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ORIGINAL ARTICLE

Association between Low Maternal Serum Cholesterol Levels and Low Birth Weight in Term Neonates

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A B S T R A C T

Background: Low birth weight (LBW) is the single most powerful predictor of mortality in the first few months of life especially in most developing countries. The physiologic hypercholesterolaemia 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 (IUGR).

Methods: This was a prospective observational cohort study designed to assess whether low maternal serum cholesterol during early pregnancy is associated with LBW in term neonates. Eligible participants were enrolled for the study at gestational age of 14 to 20 weeks over a period of 12 months. Blood samples were obtained to measure total serum cholesterol concentrations and the sera were then analyzed enzymatically by the cholesterol oxidase: p-aminophenazone (CHOD PAP) method. Association between Low maternal serum cholesterol and LBW was tested using chi-square. All significance are reported at $P<0.05$.

Results: The study showed an incidence of 10.7% for delivery of LBW babies in the low risk study patients.LBW was 2.02-times more common with low total maternal cholesterol than with midrange maternal cholesterol levels (13.4% versus 8.3%, $P=0.043$).

Conclusion: We can infer from the study that the low maternal serum cholesterol (hypocholesterolaemia) is associated with LBW in term neonates. We can therefore recommend on this basis 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 healthcare provider.

INTRODUCTION

Low birth weight (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].

Low birth weight is defined by the World Health Organization (WHO) as a birth weight <2500g. 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 because of late and infrequent access to prenatal care, inadequate documentation of the date of the last menstrual period and unavailability of early ultrasound examination. One of the reasons that LBW continues to be reported and studied by epidemiologists and public health practi-

tioners is that it can be measured with excellent validity and precision [5].

Despite widespread recognition of the importance of LBW in developing 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 UNICEF that 10.0% of new born infants in developing countries will have LBW at term [9]. Its incidence in Nigeria lies between 6- 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 8 times higher than that in infants weighing more than 2.5kg [12].Harrison [13] has shown that Nigerian singleton babies weighing less than 2.5kg contribute 41% of total perinatal mortality.

Prevention of impaired fetal growth or low birth weight 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 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 utero-placental 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 is 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 low birth weight in the Nigerian pregnant women.

MATERIALS &METHODS

The study was conducted at the Antenatal clinic and Labour ward complex of a teaching hospital in Lagos, Nigeria. It is a prospective observational 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 18 to 35 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 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 socio-economic classification scheme [24].

Venous blood samples were 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 (CHOD-PAP) method using reagents from the manufacturer (BIOLABO SA, 02160, Maizy, France).

The reference value for normal serum cholesterol is 200-239mg/dl [25]. Thus, low maternal serum cholesterol pregnancies were defined as those in which maternal serum cholesterol level fall below 200mg/dL. Gestational duration is based upon gestation from participants' last normal menstrual period confirmed or modified by ultrasound. Low birth weight in term neonates (<2.5kg) was used as confirmatory outcome variable in the analysis.

All quantitative data were entered in computer and analysed using SPSS version 17 for windows [26]. Descriptive statistics were computed for all relevant data. Association between Low maternal serum cholesterol and LBW was tested using chi-square. All significance are reported at $P<0.05$.

Ethical approval was obtained from the hospital's Health Research and Ethics committee prior to the

commencement of the study and written consent obtained from each participant before involvement in the study.

RESULTS

Our study is a prospective observational cohort study in which 320 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 of clinical data at delivery, 33 (10.3%) of the ascertained cohort subjects were excluded.

The final cohort available for analysis was therefore 287 (representing 89.7% of the study patients) which included 76 (26.5%) women with total cholesterol levels below the reference range (200-239mg/dL) and 211 (73.5%) women with higher total cholesterol with the breakdown showing 185 women with mid-range and 26 with high total cholesterol levels respectively. The 26 subjects with high total cholesterol levels were also excluded prior to the final analysis.

