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ORIGINAL ARTICLE

Maternal plasma cholesterol and duration of pregnancy: A prospective cohort study in Ghana

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Abstract

Low plasma cholesterol may be associated with preterm birth; however, results are mixed and limited primarily to high-income countries. Our objective was to determine whether maternal plasma lipid concentrations are associated with pregnancy duration. We performed a nested cohort (n = 320) study of pregnant Ghanaian women enrolled in a randomized controlled trial. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglyceride concentrations were analyzed in plasma at ≤20and 36 weeks gestation as continuous variables and also categorized into low, referent, or high (<10th, 10th–90th, >90th percentile). At ≤20 weeks, plasma lipid concentrations were not associated with pregnancy duration. At 36 weeks, total cholesterol and triglyceride concentrations were not associated with pregnancy duration. Higher HDL-C at 36 weeks was associated with a longer pregnancy duration (adjusted β-coefficient ± standard error: 0.05 ± 0.02 days mg^{-1}/dL, p = .02); pregnancy duration was 5.9 ± 2.0 (mean ± standard error) days shorter among women with low HDL-C compared with the referent group (10th–90th percentile) (p = .02) and 8.6 ± 2.6 days shorter when compared with the high HDL-C group (p = .003). Pregnancy duration was 4.9 ± 2.1 days longer among women with low low-density lipoprotein cholesterol at 36 weeks gestation when compared with the referent group (p = .051). Our data suggest that low HDL-C in the third trimester of pregnancy is associated with a shorter duration of pregnancy in this study population but do not support the hypothesis that low total cholesterol is associated with a shorter pregnancy duration.

KEYWORDS

cholesterol, Ghana, maternal health, plasma lipids, pregnancy, preterm birth

1 | INTRODUCTION

Studies have implicated both high and low concentrations of prenatal maternal cholesterol as risk factors for preterm birth (Alleman et al., 2013; Bartha et al., 2012; Catov et al., 2010; Edison et al., 2007; Harville, Viikari, & Raitakari, 2011; Kramer et al., 2009; Magnussen, Vatten, Myklestad, Salvesen, & Romundstad, 2011; Mudd, Holzman, Catov, Senagore, & Evans, 2012; Vrijkotte et al., 2012; Wiznitzer et al., 2009). Preterm birth, defined as birth at less than 37 completed weeks of gestation, is the single largest cause of neonatal mortality worldwide, accounting for an estimated 35% of all deaths in the first 28 days of life (Blencowe et al., 2012). There are also long lasting repercussions, as adults who were born preterm have a higher prevalence of chronic health disorders than those born at term (Saigal & Doyle, 2008). Many mechanisms have been proposed to explain preterm birth, including infection, stress, inflammation, utero-placental ischemia from inadequate placenta perfusion, and uterine overdistension (Goldenberg, Culhane, Iams, & Romero, 2008). However, 40–50% of preterm births remain unexplained (Beck et al., 2010).

In 2007, Edison et al. reported an increased risk of preterm birth among pregnant women in South Carolina whose total serum cholesterol, measured at 13–23 weeks gestation, was <10th percentile for the study population, compared to those with higher cholesterol. (Edison et al., 2007) This association was only evident in Caucasian

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IFA, iron and folic acid capsule; LDL-C, low-density lipoprotein cholesterol; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient capsule

women and not African-American women. Several subsequent studies have demonstrated similar associations (Bartha et al., 2012; Catov et al., 2010; Kramer et al., 2009; Mudd et al., 2012), but others have shown no relationship between low plasma lipid concentrations and preterm birth (Alleman et al., 2013; Harville et al., 2007; Magnussen et al., 2011; Vrijkotte et al., 2012; Wiznitzer et al., 2009).

Cholesterol increases the structural integrity of cell membranes, serves in essential cell signaling roles, and acts as a precursor to steroid hormones, vitamin D, and bile acids (Rosenberger, Brumell, & Finlay, 2000; Woollett, 2008). During pregnancy, plasma cholesterol and triglyceride concentrations decline in the early part of the first trimester, which may decrease risk of infection by viruses and bacteria that use cholesterol (Amir & Fessler, 2013). However, increasing fetal cell formation and placental steroid hormone production stimulates cholesterol synthesis following this initial decline, resulting in a 50% overall increase of plasma cholesterol and a twofold–fourfold increase in triglycerides by the end of pregnancy (Basaran, 2009).

Notably absent from published research on the association between low plasma cholesterol and preterm birth are studies in populations from developing countries. Globally, it is estimated that 11.1% of all births (15 million) are preterm. Out of 184 countries ranked in order of highest preterm birth rate, Ghana ranked near the highest (14th) with a preterm birth rate of 14.5%. (Blencowe et al., 2012; Beck et al., 2010) It is important to investigate how plasma lipid concentrations relate to duration of gestation among women from such areas, as it has been shown that cholesterol metabolism differs by race and latitude (Cappuccio, 1997; Eisenberg, Kuzawa, & Hayes, 2010; Godsland, Johnston, & Chaturvedi, 2007).

The aim of the current study was to determine whether low maternal plasma lipid levels (total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides at ≤20 or 36 weeks gestation are associated with pregnancy duration in Ghanaian women. Our main hypothesis was that low total plasma cholesterol, at either enrollment or 36 weeks gestation, would be associated with a shorter duration of gestation.

