ISSN 2384-5589

Volume 16 / Issue 2 / July-December 2017

African Journal of Medical and Health Sciences

Official Publication of the Federal Teaching Hospital Abakaliki (FETHA), Nigeria

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Original Article

Predictive Significance of Low Maternal Serum Cholesterol Concentrations in Early Pregnancy on Low Birth Weight in Term Neonates

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Abstract

Background: Low- birthweight (LBW) is the single most powerful predictor of mortality in the first few months of life, especially in most developing countries. The physiologic hypercholesterolemia of later pregnancy suggests an adaptive function for pregnancy maintenance or fetal growth. Decreased levels of maternal total cholesterol have been reported in association with intrauterine growth restriction. **Aim:** The aim of this study is to assess the association between low maternal serum cholesterol during early pregnancy and LBW in term neonates. **Patients and Methods:** This was a prospective cohort study in which eligible participants were enrolled at the gestational age of 14–20 weeks over a period of 12 months. Blood samples were taken to measure the total serum cholesterol concentrations, and the sera were then analyzed enzymatically by the cholesterol oxidase: p-aminophenazone method. Association between low maternal serum cholesterol and LBW was tested by using Chi-square. All significances are reported at $P < 0.05$. **Results:** The present study showed an incidence of 13.4% for delivery of LBW babies in the low-risk study patients. LBW was 2.05 times more common with low total maternal cholesterol than with normal midrange maternal cholesterol levels (21.1% vs. 10.3%, $P = 0.039$). **Conclusion:** We can infer from the study that the low maternal serum cholesterol is associated with LBW in term neonates. We can, therefore, recommend that the concept of an optimal range for maternal serum cholesterol during pregnancy may have merit and pregnant women should be encouraged to follow a healthy, balanced diet, and ensure regular antenatal visit to their health-care provider.

Keywords: *Cholesterol oxidase: P-aminophenazone, hypercholesterolaemia, intrauterine growth restriction, low birthweight, neonate*

Introduction

Low birthweight (LBW) is the single most powerful predictor of mortality in the first few months of life.[1] It is a major health problem in most African countries[2] and indeed, in most developing countries, being associated with a high incidence of neonatal mortality in these regions.[3] LBW is defined by the World Health Organization as a birth weight <2500 g.

Birth weight is a reliable index of intrauterine growth restriction (IUGR).[4] IUGR requires a valid estimate of gestational age, which is often difficult in developing countries due to late and infrequent access to prenatal care, inadequate documentation of the date of the last menstrual period, and unavailability of the early ultrasound examination. One of the reasons that LBW continues to be reported and studied by epidemiologists and public health practitioners is that it can be measured with excellent validity and precision.[5] Despite widespread recognition of the importance of LBW in developing

Access this article online

Quick Response Code:

Website: www.ajmhs.org

DOI: 10.4103/ajmhs.ajmhs_50_17

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How to cite this article: Okunade KS, Oluwole AA. Predictive significance of low maternal serum cholesterol concentrations in early pregnancy on low birth weight in term neonates. Afr J Med Health Sci 2017;16:94-8.

countries, reliable data on its magnitude and distribution remain limited. de Onis *et al*.[6] estimated that 16% of all newborns in developing countries were LBW. In India, the prevalence of LBW infants is about 33%,[7] as compared to 4.5% in industrially developed countries.[8] In the year 2000, it was estimated by the UNICEF that 10% of newborn infants in developing countries will have LBW at term.[9] Its incidence in Nigeria lies between 6% and 21%,[10] which is within the mean percent incidence reported by Amosu *et al*. in Sub-Saharan Africa.[3] LBW is found to be one of the major causes of high mortality and morbidity rates.[11] The perinatal mortality among LBW infants is about eight times higher than that in infants weighing >2.5 kg.[12] Harrison[13] has shown that Nigerian singleton babies weighing <2.5 kg contribute 41% of total perinatal mortality.