Table I: Maternal serum cholesterol levels and Socio-demographic characteristics of study patients (n=287)

Characteristics	**Study Patients by serum cholesterol levels**		***P-value**
	Low level (n=76)	**Mid-range level (n=185)**	
Cholesterol Mean±SD (mg/dl)	169.13±16.22	227.59±51.34	
Maternal Age (years)	24.75±5.24	29.52±5.27	0.007
Gestation at entry (weeks)	19.27±1.37	18.09±1.42	0.111
Maternal BMI (kg/m2)	26.74±4.44	29.05±4.54	0.032
Gestation at delivery (weeks)	37.99±2.43	38.01±2.39	0.857

Table II: Maternal serum cholesterol levels and Socio-demographic characteristics of study patients (n=287)

Characteristics		**Study Patients by cholesterol levels**		***P-value**
		Low level (N=76) (%)	**Mid-range level (N=185) (%)**	
Parity	Primigravida	8 (10.5%)	34 (18.4%)	0.534
	Multigravida	68 (89.5%)	151 (81.6%)	
Marital status	Single	6 (7.9%)	25 (13.5%)	0.064
	Married	70 (92.1%)	160 (86.5%)	
Tribe	Hausa	7 (9.2%)	26 (14.1%)	0.830
	Ibo	26 (34.2%)	41(22.2%)	
	Yoruba	35 (46.1%)	91 (49.1%)	
	Others	8 (10.5%)	27 (14.6%)	
Religion	Christianity	48 (63.2%)	120 (64.9%)	0.106
	Islam	26 (34.2%)	59 (31.9%)	
	Others	2 (2.6%)	6 (3.2%)	
Social class	Upper	9 (11.8%)	19 (10.3%)	0.049
	Middle	37 (48.7%)	147 (79.5%)	
	Lower	30 (39.5%)	19 (10.2%)	
Mode of delivery	Vaginal delivery	56 (73.7%)	128 (69.2%)	0.139
	Caesarean section	20 (26.3%)	57 (30.8%)	

Table III: Relationship between serum cholesterol and LBW in term babies

Serum cholesterol levels	**Total (%)**	**Study patients**		**Mean weight (gm)**
		Low Weight (<2500g) (%)	**Normal Weight (≥2500g) (%)**	
Low	67 (100.0)	9 (13.4)	58 (86.6)	2348.0
Mid-range	181(100.0)	15 (8.3)	166 (91.7)	2573.5
Total	264 (100.0)	38 (14.4)	226 (85.6)	2460.8
Mean±SD (mg/dl)	238.67±33.47	237.33±17.53	240.51±29.96	

P-value=0.039. RR= 2.01976 (95% CI-0.9261-5.1177)

When maternal characteristics were examined according to the serum cholesterol levels (Tables I & II), there were no significant differences found between the mothers with low total cholesterol and control subjects with mid-range total cholesterol with respect to the gestational age at enrolment or samples collection (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 linear relationships between serum cholesterol levels and maternal age (P=0.007) and BMI (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, RR=1.66; 95% CI-0.5267-4.6521).

Table III showed that among this low-risk cohort of patients used in the study, the incidence of LBW in term babies was shown to be 10.7%. LBW was 2.02-times more common with low total maternal cholesterol than in control with midrange maternal cholesterol levels (13.4% versus 8.3%, *P*=0.043).

Term infants born to mothers with low total cholesterol had a 225.5-g lower average birth weight than those born to control mothers with mid-range cholesterol levels (2348.0 vs. 2573.5-g, *P*=0.004) and this mean difference in weight was statistically significant.

DISCUSSION

This observational 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.

There was a weak but statistically significant relationship between low total cholesterol and the lower socioeconomic class when compared to women with mid-range total cholesterol. These indicate that, micronutrient deficiencies may be more common among the low-total cholesterol risk group studied here and could account for the observed outcome. Many such nutritional deficiencies have been studied as predictors of low birth weight [27].

LBWwas reported to occur in 10.7% of the term born infants in our study. This prevalence is similar to the estimate of 10.0% reported by UNICEF among full term new born infants in developing countries [9] but muchhigher than the reported prevalence of 4.5% in industrially developed countries [8]. However it is within the incidence of 6-21% reported by Lawoyin et al [10].

The working hypothesis for this study that the risk for low birth weights 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 [28], however, there was a shift towards 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 this present study where the average birth weight among these women with low maternal serum cholesterol was actually below 2500g (2348.0-g). This finding confirms that LBW neonates are commoner in the Nigerian setting compared to the industrially advanced countries like the United States where the Edison's study was done.

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

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 (hypocholesterolaemia) is associated with low birth weight 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/low birth weight 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 healthcare provider.

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