2 | SUBJECTS AND METHODS

Women for this nested cohort study were enrolled in the International Lipid-based Nutrient Supplements Project trial (iLiNS-DYAD) in Ghana, a randomized intervention trial assessing the effects of a lipid-based nutrient supplement (LNS) on maternal and child outcomes, with the primary outcome being child length at birth and 18 months of age. Detailed methods have been published elsewhere (Adu-Afarwuah et al., 2015). Briefly, we recruited pregnant women attending antenatal clinics at four health facilities in semi-urban areas in the Yilo Krobo and Lower Manya Krobo districts, about 70 km north of Accra, Ghana, and close to the equator (latitude: 5.55°N). Women were eligible if they were ≤20 weeks gestation, ≥18 years of age, had a completed antenatal health card, and signed or thumb-printed informed consent. We excluded women if they were HIV positive, had asthma, epilepsy, tuberculosis, a chronic disease that required medical attention, did not reside in the defined catchment area, had a milk or peanut allergy, or were participating in another clinical trial. We randomized women to receive daily throughout pregnancy either of the following: (a) an iron and folic acid capsule (IFA); (b) a multiple micronutrient capsule (MMN); or (c) a sachet of 20 g LNS. The details of the three supplements (Adu-Afarwuah et al., 2015) and the rationale for LNS formulation and design have been reported previously (Arimond et al., 2015). The Institutional Review Boards of the University of California, Davis; the Noguchi Memorial Institute for Medical Research, University of Ghana; and the Ghana Health Service approved the study protocol, and the trial was registered at clinicaltrials.gov (ID: NCT00970866).

At enrollment, we determined gestational age by ultrasound (Aloka SSD 500, Tokyo, Japan) and measured weight and height (SECA 874 flat scale and SECA 217 stadiometer, Seca GmbH & Co., Hamburg, Germany). Trained field workers collected sociodemographic information. At both enrollment and 36 weeks gestation, a trained phlebotomist collected blood samples by venipuncture. Lab technicians centrifuged the blood samples at 1,252 × g for 15 min and stored the resulting plasma at −33°C. Time of blood collection and the last food or drink were recorded. Plasma samples were analyzed for total cholesterol, HDL-C, and triglycerides using an enzymatic colorimetric method with the Flexor Junior Chemistry Analyzer (Vital Scientific, Dieren, Netherlands) and Elitech reagents (Puteaux, France). LDL-C was calculated using the Friedewald equation: LDL-C = total cholesterol − (HDL-C) − (triglycerides/5), mg/dL (Friedewald, Levy, & Fredrickson, 1972). This is accepted as an accurate method of determining LDL-C concentration, as long as triglyceride concentration is not ≥400 mg/dL; all of our samples were below this level.

A subsample of women were selected for analysis of plasma lipids. From the 1,320 women enrolled in the trial, 510 were excluded because they were enrolled during a period when there was an error in the labeling of the iron and folic acid and multiple micronutrient supplements, resulting in mixed exposure (Adu-Afarwuah et al., 2015). From the remaining 810 women, enrolled from October 2010

Key messages

- The highest rates of preterm birth are in low- and middle-income countries.
- Low maternal plasma cholesterol concentration may be associated with a shorter duration of pregnancy, but research has been limited primarily to high-income countries.
- In this study population of pregnant women in Ghana, low total cholesterol was not associated with pregnancy duration.
- Low high-density lipoprotein cholesterol in the third trimester of pregnancy may be associated with a shorter duration of pregnancy.

to December 2011, 369 women were randomly selected for plasma lipid analysis. Statistical analysis was limited to the 320 women who had duration of gestation data and at least one plasma lipids measurement.

3 | DATA ANALYSIS

For the biochemical outcomes in the main trial, including plasma lipid analysis, we assumed an effect size of at least 0.5 which required a subsample of 79 per group, for a total of 237 subjects. Allowing for attrition and women missing a sample at either baseline or 36 weeks gestation, 369 participants were randomly selected from the 810 women enrolled after October 1, 2010. For the present analysis, this sample size would provide us with 80% power to detect a difference of at least 0.9 days of gestation comparing those with low plasma lipids to the reference group.

We tested normality using the Shapiro–Wilk test. All plasma lipid concentrations were determined to have normal distribution. Linear regression models were used to examine the association between each plasma lipid variable and the duration of gestation, with *p*-values <.05 considered statistically significant. Models were checked using robust regression with MM-estimation, which uses a combination of breakdown value estimation and efficient estimation (Yohai, 1987), to confirm minimal leverage and influence of valid outliers. Plasma lipids were analyzed both as continuous and categorical variables (low: <10th percentile, referent: 10th–90th percentile, high: >90th percentile), and quadratic terms were utilized to assess whether a u-shaped relationship existed between plasma lipid concentrations and duration of gestation.

