RELATIONSHIP OF MATERNAL PLASMA LIPID CONCENTRATIONS IN EARLY PREGNANCY AND RISK OF PREECLAMPSIA (GESTOSIS)

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Abstract

We investigated the relationship between early pregnancy plasma lipid concentrations and risk of preeclampsia. In a prospective cohort study, maternal blood samples were collected at 13 weeks gestation on average. From the cohort, we selected 57 women who developed preeclampsia and 510 who remained normotensive. Plasma lipid concentrations were measured enzymatically by standardized assays. Logistic regression procedures were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95%CI). Women who subsequently developed preeclampsia had 10.4%, 13.6%, and 15.5% higher concentrations of LDL cholesterol, triglycerides, and LDL/HDL ratios, respectively, than controls ($p<0.05$). HDL cholesterol concentrations were 7.0% lower in cases than controls ($p<0.05$). After adjustment, there was a 3.60-fold increase in risk of preeclampsia among women with total cholesterol >205 mg/dl (95% CI 1.23-10.51) and a 4.15-fold increase in risk of preeclampsia among women with triglyceride >133mg/dl (95% CI 1.50-11.49). A linear increase in preeclampsia risk was observed with increasing tertiles of LDL cholesterol, triglyceride concentrations and the LDL/HDL ratio (all p for trend <0.05). Early pregnancy dyslipidemia is associated with an increased risk of preeclampsia. This association may be significant in understanding the pathologic processes of preeclampsia and may help in developing prevention and/or early diagnosis strategies for the disorder. We also summarize results from several cross sectional studies that have indicated association between maternal dyslipidemia and preeclampsia risk in studies of Peruvian and Zimbabwean women. Finally we report results indicating a positive association between elevated concentrations of oxidized low density lipoprotein (Ox-LDL) and preeclampsia risk.

Introduction

Preeclampsia, a syndrome defined by hypertension and proteinuria, is associated with increased maternal mortality and morbidity in the US and worldwide (Enquobahrie, et al 2004). There is no clear distinction between normotensive and preeclamptic pregnancies in terms of pathogenic factors and disease mechanisms. However, various factors are implicated in the pathogenesis of preeclampsia, including genetic, immune, vascular, and oxidative stress. These have led to the identification of potential candidate markers from cross-sectional studies.

Maternal plasma lipids are significantly elevated during pregnancy. Women who develop preeclampsia experience even more dramatic lipid changes. Most, though not all case-control studies have shown a preeclampsia-dyslipidemic pattern of increased triglycerides, cholesterol, low density lipoprotein (LDL) and decreased high density lipoprotein (HDL) concentrations. Inferences from these studies are limited by the fact that plasma lipid profiles were determined using blood samples collected after the diagnosis of preeclampsia. Evidence from few available prospective cohort studies suggest that women destined to develop the disorder are more likely to have elevated plasma triglycerides and decreased HDL cholesterol concentrations compared with their normotensive counterparts. However, results are not consistent and investigators generally have not adjusted for possible confounding factors. We therefore, used available information and plasma specimens from an ongoing prospective cohort study of women receiving prenatal care prior to 16 weeks gestation to examine whether varying concentrations of maternal plasma lipids and lipoproteins, measured in early pregnancy, are independently associated with an increased risk of preeclampsia.

Methods

The study population for this report is from a cohort of normotensive, non-diabetic pregnant women who provided a blood sample at 13 weeks gestation on average. From this cohort we identified a total of 57 preeclampsia cases. The diagnosis of preeclampsia was made using the then current American College of Obstetricians and Gynecologists (ACOG) guidelines. Controls were 510 women who remained normotensive throughout pregnancy and who did not have proteinuria.

Data Collection - From structured questionnaire and medical records, we obtained covariate information including maternal age, educational attainment, height, pre-pregnancy weight, reproductive and medical histories, and medical histories of first-degree family members. We also collected information on annual household income and maternal smoking before and during pregnancy. Pre-pregnancy body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Maternal non-fasting blood samples, collected in 10 ml Vacutainer tubes at 13 weeks gestation, on average, were frozen at -80°C until analysis. Maternal plasma cholesterol and triglyceride concentrations were measured enzymatically employing assays standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention, Atlanta, GA. High density lipoprotein (HDL) was separated from low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol by a chemical precipitation technique using dextran sulfate of 50kDa. Analytical inter-assay coefficients of variation for cholesterol, triglyceride,

and HDL-cholesterol were 1.5%, 2.5% and 3%, respectively. All assays were performed without knowledge of case-control status.

