Hypercholesterolaemia in pregnancy as a predictor of adverse pregnancy outcome

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Abstract

Background: Prevention of viable spontaneous preterm birth and low birth weight through screening is one of the key aims of antenatal care as these have implications for the child, mother and society. If women can be identified to be at high risk of these adverse birth outcomes in early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions.

Objectives: This study is therefore aimed to determine the association between elevated maternal serum cholesterol level in pregnancy and adverse pregnancy outcome.

Methods: It was a prospective observational cohort study in which eligible participants were enrolled at gestational age of 14 to 20 weeks. 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. Pregnancy outcomes were obtained by extraction from medical records and the labour ward register.

Results: The incidences of the two adverse pregnancy outcomes examined in the study (preterm births and low birth weight (LBW) in term neonates) were 8.0% and 14.4% respectively. Preterm birth was 6.89-times more common in mothers with high cholesterol than in control mothers with normal total cholesterol level (38.5% versus 5.4%, P=0.029) while LBW was

7.99-times more common in mothers with high total maternal cholesterol than in mothers with normal cholesterol (87.5% versus 10.5%, P=0.019).

Conclusion: We can infer that the high maternal serum cholesterol (hypercholesterolaemia) is associated with preterm delivery/low birth weight (LBW) in term infants. However, further validation of these findings with more robust prospective and longitudinal characterization of maternal serum cholesterol profiles is required in subsequent investigations.

Keywords: Adverse birth outcome, cholesterol, hypercholesterolaemia, LBW, preterm births

DOI: http://dx.doi.org/10.4314/ahs.v14i4.28

Introduction

Preterm birth and fetal growth restriction affect over 10% of all pregnancies and leads to significant neonatal morbidity and mortality[1]. Prevention of viable spontaneous preterm birth and low birth weight through screening is one of the key aims of antenatal care as these have implications for the child, mother and society. If women can be identified to be at high risk of these adverse birth outcomes in early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions (primary prevention).

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Maternal cholesterol is essential for both the hormonal and physical changes of early pregnancy[2]. Circulating low-density lipoprotein cholesterol is the chief substrate for placental progesterone biosynthesis[3,4]. Even though some longitudinal studies have documented that total cholesterol increases substantially during the second and third trimesters of pregnancy [5-7], it is still presently not known whether optimal levels of maternal serum cholesterol during pregnancy can be defined. This physiologic hypercholesterolemia of later pregnancy suggests an adaptive function for pregnancy maintenance or fetal growth[8]. Conversely, maternal hypercholesterolemia is also suspected to be injurious, because concentrations >300 mg/dL have been linked

to increased cholesterol deposition in the fetal aorta[9]; the "fetal origins hypothesis" links this phenomenon to subsequently increased risk for cardiovascular disease in the adult offspring[10-12]. It is also reasoned that this elevated maternal cholesterol may have a disproportionate impact during critical periods for placentation and early neuroepithelial expansion[13].

Various studies have reported a possibly increased risk for prematurity and impaired fetal growth[14-16] with very high maternal cholesterol level but the effects of hypercholesterolemia on the metabolic process of tissues that support the fetus, the placenta, and the yolk sac have yet to be established, and those effects could markedly influence the outcome of pregnancy and long-term health issues. This study will thus investigate the effect of a higher than normal level of maternal serum cholesterol during gestation on two important adverse pregnancy outcomes (preterm births and low birth weight) and thereafter describe a generic framework for combining this screening information with designing a prophylactic intervention in the future.

Materials & Methods

The study was conducted at the Antenatal clinic and Labour ward complex of a tertiary hospital in Southwest Nigeria. It was a prospective observational cohort study of pregnancy outcome in young, generally healthy pregnant women attending the antenatal clinic of the hospital over a period of 12 months.

The sample size (N) for the study was determined using the statistical formula by Schlesselman[17]. While making provision for attrition rate of 10%, a total of 320 participants were enrolled between gestational ages of 14 and 20. The women were enrolled during this period of pregnancy in order to carefully isolate the mothers' inherent cholesterol levels from the natural increases in LDL-cholesterol and total cholesterol levels that occur physiologically during the late second and third trimesters of pregnancy. Women were also not recruited in the first trimester (before 14 weeks) as our antenatal patients rarely present for booking until the early second trimester which thus suggest that our study findings can be of benefit mostly around that usual time of presentation.

