	0.01

**=Kruskal-Wallis's test, LBW: Low birth weight, NBW: Normal birth weight

Considering the gestational age-adjusted birth weight percentiles (**Table 6**), the small-for-gestational age (SGA) category had significantly higher VLDL – C (p = 0.02) and TG (p = 0.02) values. Post-Hoc multiple pairwise comparison between sub-categories of gestational age-adjusted birth weight percentiles showed that the difference in TG was between LGA and SGA (p=0.03), and the difference in VLDL-C was also between LGA and SGA (p=0.03).

Table 6: **Relationship between cord blood lipid profile parameters and gestational age-adjusted birth weight sub categories (n=167**)

Lipid parameter in mg/dL	SGA Median (IQR)	AGA Median (IQR)	LGA Median (IQR)	*χ^2	P value
TC	55.00 (22.00)	59.50 (28.25)	61.50 (19.50)	1.11	0.57
TG	49.00(33.50)	31.00(22.00)	27.50(17.75)	8.06	0.02
HDL-C	28.00(13.50)	29.00(10.50)	27.50(12.00)	0.32	0.85
LDL-C	18.00(19.20)	25.50(18.30)	25.30(6.75)	4.24	0.12
VLDL-C	9.80 (6.70)	6.20 (4.45)	5.50 (3.55)	8.07	0.02

IQR=Interquartile range, *χ^2=Kruskal-Wallis Test, SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age

The independent predictors of lipid profile (**Table 7**) assessed included gestational age, birth weight, gender of the newborn, mother's age, father's age, mother's parity, head circumference, mode of delivery, mother's booking status and socio-economic class. Gestational age was the most consistent predictor of lipid profile with a p-value of <0.001 in all cases.

Table 7: Stepwise regression result of significant socio-demographic and clinical predictors of lipid levels (n=167)

Dependent variable	Significant predictors	Standardized β coefficient	t-stat	p-value	R^2

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TG	Gestational Age	0.45	4.51	<0.001	0.070
	Paternal age	-0.20	-2.71	0.008	0.034
	Birth weight	0.26	-2.54	0.01	0.031
HDL-C	Gestational Age	-0.07	-0.65	0.002	0.051
LDL-C	Gestational Age	-0.36	-4.76	<0.001	0.121
VLDL-C	Gestational Age	0.45	4.52	<0.001	0.071
	Paternal Age	-0.20	-2.67	0.008	0.033
	Birth weight	-0.25	-2.54	0.01	0.031
TC	Gestational Age	-0.32	-4.19	<0.001	0.096

R^2=Coefficient of determination

Discussion

The median values of cord blood lipid profile parameters (TC, TG, HDL – C, and LDL – C) in the index study were all within the international reference ranges and comparable with other studies by Kermani *et al*[32] in Iran, Gomina *et al*[12] in Benin Republic, and with Ayoola *et al*[18] in Nigeria. To avoid ambiguity, newborns in this study were not categorized into normolipidemic and dyslipidemic newborns because such categorisation will be misleading. Whereas dyslipidemia refers to high blood level of TG and LDL-C (>90th percentile for age and gender) and/or low levels of HDL - C (<10th percentile for age and gender),[2] there is paucity of recent large population studies of lipid profile across different gestational ages in neonates that can reliably delineate the percentile limits. This is likely due to the perceived high variability of lipid values in neonatal age groups and infants for whom interventions are not advised.[2] For instance, in this study, VLDL-C which was not part of the parameters listed in the international reference study,[2] had a median value of 6.1mg/dl and appears to vary widely in other studies.[3,8] Meanwhile, the largely cited study[2] from which the international reference ranges were derived was done about four decades ago and it did not consider the 90th and the 10th percentiles as the upper and lower cut-off limits respectively according to the current definition of dyslipidemia. Whereas in the international reference study, the cord lipid profile values are accepted as normal if they lie between the 5th and 95th percentiles, recent evidence states that this does not imply absence of atherogenic risk because an LDL-C value of 50mg/dL (though at 95th percentile)[2] is unsafe in the newborn who is at markedly higher risk of atherosclerosis at values above 20–40mg/dl.[11] It is also known that the lipoprotein particle size plays a role in atherosclerosis. The sizes of most Apo B – containing lipoproteins (like VLDL, LDL, lipoprotein (a)) are less than 70nm which enables them to move in and out of the intima media of vessels. But as the particle sizes increase (not just the quantity), there is increased possibility of their accumulation in the intima[11] which can trigger plaque formation and atherosclerosis.[2]

This study also assessed the correlation of cord lipid profile parameters with both the gestational age and birth weight. With respect to gestational age at birth, TG and VLDL-C both had statistically significant moderate positive correlation (r_s = 0.40 p<0.001) with gestational age at birth, which on post - hoc analysis, the difference was marked between late preterm and term sub-categories. This finding may be due to the increasing demand for TG and VLDL- C by the developing foetus. Since very low-density lipoprotein (VLDL) is the major carrier of TG,[33] it explains the similarity in their pattern of correlation in this study. Also, VLDL–TG is vital in lung maturity because of their role in surfactant metabolism, such that rapid rise in blood level occurs after 34 weeks of gestation.[33] This may explain why the post-hoc analysis showed that positive correlation of TG and VLDL-C with gestational age was more marked between the late preterm and term categories, which corresponds to the metabolic demand for VLDL-C and TG in the same foetal period.

