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LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors

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BACKGROUND: Vast amounts of data show associations between maternal obesity, dysglycemia, diabetes, and undernutrition during pregnancy and increased cardiovascular disease risk in offspring. However, elevated maternal LDL cholesterol (LDL-C) in pregnancy and offspring cardiovascular disease (CVD) risk has scarcely been studied.

OBJECTIVE: Our objective was to investigate the associations between elevated maternal LDL-C in pregnancy and CVD risk factors in 6-to-13-year-old offspring.

METHODS: We recruited 6-to-13-year-old children whose mothers attended a pregnancy cohort and who had high or low cholesterol in pregnancy, defined as LDL-C over the 90th percentile or below the 10th percentile within the pregnancy cohort, respectively. We measured CVD risk factors in the children in the 2 groups.

RESULTS: Maternal plasma LDL-C at gestational week 14 to 16 was 4.0 and 1.4 mmol/L in the hypercholesterolemic (n = 27) and hypocholesterolemic (n = 34) groups, respectively ($P < .001$). Interestingly, offspring plasma LDL-C was 0.4 mmol/L higher in children whose mothers had hypercholesterolemia during pregnancy ($P < .01$). We found no difference in birthweight or any other clinical or biochemical CVD risk factors or dietary intake between the children at 6–13 years.

CONCLUSIONS: Women with elevated LDL-C during early pregnancy have offspring with higher LDL-C already at the age of 6–13 years. Unless cholesterol-reducing measures are successfully implemented, the affected children may be at increased cardiovascular risk.

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Introduction

Cardiovascular disease (CVD) is primarily caused by atherosclerosis, which is a slowly progressing process of subintimal lipid accumulation, with subsequent involvement of immune cells, inflammatory mediators, and the hemostatic system.[1] Atherosclerosis begins in early life, potentially even *in utero*, and children, adolescents, and young adults already have the presence of fatty streaks and advanced atherosclerotic lesions.[2–5] Data support that gestational risk factors such as maternal obesity, dysglycemia, and diabetes and undernutrition affect offspring cardiovascular health.[6–8] Although not always the case, variation in offspring birth size and newborn body composition might be an important mediator of disease risk across generations.[9–13] Surprisingly, however, the relationship between maternal LDL cholesterol concentration (LDL-C) during pregnancy and offspring birthweight and long-term disease risk is less studied compared to the above-mentioned maternal risk factors. This scarcity of data is paradoxical for several reasons. First, Napoli et al. performed autopsies and found associations between maternal gestational hypercholesterolemia and fetal and child atherogenesis as measured by early lesion formation.[4,5] In addition, atherogenic dyslipidemia often occurs in parallel with obesity, which is currently increasing in prevalence worldwide, including among young fertile women.[14,15] Moreover, healthy pregnancies are characterized by physiological increases in most atherogenic lipid fractions toward end of pregnancy, including an approximate 50%–100% increase in total and LDL-C and 100%–300% increase in triglycerides.[16,17] And importantly, LDL-C has well-known causal roles in atherosclerosis in adults.[18] Therefore, elucidating associations between maternal gestational hypercholesterolemia and offspring health may be of great importance to both public health policies and clinical guidelines.

The aim of the present study was to investigate the associations between early-pregnancy elevated LDL-C and CVD risk factors in 6-to-13-year-old offspring.

Subjects and methods

Study design and participants

We recruited women who participated in the Stork pregnancy cohort study that had either high or low LDL-C in early pregnancy, and examined and compared their 6-to-13-year-old offspring with respect to CVD risk factors. The Stork study design is presented in detail elsewhere and briefly summarized here.[9] In the period 2001 to 2008, the Stork cohort followed 1031 pregnant women at 4 visits during pregnancy (visit 1, gestational week 14–16; visit 2, gestational week 22–24; visit 3, gestational week 30–32; and visit 4: gestational week 36-38). All women were of Caucasian origin and scheduled to give birth at the National Hospital in Oslo, Norway. Exclusion criteria included multiple pregnancies, known pre-gestational diabetes, and severe chronic disease.

We included two groups of women and children to attend a follow-up visit: hypercholesterolemia during pregnancy (LDL-C at gestational week 14–16 over the 90th percentile within the study population) and hypocholesterolemia during pregnancy (LDL-C at gestational week 14–16 under the 10th percentile within the study population). Exclusion criteria were prematurity, missing data on gestational length, known familial hypercholesterolemia (FH), and use of cholesterol-lowering medications. We invited 100 mother–children pair in each group, and we expected 30% participation rate. To reduce the probability of information bias, both participants and investigators were blinded to group affiliation.

All offspring data collection was performed in the time period April to October 2015, at the Center for Clinical Nutrition at the Department of Nutrition, University of Oslo, except DXA scans, which were performed at Department of Endocrinology, Rikshospitalet. All data were collected at the same day for all participants, except for one child who attended a second visit for blood sampling. Ethical approval was obtained from the regional ethics committee of Norway (ref. no.: 2014/1216). Informed consent was obtained from all participants.

Variables

Most maternal variables (clinical, biochemical, dietary, and socioeconomic) were measured during pregnancy as previously described.[9] However, fasting maternal serum samples were collected in pregnancy and stored at −80°C, and lipids and CRP were measured February 2015. No maternal serum samples had been previously thawed. Maternal LDL-C in mmol/L was determined by Friedewald's formula. In a subset of 100 randomly selected women, we also measured LDL-C by direct measurement, both early and late in pregnancy. Correlations and Bland–Altman plots between the LDL-C measured by these two methods showed that the Friedewald's equation was applicable in our population of pregnant women (data not shown). HOMA indices were determined using the Oxford calculator (excel sheet download: https://www.dtu.ox.ac.uk/homacalculator/download.php).

Small for gestational age and large for gestational age were defined as birthweight according to gestational age below the 10th percentile and above the 90th percentile, respectively, whereas appropriate for gestational age was defined as birthweight according to gestational age between the 10th and 90th percentile.

Offspring weight and height were measured using a SECA 285 digital measuring station (SECA, UK). Waist, hip, and upper arm circumferences were measured using a standard measuring tape. Blood pressure and pulse were measured using a V100 Dinamap Technology automatic blood pressure monitor (GE Healthcare). Appropriate blood pressure cuff (GE Healthcare) was selected based on upper arm circumference. Average systolic and diastolic blood pressure and pulse from three readings were used in the analyses. Mean arterial