Prevention of impaired fetal growth or LBW through screening is one of the key aims of antenatal care as these have implications for child, mother, and society. If women can be identified to be at high risk from early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions (primary prevention). This, therefore, supports the need to investigate the association between impaired fetal growth and basic biochemical functions of the body of which cholesterol biosynthesis is among. Maternal cholesterol is an essential for both the hormonal and physical changes of early pregnancy.[14] Circulating low-density lipoprotein cholesterol is the chief substrate for placental progesterone biosynthesis.[15,16] Subclasses of high-density lipoprotein cholesterol also participate in placental cholesterol balance.[17] Cholesterol in plasma membranes is a bulk constituent of decidual tissue critical to implantation and uteroplacental vascularization.[18] Alterations in placental cholesterol concentrations have been associated with changes in placental transport functions during gestation.[19] The physiologic hypercholesterolemia of later pregnancy[20,21] therefore suggests an adaptive function for pregnancy maintenance.[22] It is thus hypothesized specifically that low maternal serum cholesterol may increase the risk of impaired fetal growth. It is not known whether optimal levels of maternal serum cholesterol during pregnancy can be defined. There are presently very few data addressing any potential risk to the pregnancy when maternal serum cholesterol falls below a lower bound. This study will, therefore, aim to investigate whether low maternal serum cholesterol levels during early gestation may be associated with impaired fetal growth or LBW in the Nigerian pregnant women.

Patients and Methods

The study was conducted at the antenatal clinic and labor ward complex of a teaching hospital in Lagos, Nigeria. This is a prospective cohort study of pregnancy outcome in young, generally healthy pregnant women attending the antenatal clinic of the hospital.

The sample size for the study was determined using the statistical formula by Schlesselman.[23] While making provision for attrition rate of 10%, a total of 320 participants were enrolled at gestational ages of 14 and 20. Eligible participants were pregnant women aged 15–49 years and have a singleton gestation. Excluded from the study were pregnant women with multiple gestations, history of diabetes or hypertension, HIV, current or previous history of smoking, other described substance use, and reports of previous abnormal pregnancy history. Additional patients were excluded at delivery when records indicated significant intercurrent infections or other illness, preeclampsia, or other gestational disorders.

Participants for the study were selected by using consecutive sampling method over a period of 12 months. A structured interviewer-administered questionnaire was used to collect relevant data. Social classes were determined using the Oyedeji socioeconomic classification scheme.[24] Venous blood samples were then obtained from fasting patient in the morning to measure total serum cholesterol concentrations between 14 and 20 weeks' gestation. Samples were collected in lithium heparin specimen bottles. Total cholesterol in serum was then analyzed enzymatically by the cholesterol oxidase: P-aminophenazone method using reagents from the manufacturer (BIOLABO SA, 02160, Maizy, France). The reference value for normal serum cholesterol is 200–239 mg/dL.[25] Thus, low maternal serum cholesterol pregnancies were defined as those in which maternal serum cholesterol level fall below 200 mg/dL. Gestational duration is based on gestation from participants' last normal menstrual period confirmed or modified by ultrasound. LBW in term neonates (<2.5 kg) was used as confirmatory outcome variable in the analysis.

All quantitative data were entered into the computer and analyzed using SPSS version 20 for windows manufactured by IBM Corp., Armonk, NY, USA. Descriptive statistics were computed for all relevant data. The associations between any two groups of continuous variables were tested using the independent sample *t*-test the association between low maternal serum cholesterol and LBW was tested using Chi-square or Fisher's exact test as appropriate. All significance are reported at $P < 0.05$. Ethical approval was obtained from the Hospital's Health Research and Ethics Committee before the commencement of the study and written consent obtained from each participant before involvement in the study.

Results

The study is a prospective cohort study in which 297 pregnant women with singleton gestation between the gestational age of 14 and 20 weeks were enrolled at the point of sample collections. However, on review at delivery, only the clinical data of 261 women who delivered at term (representing 87.9% of the study cohorts) and which included 76 (25.6%) women with total cholesterol levels below the reference range (200–239 mg/dL) and 185 (70.9%) women with normal midrange total cholesterol levels were used in the final analysis after excluding the 10 (0.3%) women with high total cholesterol levels [Figure 1].

When maternal characteristics were examined according to the serum cholesterol levels [Tables 1 and 2], there were no significant differences found between the mothers with low total cholesterol and controls with mid-range total cholesterol with respect to the gestational age at enrolment (P = 0.111), gestation at delivery (P = 0.857), parity (P = 0.534), marital status (P = 0.064), tribe (P = 0.830), religion (P = 0.106), and mode of delivery (P = 0.139). However, there were positive relationships between serum cholesterol levels and maternal age (P = 0.007) and body mass index (P = 0.032). A weak but statistically significant relationship was found between low total cholesterol and the lower socioeconomic class when compared to women with mid-range total cholesterol (P = 0.044, risk ratio = 1.66; 95% confidence interval [CI]: 0.5267–4.6521).