Based on previous literature, variables defined a priori as potential confounders and included in the multivariable model were parity, gestational age at enrollment, baseline body mass index (body mass index [BMI] = kg/m^2), woman's age, infant gender, household asset index, and time since last meal. Assigned supplement group in trial was included in all adjusted models, even though preliminary analyses showed plasma lipid concentrations measured at 36 weeks gestation did not differ between intervention groups (unpublished results). We created an asset index based on household drinking water supply, sanitation facilities, flooring materials, lighting source, radio, television, refrigerator, cell phone, and stove using principal components analysis. (Vyas & Kumaranayake, 2006) Interactions with maternal age, parity, and supplement group were examined and determined significant at $p < .10$, and stratified analyses were performed for significant interactions. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

4 | RESULTS

Plasma lipid measurements were obtained at baseline and 36 weeks gestation for 347 and 295 women, respectively. Of those missing 36 weeks plasma lipid data, eight delivered preterm. Compared with women without baseline plasma lipid data, women with baseline plasma lipid data were similar in age, parity, BMI, and gestational age at enrollment; had a better asset index *z*-score (0.23 vs. −0.08, $p < .0001$); and had a longer pregnancy duration (39.6 vs. 39.1 weeks, $p < .0001$). Of those with plasma lipid measurements, we had dates of delivery for 320. Of the 27 with missing delivery dates, one had moved out of the study area, two had a loss of pregnancy, seven reported a stillbirth, and the remaining 17 were lost to follow-up. There were no significant differences in plasma lipid concentrations or baseline characteristics between women missing delivery date data versus women with delivery date data. Mean (SD) duration of gestation for this cohort was 39.6 (1.6) weeks. Baseline characteristics and lipid profiles at ≤20 and 36 weeks gestation are presented in Table 1.

Baseline lipid concentrations were not associated with pregnancy duration in either unadjusted or adjusted models. At 36 weeks gestation, total cholesterol and triglycerides were not significantly associated with pregnancy duration (Tables 2 and 3). HDL-C was positively correlated with duration of gestation in unadjusted models, and the relationship became stronger and more significant in adjusted models, with a 0.5 day longer duration of gestation for every 10 mg/dL increase in HDL-C. Duration of gestation was on average 5.9 (2.0) (mean (SE)) days shorter among women with low HDL-C at 36 weeks gestation (HDL-C < 27 mg/dL; mean duration of gestation: 273 days) when compared with the referent group (mean duration of gestation: 279 days); $p = .02$) and 8.6 (2.6) days shorter when compared with the high HDL-C group (HDL-C > 108 mg/dL; mean duration of gestation: 281 days; $p = .003$). Duration of gestation was on average 4.9 (2.1) days longer among women with low LDL-C at 36 weeks gestation when compared with the referent group ($p = .051$). No evidence of a u-shaped relationship with duration of gestation was found for any plasma lipid variable (Figure 1).

There was a significant interaction between parity and triglycerides measured at both baseline ($p = .01$) and 36 weeks gestation ($p = .03$), with a significant negative association between triglyceride concentration and duration of gestation among primiparous women

TABLE 1 Characteristics of study cohort of pregnant women in Ghana ($n = 320$)

Characteristic	Mean (SD) or %
≤20 weeks gestation	
Maternal age (year)	26.5 (5.2)
Gestational age (weeks)	16.2 (3.0)
Primiparous (%)	36.3%
Parity (total births)	1.2 (1.2)
BMI (kg/m^2)	24.8 (4.0)
Overweight or obese (%, BMI ≥ 25 kg/m^2)	37.9%
Total cholesterol (mg/dL)	144.5 (34.7)
HDL-C (mg/dL)	57.0 (22.6)
LDL-C (mg/dL)	63.7 (27.9)
Triglycerides (mg/dL)	119.1 (58.1)
36 weeks gestation	
Total cholesterol (mg/dL)	165.5 (41.8)
HDL-C (mg/dL)	66.9 (30.5)
LDL-C (mg/dL)	68.4 (33.0)
Triglycerides (mg/dL)	147.7 (74.7)

Note. BMI = body mass index; SD = standard deviation; HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

TABLE 2 Adjusted and unadjusted beta coefficients for total cholesterol, HDL-C, LDL-C, and triglycerides at ≤20 weeks (n = 320) and 36 weeks gestation (n = 282), in 10 mg/dL increments, in association with duration of gestation (days) in pregnant women in Ghana

	Unadjusted β (SE)	p	Adjusted[a] β (SE)	p
Total cholesterol, 10 mg/dL				
≤20 weeks gestation	−0.07 (0.02)	.69	−0.02 (0.02)	.91
36 weeks gestation	0.01 (0.01)	.96	0.02 (0.01)	.88
HDL-C, 10 mg/dL				
≤20 weeks gestation	0.04 (0.03)	.90	0.2 (0.03)	.48
36 weeks gestation	0.4 (0.02)	.04	0.5 (0.02)	.02
LDL-C, 10 mg/dL				
≤20 weeks gestation	0.02 (0.02)	.95	−0.05 (0.02)	.82
36 weeks gestation	−0.3 (0.02)	.11	−0.3 (0.02)	.07
Triglycerides, 10 mg/dL				
≤20 weeks gestation	−0.08 (0.01)	.49	−0.03 (0.01)	.83
36 weeks gestation	−0.02 (0.01)	.83	−0.01 (0.01)	.87

Note. HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol; SE = standard error.