Statistical Analysis - Student's t test was used to evaluate mean differences in maternal plasma lipid concentrations between cases and controls. To estimate the relative association between preeclampsia and varying concentrations of lipids and lipoproteins, we categorized each subject according to tertiles determined by the distribution of each analyte among normotensive control subjects. Using the lowest lipid category as the referent group (for all lipid variables except HDL), odds ratios (OR) and their 95% confidence intervals (CI) were estimated.

The Mantel extension test for linear trend was used in univariate analyses to test for a linear component of trend in risk between preeclampsia and each analyte. Logistic regression procedures were used to calculate maximum likelihood estimates for the coefficients and their standard errors were used to calculate odds ratios and 95% confidence intervals, adjusted for confounders. In multiple logistic regression models, significance for monotonic (linear) trend was assessed by treating the tertiles as a continuous variable after assigning a score as its value. We also explored the possibility of a nonlinear relation between plasma lipid concentrations and preeclampsia risk by fitting a multivariable logistic regression model that implemented the generalized additive modeling (GAM) method.

To assess confounding, we entered variables into a logistic regression model one at a time, then compared the adjusted and unadjusted odds ratios. Final logistic regression models included covariates that altered unadjusted ORs by at least 10%. Candidate confounding variables considered were maternal age, nulliparity, maternal adiposity, race/ethnicity, annual household income, educational attainment, first-degree family history of chronic hypertension, gestational age at blood collection, physical activity before pregnancy, and hours since last meal. Statistical analyses were performed using SPSS (version 10.1, SPSS Inc. Chicago, IL) and S-Plus (version 6.1, Insightful Inc. Seattle, WA) software. All reported p values are two tailed, and confidence intervals were calculated at the 95% level.

Results

Sociodemographic and reproductive characteristics of the study cohort are summarized according to preeclampsia status. Overall, participants included in this analysis were primarily white, nulliparous, and well educated. Compared with controls, women who developed preeclampsia were less well educated, nulliparous and overweight.

Several maternal plasma lipid and lipoprotein concentrations showed statistically significant differences depending on preeclampsia status. Women who subsequently developed preeclampsia had 10.4%, 13.6% and 15.5% higher concentrations of LDL cholesterol, triglycerides and LDL/HDL ratios, respectively, than controls (all p values were <0.05). Total cholesterol concentrations were 3.9% higher, on average, among preeclampsia cases as compared with normotensive women, though this difference did not reach statistical significance ($p=0.069$). Notably, HDL cholesterol concentrations were 7.0% lower in cases as compared with controls ($p=0.028$).

We estimated the relative risk (odds ratio) of preeclampsia associated with varying concentrations of maternal plasma lipids and lipoproteins. We noted a 2.59-fold increase in risk of preeclampsia among women with total cholesterol >205mg/dl (upper tertile), as compared with those women whose total cholesterol concentrations were <172 mg/dl (lower tertile) (OR=2.59, 95% CI 1.12-5.99). This association was strengthened after adjusting for confounders (adjusted OR=3.60, 95% CI 1.23-10.51).

The OR for preeclampsia increased across increasing tertiles of LDL-cholesterol concentration (adjusted p-value for trend=0.020). After adjusting for confounders, women in the highest tertile experienced a 2.91-fold increased risk of preeclampsia as compared with women in the lowest tertile (95% CI 1.12-7.55). In univariate analyses, we noted a strong inverse relationship between plasma concentrations of HDL-cholesterol with risk of preeclampsia (p-value for trend=0.006), though this association was attenuated considerably after adjusting for confounders (p-value=0.35). After adjusting for confounders, the risk of preeclampsia across successively lower tertiles of plasma HDL-cholesterol were as follows: ORs=1.00, 2.38, and 1.71, with the highest tertile as referent.

We next evaluated preeclampsia risk in relation to maternal LDL/HDL-cholesterol ratio. Here, we noted that the risk of preeclampsia increased as the ratio increased (adjusted p-value for trend=0.001). After accounting for confounding, women with the highest ratio values (upper tertile values >1.60) experienced an almost 4-fold increased risk of preeclampsia (adjusted OR=3.98, 95% CI 1.44-10.94) as compared with women whose ratio values were <1.21. Lastly, we noted a strong positive relationship between plasma triglyceride concentrations and risk of preeclampsia. The risk of preeclampsia increased with successively higher tertiles of plasma triglycerides (adjusted OR: 1.00, 2.06, and 3.07, with the lowest tertile as referent; p-value for trend=0.004). Adjusting for confounding factors strengthened the associations. Women in the highest tertile for triglycerides experienced a 4.15-fold increased risk of preeclampsia as compared with those women in the lowest tertile (adjusted OR=4.15, 95% CI 1.50-11.49).