Table 3 shows that among this low-risk cohort of participants used in the study, the incidence of LBW in term babies was shown to be 13.4%. LBW was 2.05 times more common with low total maternal cholesterol than in control with midrange maternal cholesterol levels (21.1% vs. 10.3%). Term infants born to mothers with low total cholesterol had a statistically significant lower average birth weight than those born to control mothers with mid-range cholesterol levels (2348.0 vs. 2573.5-g, P = 0.039). Further analysis of the predictive value of low maternal serum cholesterol concentration (using the cutoff value of <200 mg/dL) as a marker of future delivery of LBW neonates was done with logistic regression model and receiver operating characteristics curve and these revealed a test sensitivity, specificity, positive, and negative predictive values of 76.0, 84.4, 66.7, and 75.7% (area under the curve = 0.982; 95% CI: 0.457–1.023) [Figure 2].

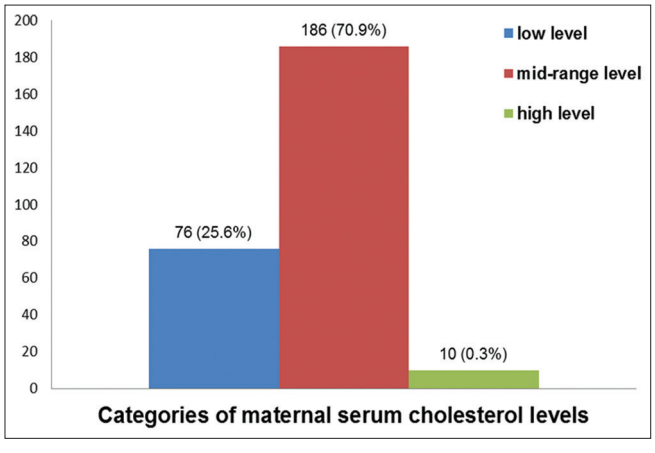

Figure 1: On review of clinical data at delivery, there were 261 women who delivered at term (representing 87.9% of the study cohorts) and these included 76 (25.6%) women with total cholesterol levels below the reference range (200–239 mg/dL) and 185 (70.9%) women with normal midrange total cholesterol levels who were used in the final analysis after excluding the 10 (0.3%) women with high total cholesterol levels

Discussion

This cohort study examined how a substantially low value of maternal serum cholesterol levels in early pregnancy which represents a relatively normal periconceptional cholesterol level that failed to rise as expected in the second trimester, would affect later events, such as fetal growth. The weak but statistically

Table 1: Maternal serum cholesterol levels and socio-demographic characteristics of study patients (n=261)

Characteristics	Cholesterol levels of study cohorts (Mean±SD)		*P*
	Low level (n=76)	Mid-range level (n=185)	
Cholesterol (mg/dL)	169.13±16.22	227.59±51.34	
Maternal Age (years)	24.75±5.24	29.52±5.27	0.007
GA at entry (weeks)	19.27±1.37	18.09±1.42	0.111
Maternal BMI (kg/m^2)	26.74±4.44	29.05±4.54	0.032
GA at delivery (weeks)	37.99±2.43	38.01±2.39	0.857

*SD: Standard deviation, GA: Gestational age

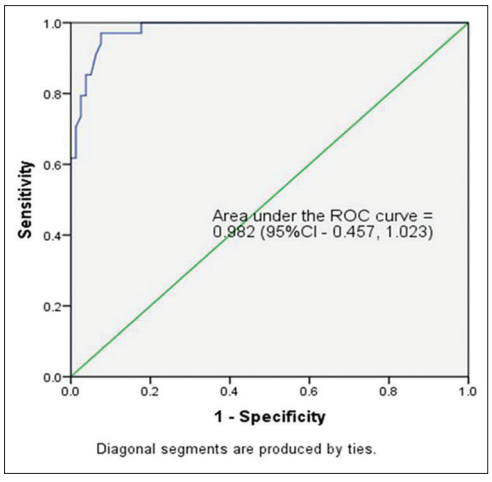

Figure 2: Receiver operating characteristics curve of maternal hypocholesterolaemia as a predictor of low birth weight in term neonates

Table 2: Maternal serum cholesterol levels and socio-demographic characteristics of study patients (*n*=261)