[a]Multivariate model includes supplement group, gestational age at enrollment baseline BMI, age, parity, infant gender, season at enrollment asset index, and time since last meal.

and no significant association among multiparous women (Table 4). There was no interaction between parity and cholesterol, nor was there interaction with maternal age or supplement group in any of the models. In our subsample, 11 (3.4%) women gave birth preterm, which resulted in too high a level of model uncertainty for the outcome of preterm birth to be included as part of our analyses.

We compared plasma lipid measurements between women who, by self-report, had not eaten in the previous 8 hr before the blood draw (n = 34 at baseline and n = 26 at 36 weeks gestation) and women who had eaten within 8 hr of the blood draw. There were no significant differences in any of the plasma lipid concentrations between these two groups of women (data not shown). We also re-examined all associations using a Bonferroni correction to account for multiple comparisons. Adjusting for the eight comparisons performed (4 lipids and 2 time points), the 8.6 day difference between women with low versus high HDL remained significant, while all other associations became nonsignificant.

5 | DISCUSSION

Our aim was to determine whether maternal plasma lipid concentrations during pregnancy were associated with duration of gestation in a cohort of pregnant women in Ghana. Our data do not support the hypothesis that low total cholesterol is associated with a shorter duration of gestation. None of the plasma lipids measured at ≤20 weeks gestation were associated with duration of gestation, and at 36 weeks gestation, total cholesterol and triglyceride concentrations were not associated with duration of gestation. However, low HDL-C at 36 weeks was significantly associated with a shorter duration of gestation, and there was a nearly significant association between low LDL-C and a longer duration of gestation (p = .051).

In comparison with other cohorts of pregnant women (Alleman et al., 2013; Bartha et al., 2012; Catov et al., 2010; Edison et al., 2007; Harville et al., 2011; Magnussen et al., 2011; Mudd et al., 2012; Vrijkotte et al., 2012; Wiznitzer et al., 2009), this cohort had similar mean HDL-C and triglyceride concentrations but lower total cholesterol and LDL-C concentrations. Changes in cholesterol and triglyceride concentrations during pregnancy were more modest than expected based on previous studies (Basaran, 2009). In general, the women in this study appeared to have adequate energy intake, with only 2.6% underweight (BMI < 18.5 kg/m^2) and 41.5% overweight or obese (BMI > 25 kg/m^2) at baseline. There was no correlation between BMI and cholesterol in this study population, which is similar to what was seen in the cohort of pregnant women examined by Edison et al (Edison et al., 2007).

Some studies have shown low total cholesterol to be associated with increased risk of preterm birth (Bartha et al., 2012; Catov et al., 2010; Edison et al., 2007; Mudd et al., 2012; Oluwole, Adegbesan-Omilabu, & Okunade, 2014); however, several studies have not shown such an association, which is consistent with our findings (Alleman et al., 2013; Harville et al., 2011; Kramer et al., 2009; Magnussen et al., 2011; Vrijkotte et al., 2012; Wiznitzer et al., 2009). The association between HDL-C and duration of gestation in our study is similar to the results from other studies (Bartha et al., 2012; Kramer et al., 2009; Magnussen et al., 2011). Canadian women with mid-pregnancy HDL-C above the study median were 50% less likely to have a preterm birth than women with HDL-C below the median (Kramer et al., 2009). Magnussen et al. found that women with low HDL-C before pregnancy had increased odds of preterm birth (Magnussen et al., 2011), and Bartha et al. showed that women delivering preterm had lower HDL-C in the third trimester than those delivering at term (Bartha et al., 2012). No significant association was seen between HDL-C and preterm birth in three other studies that assayed samples either before pregnancy (Catov et al., 2010; Harville et al., 2011) or during the first and second trimesters (Alleman et al., 2013; Catov et al., 2010; Harville et al., 2011), supporting our null associations with plasma lipids at ≤20 weeks gestation.

There is less evidence of an association between LDL-C and preterm birth, with the majority of studies presenting no association (Alleman et al., 2013; Catov et al., 2010; Harville et al., 2011; Kramer et al., 2009). However, Bartha et al. showed that women delivering preterm

TABLE 3 Mean difference in duration of gestation by percentile groups for total cholesterol, HDL-C, LDL-C, and triglycerides at ≤20 and 36 weeks gestation in cohort of pregnant women in Ghana