Eligible participants were pregnant women aged 18 to 35 years and have a singleton gestation. Exclusion criteria included 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 other illnesses, preeclampsia or other gestational disorders such as gestational diabetes.

Participants for the study were selected by consecutive sampling method and a structured interviewer administered questionnaire was used to collect data from each participant upon explanation of the nature and purpose of the study. Social classes were determined using the Oyedeji socio-economic classification scheme[18].

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[19]. Thus, high maternal serum cholesterol pregnancies were defined as those in which maternal serum cholesterol level was above 239mg/dL. Gestational duration was based upon gestation from participants' last normal menstrual period confirmed or modified by ultrasound. Preterm delivery and low birth weight in term neonates were used as confirmatory outcome variables in the analysis.

All quantitative data were entered in computer and analysed using SPSS version 17 for windows[20]. Descriptive statistics were computed for all relevant data. Association between Low maternal serum cholesterol and the two outcome variables were tested using chi-square. All significance are reported at $P<0.05$.

Ethical approval for the study 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

The study was 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. These included 16 women who were lost to follow-up while another 17 were excluded from the study based on the exclusion criteria (7 with medically indicated preterm delivery, 4 women who developed gestational hypertension, 2 women with gestational diabetes, 1 woman diagnosed with IUGR, 1 who had twin delivery, 1 whose neonate was diagnosed with structural cardiac defect at delivery, and another 1 who had IUFD).

The final cohort available for analysis was therefore 287 (representing 89.7% of the study patients) which included 26 (9.1%) women with total cholesterol levels above the reference range (200-239mg/dL), 185 (64.4%) with normal or mid-range levels and 76 (26.5%) women with low total cholesterol levels.

When maternal characteristics were examined according to the serum cholesterol levels (Table I & II), there were no statistically significant differences found between the mothers with high total cholesterol and control subjects with normal total cholesterol with respect to the gestational age at enrolment for the study (P=0.935), gestation at delivery (P=1.001), parity (P=0.078), marital status (P=0.055), tribe (P=1.333), religion (P=0.097) and mode of delivery (P=0.788).

However, there were positive linear relationships between serum cholesterol levels with maternal age (P=0.014) and BMI (P=0.039). A weak but statistically significant relationship was found between high total cholesterol and the upper socioeconomic class (P=0.045) when compared to women with normal total cholesterol.

TableI-Maternal serum cholesterol levels and Socio-demographic characteristics of study patients

CHARACTERISTICS	Study patients by cholesterol levels			P-value
	High	Normal	Low	
	N=26	N=185	N=76	
Cholesterol Mean±SD (mg/dl)	275.28±36.05	227.59±11.34	169.13±16.22	
Maternal Age (years)	33.73±5.14	29.52±5.27	24.75±5.24	0.014
G.A at entry (weeks)	19.72±1.48	18.09±1.42	19.27±1.37	0.935
Maternal BMI (kg/m2)	30.54±4.36	29.05±4.54	26.74±4.44	0.039
G.A at delivery (weeks)	37.17±2.41	38.01±2.39	37.99±2.43	1.001

*G.A (Gestational Age), **BMI (Body Mass Index)

TableII-Maternal serum cholesterol levels and Socio-demographic characteristics of study patients

CHARACTERISTICS	Study patients by cholesterol levels			P-value
	High	Normal	Low	
	N (%)	N (%)	N (%)	
PARITY				
Primigravida	7 (26.9)	34 (18.4)	8 (10.5)	0.078
Multigravida	19 (73.1)	151 (81.6)	68 (89.5)	
MARITAL STATUS				
Single	10 (38.5)	25 (13.5)	6 (7.9)	0.055
Married	16 (61.5)	160 (86.5)	70 (92.1)	
TRIBE				
Hausa	4 (15.4)	26 (34.2)	7 (9.2)	1.333
Ibo	5 (19.2)	41 (22.2)	26 (34.2)	
Yoruba	9 (34.6)	91 (49.1)	35 (46.1)	
Others	8 (30.8)	27 (14.6)	8 (10.5)	
RELIGION				
Christianity	12 (46.2)	120 (64.9)	48 (63.2)	0.097
Islam	13 (50.0)	59 (31.9)	26 (34.2)	
Others	1 (3.8)	6 (3.2)	2 (2.6)	
SOCIAL CLASS				
Upper	12 (46.1)	19 (11.8)	9 (11.8)	0.045
Middle	8 (38.8)	147 (79.5)	37 (48.7)	
Lower	6 (23.1)	19 (10.2)	30 (39.5)	
MODE OF DELIVERY				
Vaginal delivery	17 (65.4)	128 (69.2)	56 (73.7)	0.788
Caesarean section	9 (34.6)	57 (30.8)	20 (26.3)	
TOTAL	**26 (100.0)**	**185 (100.0)**	**76 (100.0)**	

Table III showed that even among this low-risk cohort of patients used in the study, the incidence of preterm birth was found to be 8.0%. Preterm birth was 6.89-times more common with high total maternal cholesterol than with normal maternal cholesterol (38.5% vs. 5.4%; P=0.029).