Characteristics	*n* (%)	Cholesterol levels of study cohorts		*P*
		Low level *n*=76 (%)	Mid-range level *n*=185 (%)	
Parity				
Primigravida	42 (16.0)	8 (10.5)	34 (18.4)	0.534
Multigravida	219 (84.0)	68 (89.5)	151 (81.6)	
Marital status				
Single	31 (11.9)	6 (7.9)	25 (13.5%)	0.064
Married	230 (88.1)	70 (92.1)	160 (86.5)	
Tribe				
Hausa	33 (20.6)	7 (9.2)	26 (14.1)	0.830
Igbo	67 (25.7)	26 (34.2)	41 (22.2)	
Yoruba	126 (48.3)	35 (46.1)	91 (49.1)	
Others	35 (13.4)	8 (10.5)	27 (14.6)	
Religion				
Christianity	168 (64.4)	48 (63.2)	120 (64.9)	0.106
Islam	85 (32.6)	26 (34.2)	59 (31.9)	
Others	8 (3.0)	2 (2.6)	6 (3.2)	
Social class				
Upper	28 (10.7)	9 (11.8)	19 (10.3)	0.049
Middle	184 (70.5)	37 (48.7)	147 (79.5)	
Lower	49 (18.8)	30 (39.5)	19 (10.2)	
Mode of delivery				
Vaginal delivery	184 (70.5)	56 (73.7%)	128 (69.2%)	0.139
Caesarean delivery	77 (29.5)	20 (26.3)	57 (30.8)	

Table 3: Relationship between serum cholesterol and LBW in term babies (*n*=261)

Serum cholesterol levels	*n* (%)	Birth weights in Study cohorts		Mean weight (g)
		Low weight (<2500g) (%)	Normal weight (≥2500g) (%)	
Low level	76 (29.1)	16 (21.1)	60 (78.9)	2348.0
Mid-range level	185 (70.9)	19 (10.3)	166 (89.7)	2573.5
Total	261 (100.0)	35 (13.4)	226 (86.6)	2460.8

**P*=0.039, RR=2.0485 (95% CI: 1.0261-5.1177)

significant relationship between low total cholesterol and low socioeconomic class in the study indicated that micronutrient deficiencies might be more common among the low total cholesterol risk group studied here and this could account for the outcome noted here. Many such nutritional deficiencies have been studied as predictors of LBW.[26]

LBW was reported to occur in 13.4% of the term born infants in our study. This prevalence is somewhat similar to the estimate of 10% reported by the UNICEF among full-term newborn infants in developing countries[9] but much higher than the reported prevalence of 4.5% in industrially developed countries.[8] However, it is within the incidence of 6%–21% reported by Lawoyin and Oyediran.[10] These variations are another indication of the disparities that exist between our developing countries and the more advanced developed countries of the world that have largely instituted interventions to prevent the occurrence of LBW in their settings.

The working hypothesis for this study that the risk for LBWs would be increased among infants who are born to mothers with low maternal serum cholesterol was also confirmed statistically; the statistical trend estimated a two-fold increase in risk in mothers with low total maternal cholesterol compared to control mothers with mid-range cholesterol. This was consistent with the reported risk from the study by Edison *et al*.,[27] however, there was a shift toward lower birth weights still within the reference range among term infants who were born to mothers with low maternal serum cholesterol in their study, which was at variance with the data from the present study where the average birth weight among these women with low maternal serum cholesterol was actually below 2500 g (2348.0 g). This finding confirms that LBW neonates are more common in the Nigerian setting compared to the industrially advanced countries like the United States where Edison's study was done.

Since the current study is hospital-based, there was the likelihood of bias in the enrollment of participants thus limiting the generalizability of the study to the whole population. The incessant strike actions during the study by the hospital staff also resulted in a higher than expected fall-out rate of the recruited participants in the study.

We will also like to point out that the association we observed in the study cannot determine causality. However, the strengths of the study are its prospective design and careful recording of the confirmatory outcome variable by a single researcher who was blind to the cholesterol status of the participants.

Conclusion

Cholesterol plays an important role in fetal development, and this study sheds some light on its importance, especially during pregnancy. We can, therefore, infer that the low maternal serum cholesterol (hypocholesterolemia) is associated with LBW in term neonates. We then recommend that the concept of an optimal range for maternal serum cholesterol during pregnancy may have merit. However, further prospective and longitudinal characterization of maternal serum cholesterol profiles in subsequent investigations of impaired fetal growth/LBW be carried out, and until such more studies are performed, pregnant women should be encouraged to follow a healthy, balanced diet, and regular antenatal visit to their health-care provider.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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