Percentiles by weeks of gestation	mg/dL	*n*	Unadjusted		Adjusted[b]	
			Mean (95% CI) difference in duration of gestation (days)	*p*[a]	Mean (95% CI) difference in duration of gestation (days)	*p*[a]
Total cholesterol						
≤20 weeks						
<10th	<102.5	34	−1.1 (−5.7, 3.5)	.64	−0.9 (−6.6, 4.8)	.93
10th–90th	102.5–185.6	272	Ref	Ref	Ref	Ref
>90th	>185.6	40	−1.1 (−5.1, 2.9)	.59	−0.9 (−5.8, 4.1)	.91
36 weeks						
<10th	<112.1	26	0.9 (−3.0, 4.8)	.65	1.3 (−3.5, 6.1)	.79
10th–90th	112.1–220.4	238	Ref	Ref	Ref	Ref
>90th	>220.4	31	−2.2 (−5.8, 1.5)	.24	−1.9 (−6.5, 2.7)	.59
HDL-C						
≤20 weeks						
<10th	<30.9	30	−2.3 (−6.8, 2.2)	.31	−3.2 (−8.8, 2.4)	.37
10th–90th	30.9–85.1	278	Ref	Ref	Ref	Ref
>90th	>85.1	39	−0.9 (−4.9, 3.0)	.64	−0.8 (−5.8, 4.2)	.93
36 weeks						
<10th	<27.1	24	−6.2 (−10.1, −2.3)	.002	−5.9 (−10.7, −1.1)	.01
10th–90th	27.1–108.3	239	Ref	Ref	Ref	Ref
>90th	>108.3	32	2.0 (−1.5, 5.4)	.27	2.7 (−1.7, 7.0)	.31
LDL-C						
≤20 weeks						
<10th	<30.9	32	0.7 (−3.7, 5.0)	.77	1.0 (−4.5, 6.5)	.91
10th–90th	30.9–98.6	275	Ref	Ref	Ref	Ref
>90th	>98.6	39	1.0 (−3.0, 5.0)	.62	0.6 (−4.2, 5.5)	.95
36 weeks						
<10th	<30.9	25	3.4 (−0.5, 7.4)	.08	4.9 (0.02, 9.8)	.05
10th–90th	30.9–112.1	234	Ref	Ref	Ref	Ref
>90th	>112.1	36	0.1 (−3.4, 3.6)	.95	0.6 (−3.7, 5.0)	.94
Triglycerides						
≤20 weeks						
<10th	<53.1	34	2.7 (−1.6, 7.1)	.22	2.0 (−3.4, 7.3)	.67
10th–90th	53.1–194.9	276	Ref	Ref	Ref	Ref
>90th	>194.9	37	0.8 (−3.2, 4.8)	.69	0.6 (−4.3, 5.6)	.95
36 weeks						
<10th	<53.1	30	2.2 (−2.7, 7.0)	.38	2.6 (−3.3, 8.4)	.55
10th–90th	53.1–256.9	234	Ref	Ref	Ref	Ref
>90th	>256.9	31	−1.8 (−5.4, 1.7)	.31	−1.8 (−6.5, 3.0)	.65

Note. CI = confidence interval; HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

[a]*p*-value obtained from *t*-test in comparison with the 10th–90th percentile.

[b]Multivariate model includes supplement group, gestational age at enrollment baseline body mass index, age, parity, infant gender, season at enrollment asset index, and time since last meal.

had significantly lower LDL-C in the third trimester than those delivering at term (Bartha et al., 2012), which is counter to our results suggesting that women with low LDL-C had a longer duration of gestation. On the other hand, Mudd et al. showed that women with LDL-C ≥ 70th percentile had significantly increased odds of a spontaneous preterm birth.

Studies also generally have not shown an association between triglyceride concentrations and preterm birth (Bartha et al., 2012; Catov et al., 2010; Harville et al., 2011; Vrijkotte et al., 2012), although two studies observed that women with high triglycerides had increased odds for preterm birth (Magnussen et al., 2011; Mudd et al., 2012), which is consistent with our study suggesting an association between triglycerides and duration of gestation among primiparous women. It is unclear why we found this association only among primiparas. Magnussen et al. determined that the association between high triglycerides and preterm birth in their cohort could be partly explained by hypertensive disorders during pregnancy, such as preeclampsia and