TableIII-Relationship between low maternal serum cholesterol and preterm delivery

Serum cholesterol level	Study patients		Total
	Preterm delivery (<37wksG.A)	Term delivery (≥37wksG.A)	
	N(%)	N(%)	
High	10 (38.5)	16 (61.5)	26 (100.0)
Normal	10 (5.4)	175 (94.6)	185 (100.0)
Low	3 (3.9)	73 (96.1)	76 (100.0)
Total	**23 (8.0)**	**264 (92.0)**	**287 (100.0)**

P-value=0.029. RR= 6.8917 (95% CI-2.3897-11.3376)

In Table IV, the incidence of low birth weight (LBW) in term babies was shown to be 14.4%. LBW was 7.99-times more common in mothers with high total maternal cholesterol than in control mothers with normal cholesterol (87.5% vs. 10.5%, P=0.019). Term infants born to mothers with high cholesterol had a much lower average birth weight (989.5-g) than those born to control mothers with normal cholesterol levels (2460.5 vs. 3450.0-g).

Table IV-Relationship between serum cholesterol and LBW in term neonates

Serum cholesterol	Mean weight (g)	Study patients		Total
		Low Weight (? 2500g)	Normal Weight (=2500g)	
		N (%)	N (%)	
High	2460.5	14 (87.5)	2 (12.5)	16 (100.0)
Normal	3450.0	19 (10.5)	162 (89.5)	181 (100.0)
Low	2350.0	5 (7.5)	62 (92.5)	67 (100.0)
Total	**2680.3**	**38 (14.4)**	**226 (85.6)**	**264 (100.0)**

P-value=0.019. RR=7.9932 (95% CI-5.8719-17.6011)

Discussion

This observational cohort study carried out among pregnant women at a tertiary hospital in South-west Nigeria examined how a substantially high value of maternal serum cholesterol levels in early pregnancy would affect and be used as predictor for later events, such as week of delivery and fetal growth.

Our study found an the incidence of 8.0% for preterm births in this highly selected study cohort which was only slightly higher than the figure reported by Edison et al (6.6%)[21], but it is still within the range quoted by Kierse at 5-10%[22] and from a study done in Nigeria by Ezechukwu et al (5-25%)[23].This was probably due to the similarities in the study groups used in all these studies especially with regard to the patients' age range. Preterm birth is known to be initiated by multiple mechanisms and various reports have suggested a possibly increased risk for prematurity with very high maternal cholestero[l2,24,25]. Finding by Catov and coworkers[26] showed that an elevation in maternal cholesterol level early in gestation was associated with an increased risk of preterm delivery. This was corroborated by the finding from this present cohort study where we reported an elevated risk for preterm birth among mothers with high maternal cholesterol.

LBW was reported to occur in 14.4% of the term born infants in our study. This prevalence is slightly higher than the estimate of 10.0% reported by UNICEF among full term new born infants in developing countries[27] but it's within the incidence of 6-21% reported by Lawoyin et al[28].

The working hypothesis for this study that the risk for low birth weights would be increased among infants who are born to mothers with high maternal serum cholesterol was also confirmed statistically; the statistical trend estimated a seven-fold increase in risk in mothers with high total maternal cholesterol compared to control mothers with normal cholesterol. This positive correlation was consistent with the finding by Fakhar-un-Nisa et al[25].

Limitations to the study

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.

Conclusion

We can infer from this study that increase maternal age and high maternal BMI are associated with high maternal serum cholesterol (hypercholesterolaemia) which in turn is associated with preterm birth and low birth weight in term neonates. We therefore recommend that further validation of these findings with more robust prospective and longitudinal characterization of maternal serum cholesterol profiles in pregnancy, with elimination of major confounding variables such as maternal age and BMI, be carried out in subsequent investigations to determine the optimal cholesterol range in pregnancy, 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.

Source(s) of support:
None
Conflicting Interest:
None declared

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