There was no significant correlation between both TG and VLDL – C with birth weight. This is comparable to the finding by Donega.[34] Also TG and VLDL – C had no significant association with sub-categories of birth weight (low birth weight, normal birth weight and macrosomia) which is in keeping with the relationship already established with birth weight in the index study. This finding suggests that the chronological timeline of foetal development rather than size or weight of the foetus drives the metabolism of these lipid fractions.[33]

With respect to gestational age - adjusted weight percentiles, both TG and VLDL - C were significantly higher in the SGA sub categories as opposed to the large for gestational age (LGA) sub categories. This finding is in keeping with the study by Nayak et al[35] in which TG particularly increases in SGA. The increase may be due to the possible mobilization of fetal adipose tissue stores

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in response to intra uterine stress in the SGA sub category.[13]

Total cholesterol, HDL - C and LDL-C generally shared similar patterns of relationships with gestational age and birth weight. They had weak negative correlation (Spearman $r_s < -0.3$) with both weight and gestational age at birth. Total cholesterol (TC) and LDL – C were significantly higher in premature babies and in low-birth-weight sub categories. Since TC and LDL – C are atherogenic lipid fractions, this finding (though insignificant) agrees with the Fetal Origin of Adult Disease (FOAD) hypothesis which suggests higher atherogenicity in small sized or preterm babies.[5] This is also comparable to Margon et al[36] who found similar relationship with TC and LDL – C as well as other studies[23,34,37]

Generally, cord blood lipid profile in this study weakly correlated with birth weight. Similarly, Donega *et al*[34] in Brazil reported lack of significant relationship between cord blood lipid profile and birth weight. It has been argued that gestational age rather than birth weight plays a major role in lipid metabolism such that, as the foetus matures, cholesterol reduces and the TG increases.[34] Fatty acid beta-oxidation in the fetus is low but as gestational age increases, foetal fat accretion begins at about 30 weeks of life with fatty acids being preferentially taken to adipose tissues and in the liver for TG synthesis and storage. This timeline drives the lipid metabolism such that by term, the fat deposition must have accounted for over 90 percent of the calories accumulated by the foetus.[38]

The weak negative correlation that HDL – C had with both weight and gestational age at birth is comparable to the study by Atiy *et al*.[8] However, HDL – C had the lowest significant relationships in this study. This is because of its role in counterbalancing the deposition of LDL – C in blood vessels by transporting the lipids back to the liver. Hence, its value is variable depending on its transport function per time.[39] More studies to elucidate this relationship will be needed.

An additional finding in this study following stepwise regression analysis showed that out of all predictors assessed which included socio-demographic factors, gestational age was the most consistent predictor of lipid profile. Triglyceride and VLDL – C have similar significant predictors in all cases and they include gestational age, paternal age, and birth weight of newborns. Paternal age had a significant inverse relationship with VLDL – C and TG though weakly correlated. This similar striking relationship of paternal age with both VLDL –C and TG needs further research.

The socioeconomic class of these newborns was not a significant predictor of the lipid profile. This is similar to reports by Taylor et al,[16] and Okolo et al.[15] The expectation that being of a higher socioeconomic class implies that the mothers may have more fat stores which will inflate foetal lipid profile is yet to be proven scientifically. This is because the maternal lipids do not cross the placenta except for the selective uptake of free fatty acids that occur mainly during foetal stress.[38] A comparison of the maternal lipid profile with that of the newborn would seem needful but not practicable since maternal blood lipids increase especially in the last trimester irrespective of the mother's socioeconomic class.[16,18] Meanwhile, Ayoola *et al*[18] found no correlation between maternal and cord blood lipids.

Gender, on the other hand, did not influence the lipid profile as has been observed in some studies.[17,40] This may be attributable to the fact that gender influence on lipid profile is likely to occur later in life in line with subsequent hormonal changes. Gender influence on lipid profile is related to hormonal influences such that females less than 20 years of age have more cholesterol than males of the same age, though the trend is said to reverse after 20 to 45 years of age.[10]

The normal ranges of cord blood lipid profile values in this study should not give a false sense of safety in the studied population since only apparently healthy newborns who met the study criteria were studied.

Recommendations

A high index of suspicion among healthcare workers is needed to detect dyslipidemia in at–risk neonates. Efforts should be made to carry out newborn lipid screening routinely including even the healthy neonates. Meanwhile, a longitudinal study is needed to establish direct cause-and-effect relationship.

Limitations of the study

Non-inclusion of the extremely preterm neonates due to natural factors during the period of study may have skewed the findings to more mature babies. Their inclusion would have given a broader representation of the study population. Exclusion of newborns with family history of hypercholesterolemia was largely dependent on access to a past documented evidence which was lacking in most cases. Also, a longitudinal

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study could have helped to elucidate the outcome of the findings over time. The study of important lipid like Apoprotein A and B was hampered by dearth of facilities.

Conclusion

The median values of cord blood lipid profile in this study were within the international reference ranges. These values of the cord blood lipid parameters in this study should be a guide to wider studies to establish reference values. The VLDL-C and TG were positively correlated with gestational age and were also significantly higher in SGA babies. The inverse relationship of paternal age with VLDL-C and TG is a finding that deserves further study.

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Ethical conformity: Ethical clearance was duly obtained from the Health Research Ethics Committee (HREC) of the Federal Medical Centre, Umuahia, Abia State, Nigeria, with the reference number: FMC/QEH/G.596/Vol.10/461

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