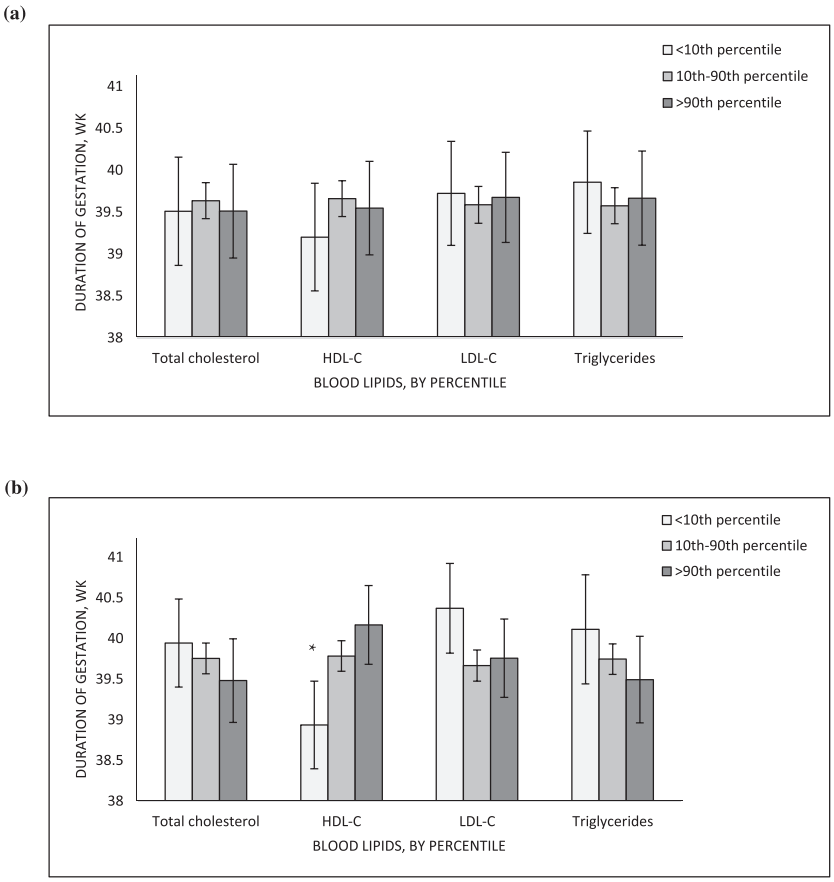

FIGURE 1 Mean pregnancy duration by percentiles of plasma lipids at (a) ≤20 weeks gestation (n = 320) and (b) 36 weeks gestation (n = 282). Adjusted for supplement group, gestational age at enrollment baseline body mass index, age, parity, infant gender, season at enrollment asset index, and time since last meal. Error bars = 95% CI. (*) = p < .05 compared with 10th–90th percentile and >90th percentile

TABLE 4 Beta-coefficients for triglycerides, in 10 mg/dL increments, in association with the duration of gestation (days) by parity

	Unadjusted β (SE)	p	Adjusted[a] β (SE)	p
Triglycerides at ≤20 weeks gestation, 10 mg/dL				
Primiparous	−0.5 (0.02)	.01	−0.5 (0.02)	.01
Multiparous	0.1 (0.01)	.44	0.2 (0.01)	.22
Triglycerides at 36 weeks gestation, 10 mg/dL				
Primiparous	−0.2 (0.02)	.03	−0.3 (0.02)	.01
Multiparous	0.1 (0.01)	.24	0.1 (0.01)	.17

Note. SE = standard error.

[a]Multivariate model includes supplement group, gestational age at enrollment baseline body mass index, age, parity, infant gender, season at enrollment asset index, and time since last meal.

pregnancy-induced hypertension (Magnussen et al., 2011). These disorders are more common in primiparous women (Duckitt & Harrington, 2005), and further research could explore this pathway.

With the biological mechanisms of preterm birth still needing more complete elucidation, it is difficult to identify the nature and direction of the physiological pathways underlying these findings. HDL-C has anti-inflammatory effects, and it is possible that inflammation mediates the relationship between HDL-C and duration of gestation. Preliminary analyses did not show an association between markers of inflammation (CRP, AGP) and duration of gestation in this study population (Oaks et al., 2015), although it is possible that alternative markers of inflammation (such as IL-6) (Wei, Fraser, & Luo, 2010) might have yielded different results.

It has been established that HDL not only transports excess cholesterol back to the liver, but has a number of additional atheroprotective functions.(Assmann & Nofer, 2003; Mineo, Deguchi, Griffin, & Shaul, 2006) Additionally, LDL is atherogenic when it enters arterial walls and becomes oxidized.(Berliner & Heinecke, 1996) Given that both maternal LDL and HDL are taken up by placental trophoblasts (Woollett, 2011), women with low HDL might have poor placental function, while women with low LDL would be less likely to have placental vasculopathy, an established risk factor for preterm birth. (Arias, Rodriquez, Rayne, & Kraus, 1993) Thus, the associations between HDL-C or LDL-C and duration of gestation might be evident only in later gestation, after enough time has passed to exert a substantial effect on the placental vasculature.

Strengths of our study include the use of ultrasound at baseline to determine gestational age and the ability to control for an extensive number of potentially confounding variables. In addition, while some previous studies have reported only certain plasma lipid measurements, we were able to analyze all plasma lipids that are reported in a standard plasma lipid profile.

However, there are limitations that should be noted. First, multiple relationships were examined, and there is the possibility that an association was significant due to chance. We addressed this by re-examining our data using a Bonferroni correction to account for multiple comparisons, and the difference in duration of gestation between women with high versus low HDL cholesterol concentration remained significant. Second, the subsample of women for these analyses had a

longer duration of gestation than others in the main trial (39.6 vs. 39.1 weeks), possibly limiting our ability to generalize to those who deliver earlier. The preterm birth rate for women in the main trial was lower than previous country estimates (8.5% vs. 14.5%) (Adu-Afarwuah et al., 2015), and even lower in our subsample (3.4%), so we were not able to include the outcome of preterm birth in our analyses. However, a significant difference in mean pregnancy duration could translate to a difference in preterm birth rates, and future research should examine this outcome. Lastly, because of the difficulty of obtaining fasting blood samples from pregnant women, nonfasting blood samples were collected. However, we were able to adjust for time between last meal and sample collection, and studies comparing fasting versus nonfasting plasma lipid measurements show minimal effect of fasting on total cholesterol, HDL-C, and LDL-C (although triglycerides tend to be approximately 15% higher in nonfasting vs. fasting samples) (Langsted, Freiberg, & Nordestgaard, 2008; Mora, Rifai, Buring, & Ridker, 2008). In our study, there were no significant differences in plasma lipids between women who, by self-report, had fasted and women who had not fasted. Moreover, any effects of nonfasting would bias the results towards the null.

Our results indicate that while low total cholesterol is not associated with duration of gestation, low HDL-C may be associated with a shorter duration of gestation, with a difference of approximately 6 days between those with low (<10th percentile) and referent (10th–90th percentile) HDL-C. This is notable given that much smaller differences, 1–2 days, have been observed between groups in nutrition interventions that have increased duration of gestation (West et al., 2014; Zeng et al., 2008). While a variety of mechanisms might underlie this association, we propose vasculopathy of the placenta as the most likely pathway.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

CONTRIBUTIONS

B M O: Dr. Oaks conceptualized and designed the cohort study, carried out the data analyses, provided interpretation of the data, drafted the initial manuscript, and approved the final manuscript as submitted.