To further explore the relationship between maternal plasma triglycerides concentrations and preeclampsia risk, we modeled the risk of preeclampsia in relation to triglycerides concentrations expressed as continuous variables using logistic regression procedures based on a general additive model (GAM). Results from these analyses confirmed a strong positive association between triglycerides concentrations and the log odds of preeclampsia risk.

Discussion

In this study, we observed an association between maternal early pregnancy dyslipidemia, particularly hypertriglyceridemia, and the subsequent risk of preeclampsia. Pregnant women who subsequently developed preeclampsia had increased cholesterol and LDL-cholesterol concentrations as compared with pregnant women who remained normotensive. The expected inverse relationship between preeclampsia risk and HDL-concentrations, however, was not as evident.

Our findings are consistent with results from the few available prospective cohort studies, and many case-control studies, of maternal fasting or non-fasting plasma lipid and lipoprotein concentrations in preeclamptic and normotensive pregnancies.

In a case-control study of Peruvian women, Ware-Jauregui et al reported that women with triglyceride concentrations >284 mg/dl had a 5-fold increased risk of preeclampsia as compared with women whose concentrations were <189.0 mg/dl (Ware-Jauregui, et al 1999). The investigators also noted a statistically significant lower concentration of maternal HDL-cholesterol in cases versus controls (38.97±1.15 vs. 42.30±0.96 mg/dl, p=0.027). In that particular study, a statistically significant inverse relation between preeclampsia risk and HDL-cholesterol concentrations (p-value for trend=0.017) was observed. The OR for extreme quartile of HDL-cholesterol (<33.01 vs. >50.00 mg/dl) was 0.38 (95% CI 0.18-0.81), after adjusting for confounders. These observations were consistent with results from a study of Sub-Saharan African women, where Williams et al reported an inverse association between preeclampsia risk and HDL-cholesterol concentration (OR: 1.00, 0.87, 0.66, 0.68 with first quartile as the referent; p-value for trend 0.169) (Williams, et al 2003).

The association between dyslipidemia and the risk of preeclampsia is biologically plausible and is compatible with what is known about the pathophysiology of preeclampsia. At least four hypothesized mechanisms for the dyslipidemia and preeclampsia association have been described in the literature. First, investigators have noted that elevated plasma lipid and lipoproteins may induce endothelial dysfunction secondary to oxidative stress. They also noted that dyslipidemia may impair trophoblast invasion thus contributing to a cascade of pathophysiologic events that lead to the development of preeclampsia. This thesis is supported by the fact that triglyceride accumulation in endothelial cells is associated with decreased release of prostacyclin. An increase in triglyceride has also been associated with a significant shift in LDL particle sizes to subtypes of smaller diameter. Formation of the smaller variant of LDL has been shown to contribute to endothelial dysfunction in preeclampsia through stimulation of thromboxane synthesis by endothelial cells and increase in intracellular calcium in vascular smooth muscle.

The second mechanism is the pathologic process of preeclampsia via dysregulation of lipoprotein lipase resulting in a dyslipidemic lipid profile. Pre-heparin hepatic lipase activity in eight preeclamptic cases was found to be significantly elevated in third trimester (p=0.04) compared with eight normotensive controls.

A third possible mechanism may be via the metabolic syndrome. Metabolic characteristics of "insulin resistance syndrome" namely, hyperinsulinemia and hyperuricemia are also present in preeclampsia. Moreover, women with a history of preeclampsia, as compared with their BMI-matched counterparts without such a history, have higher circulating concentrations of fasting insulin, lipid, inflammatory and coagulation factors years after delivery. Thus genetic and environmental factors that contribute to the pathogenesis of metabolic syndrome and related vascular disorders may also be important in determining the occurrence of preeclampsia.

Oxidative conversion of low density lipoproteins (LDL) to oxidized-LDL (Ox-LDL) is considered an important step in transforming macrophages into lipid-laden foam cells destined to develop into early atherosclerotic-like lesions. In two independent study populations (Qiu, et al, 2005; and Sanchez, et al 2005), we noted that maternal plasma ox-LDL concentrations ≥73 U/L were associated with a 2.7-fold increased risk of preeclampsia. We also noted that women with

elevated ox-LDL concentrations and who also had elevated TG concentrations experienced the highest risk of preeclampsia (OR = 9.6). These data will be summarized in greater detail.

References

*__Note__: Please see reference lists from these four manuscripts for complete citations.

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