C P S: Dr. Stewart advised on the analyses, provided interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

K D L: Dr. Laugero advised on the analyses, provided interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

S A -A: Dr. Adu-Afarwuah designed iLiNS-DYAD-Ghana, conducted the research, coordinated and supervised data collection for iLiNS-DYAD-Ghana, reviewed and revised the manuscript, and approved the final manuscript as submitted.

A L: Dr. Lartey designed iLiNS-DYAD-Ghana, conducted the research, reviewed and revised the manuscript, and approved the final manuscript as submitted.

S A V: Dr. Vosti designed iLiNS-DYAD-Ghana, reviewed and revised the manuscript, and approved the final manuscript as submitted.

P A: Dr. Ashorn designed iLiNS-DYAD-Ghana, provided interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

K G D: Dr. Dewey designed iLiNS-DYAD-Ghana, advised on the analyses, provided interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

REFERENCES

Adu-Afarwuah, S., Lartey, A., Okronipa, H., Ashorn, P., Zeilani, M., Peerson, J. M., … Dewey, K. G. (2015). Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. *American Journal of Clinical Nutrition*, *101*(4), 835–846.

Alleman, B. W., Smith, A. R., Byers, H. M., Bedell, B., Ryckman, K. K., Murray, J. C., & Borowski, K. S. (2013). A proposed method to predict preterm birth using clinical data, standard maternal serum screening, and cholesterol. *American Journal of Obstetrics and Gynecology*, *208*(6), 472.e1–472.11.

Amir, D., & Fessler, D. M. T. (2013). Boots for Achilles: Progesterone's reduction of cholesterol is a second-order adaptation. *QUARTERLY REVIEW OF BIOLOGY*, *88*(2), 97–116.

Arias, F., Rodriquez, L., Rayne, S. C., & Kraus, F. T. (1993). Maternal placental vasculopathy and infection: Two distinct subgroups among patients with preterm labor and preterm ruptured membranes. *American Journal of Obstetrics and Gynecology*, *168*(2), 585–591.

Arimond, M., Zeilani, M., Jungjohann, S., Brown, K. H., Ashorn, P., Allen, L. H., & Dewey, K. G. (2015). Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: Experience from the International Lipid-Based Nutrient Supplements (iLiNS) project. *Maternal and Child Nutrition*, *11*(Suppl 4), 31–61.

Assmann, G., & Nofer, J. R. (2003). Atheroprotective effects of high-density lipoproteins. *Annual Review of Medicine-Selected Topics in the Clinical Sciences*, *54*, 321–341.

Bartha, J. L., Fernandez-Deudero, A., Bugatto, F., Fajardo-Exposito, M. A., Gonzalez-Gonzalez, N., & Hervias-Vivancos, B. (2012). Inflammation and cardiovascular risk in women with preterm labor. *Journal of Womens Health*, *21*(6), 643–648.

Basaran, A. (2009). Pregnancy-induced hyperlipoproteinemia: Review of the literature. *Reproductive Sciences*, *16*(5), 431–437.

Beck, S., Wojdyla, D., Say, L., Betran, A. P., Merialdi, M., Requejo, J. H., … Van Look, P. F. A. (2010). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bulletin of the World Health Organization*, *88*(1), 31–38.

Berliner, J. A., & Heinecke, J. W. (1996). The role of oxidized lipoproteins in atherogenesis. *Free Radical Biology and Medicine*, *20*(5), 707–727.

Blencowe, H., Cousens, S., Oestergaard, M. Z., Chou, D., Moller, A. B., Narwal, R., … Lawn, J. E. (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *Lancet*, *379*(9832), 2162–2172.

Cappuccio, F. P. (1997). Ethnicity and cardiovascular risk: Variations in people of African ancestry and South Asian origin. *Journal of Human Hypertension*, *11*(9), 571–576.

Catov, J. M., Ness, R. B., Wellons, M. F., Jacobs, D. R., Roberts, J. M., & Gunderson, E. P. (2010). Prepregnancy lipids related to preterm birth risk: The Coronary Artery Risk Development in Young Adults Study. *Journal of Clinical Endocrinology & Metabolism*, *95*(8), 3711–3718.

Duckitt, K., & Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. *British Medical Journal*, *330*(7491), 565–567.

Edison, R. J., Berg, K., Remaley, A., Kelley, R., Rotimi, C., Stevenson, R. E., & Muenke, M. (2007). Adverse birth outcome among mothers with low serum cholesterol. *Pediatrics*, *120*(4), 723–733.

Eisenberg, D. T. A., Kuzawa, C. W., & Hayes, M. G. (2010). Worldwide allele frequencies of the human apolipoprotein E gene: Climate, local adaptations, and evolutionary history. *American Journal of Physical Anthropology*, *143*(1), 100–111.

Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of concentration of low-density lipoprotein cholesterol in plasma, without us of preparative ultracentrifuge. *Clinical Chemistry*, *18*(6), 499–502.

Godsland, I. F., Johnston, D. G., & Chaturvedi, N. (2007). Mechanisms of disease: Lessons from ethnicity in the role of triglyceride metabolism in ischemic heart disease. *Nature Clinical Practice Endocrinology & Metabolism*, *3*(7), 530–538.

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Preterm birth 1 – Epidemiology and causes of preterm birth. *Lancet*, *371* (9606), 75–84.

Harville, E. W., Savitz, D. A., Dole, N., Herring, A. H., Thorp, J. M., & Light, K. C. (2007). Patterns of salivary cortisol secretion in pregnancy and implications for assessment protocols. *Biological Psychology*, *74*(1), 85–91.

Harville, E. W., Viikari, J. S. A., & Raitakari, O. T. (2011). Preconception cardiovascular risk factors and pregnancy outcome. *Epidemiology*, *22*(5), 724–730.

Kramer, M. S., Kahn, S. R., Rozen, R., Evans, R., Platt, R. W., Chen, M. F., … Genest, J. (2009). Vasculopathic and thrombophilic risk factors for spontaneous preterm birth. *International Journal of Epidemiology*, *38*(3), 715–723.

Langsted, A., Freiberg, J. J., & Nordestgaard, B. G. (2008). Fasting and nonfasting lipid levels influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. *Circulation*, *118*(20), 2047–2056.

Magnussen, E. B., Vatten, L. J., Myklestad, K., Salvesen, K. A., & Romundstad, P. R. (2011). Cardiovascular risk factors prior to conception and the length of pregnancy: Population-based cohort study. *American Journal of Obstetrics and Gynecology*, *204*(6), 526.e1–526.e8.

Mineo, C., Deguchi, H., Griffin, J. H., & Shaul, P. W. (2006). Endothelial and antithrombotic actions of HDL. *Circulation Research*, *98*(11), 1352–1364.

Mora, S., Rifai, N., Buring, J. E., & Ridker, P. M. (2008). Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. *Circulation*, *118*(10), 993–1001.

Mudd, L. M., Holzman, C. B., Catov, J. M., Senagore, P. K., & Evans, R. W. (2012). Maternal lipids at mid-pregnancy and the risk of preterm delivery. *Acta Obstetricia et Gynecologica Scandinavica*, *91*(6), 726–735.

Oaks, B. M., Stewart, C. P., Laugero, K. D., Adu-Afarwuah, S., Lartey, A., Baldiviez, L. M., … Dewey, K. G. (2015). Associations of maternal cortisol, inflammation, hemoglobin, iron status, and BMI with birth outcomes in pregnant women in Ghana. *The FASEB Journal*, *29*(1 Supplement), 579.1.

Oluwole, A. A., Adegbesan-Omilabu, M. A., & Okunade, K. S. (2014). Preterm delivery and low maternal serum cholesterol level: Any correlation? *Nigerian Medical Journal : Journal of the Nigeria Medical Association*, *55*(5), 406–410.

Rosenberger, C. M., Brumell, J. H., & Finlay, B. B. (2000). Microbial pathogenesis: Lipid rafts as pathogen portals. *Current Biology*, *10*(22), R823–R825.

Saigal, S., & Doyle, L. W. (2008). Preterm birth 3 – An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*, *371* (9608), 261–269.

Vrijkotte, T. G. M., Krukziener, N., Hutten, B. A., Vollebregt, K. C., van Eijsden, M., & Twickler, M. B. (2012). Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: The ABCD Study. *Journal of Clinical Endocrinology & Metabolism*, *97*(11), 3917–3925.

Vyas, S., & Kumaranayake, L. (2006). Constructing socio-economic status indices: How to use principal components analysis. *Health Policy and Planning*, *21*(6), 459–468.

Wei, S. Q., Fraser, W., & Luo, Z. C. (2010). Inflammatory cytokines and spontaneous preterm birth in asymptomatic women: A systematic review. *Obstetrics and Gynecology*, *116*(2), 393–401.

West, K. P., Shamim, A. A., Mehra, S., Labrique, A. B., Ali, H., Shaikh, S., … Christian, P. (2014). Effect of maternal multiple micronutrient vs iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: The JiVitA-3 randomized trial. *Jama-Journal of the American Medical Association*, *312*(24), 2649–2658.

Wiznitzer, A., Mayer, A., Novack, V., Sheiner, E., Gilutz, H., Malhotra, A., & Novack, L. (2009). Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: a population-based study. *American Journal of Obstetrics and Gynecology*, *201*(5), 482.e1–482.e8.

Woollett, L. A. (2008). Where does fetal and embryonic cholesterol originate and what does it do? *Annual Review of Nutrition*, *28*, 97–114.

Woollett, L. A. (2011). Review: Transport of maternal cholesterol to the fetal circulation. *Placenta*, *32*, S218–S221.

Yohai, V. J. (1987). High breakdown-point and high-efficiency robust estimates for regression. *Annals of Statistics*, *15*(2), 642–656.

Zeng, L. X., Cheng, Y., Dang, S. N., Yan, H., Dibley, M. J., Chang, S. Y., & Kong, L. Z. (2008). Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: Double blind cluster randomised controlled trial. *British Medical Journal*, *337*, a2001.

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