RELATIONSHIP OF MATERNAL PLASMA LEPTIN, PHYSICAL ACTIVITY AND RISK OF PREECLAMPSIA (GESTOSIS): A PROSPECTIVE STUDY

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Abstract

We measured maternal plasma leptin concentrations in 55 women with preeclampsia and 487 normotensive women to determine whether elevated leptin concentrations were associated with the occurrence of preeclampsia. Maternal blood samples were collected at 13 weeks gestation, on average. Plasma leptin was determined using immunoassay. Logistic regression procedures were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). Leptin concentrations were 78% higher in cases than control subjects (median: 34.6 vs. 19.5 ng/ml; p <0.001). Relative to women with leptin concentrations <27.4 ng/ml, those with elevated leptin concentrations (≥27.4 ng/ml) experienced a 2.3-fold increased risk of preeclampsia (OR=2.3; 95% CI 1.1-4.6). Each 10 ng/ml increase in leptin was associated with a 30% increase in preeclampsia risk (OR=1.3; 95% CI 1.1-1.5). Elevated plasma leptin and maternal overweight status are independently associated with an increased risk of preeclampsia. We also investigated the relationship between maternal physical activity type, frequency, and duration in early pregnancy and plasma leptin concentrations. Mean leptin was 5.8 ng/ml lower among active vs. inactive women (p=0.001). Mean leptin was lower among women in the highest levels (>12.8 hours/week) of time performing physical activity (-8.1 ng/ml, p<0.001) and energy expenditure (-8.3 ng/ml, p=0.001), compared with inactive women. Our findings indicate that elevated leptin in early pregnancy is a risk factor for preeclampsia. Additionally, physical activity is associated with reductions in leptin concentrations. Taken together, our results suggest that the observed reduction of preeclampsia risk in active women may, in part, be attributable to its favorable effects on leptin metabolism in early pregnancy.

Leptin and Preeclampsia (Ning, et al 2004)

Introduction

Leptin, a 16-kDA peptide, is an adipocyte-derived hormone that is also produced by the placenta in humans. Leptin, released by adipocytes into peripheral circulation, is thought to regulate fat mass and to reduce food intake and stimulate thermogenesis. Activation of the sympathetic nervous system by leptin is considered the primary mechanism mediating this increase in energy expenditure. Obesity is positively associated with plasma leptin concentrations, with secretion being in proportion to fat mass. Weight loss, fasting and starvation are known to induce reductions in leptin concentrations, whilst concentrations are known to be increased with weight gain, and with systemic inflammation. Changes in circulating leptin concentrations in pregnant women appear to be generally consistent with changes in maternal fat stores and energy metabolism.

Maternal leptin concentrations are known to increase 2-3 fold above non-pregnant concentrations, with the peak occurring the late mid-trimester. Results from clinical studies indicate that pregnancy-associated increases in maternal plasma leptin is, in part, attributable to an up-regulation of adipocyte synthesis and release of leptin in the presence of insulin resistance and hyperinsulinemia. Additionally, investigators have shown that placental leptin synthesis is increased in the presence of hypoxemia.

On the basis of these observations, investigators have studied the relationship between elevated leptin concentrations and preeclampsia risk. Preeclampisa, a hypertensive disorder of pregnancy, is known to be associated with placental hypoxemia secondary to shallow endovascular cytotrophoblast invasion in spiral arteries, insulin resistance and hyperinsulinemia, chronic systemic inflammation, maternal pre-gestational adiposity, and sympathetic nervous system over-reactivity. Some, though not all, investigators have noted that leptin concentrations are elevated in women with preeclampsia as compared with normotensive pregnant women. In a study of 38 women with preeclampsia and 192 normotensive women, Williams et al (1999) reported that among lean women (pre-pregnancy body mass index [BMI] < 25 kg/m^2), maternal second trimester serum leptin concentrations were 33% higher on average for preeclamptics as compared with normotensive women (20.5 ± 10.91 vs. 13.6 ± 6.8 ng/ml; $p = 0.005$). However, no such differences were observed among overweight (pre-pregnancy BMI ≥ 25 kg/m^2) preeclampsia cases and controls (22.3 ± 7.5 vs. 27.8 ± 12.1 ng/ml; $p = 0.084$). Inferences from this research, however, were hindered by the small sample size. Moreover, the magnitude of the association of preeclampsia with varying concentrations of leptin was not assessed in most of the earlier studies.

The primary goal of the present study was to examine whether maternal leptin concentration, measured in early pregnancy, is independently associated with an increased risk of preeclampsia (i.e., independent of maternal adiposity). We also sought to re-evaluate the extent to which the relation between leptin and preeclampsia risk differed for lean and obese women.

Our secondary goal was to determine the extent to which, if at all, maternal physical activity during pregnancy (which is a determinant of adiposity and a risk factors for preeclampsia) is associated with maternal plasma leptin concentrations in pregnancy.

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 55 preeclampsia cases. The diagnosis of preeclampsia was made using the then current American College of Obstetricians and Gynecologists (ACOG) guidelines. Controls were 487 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, were frozen at -80°C until analysis. Plasma leptin concentrations were measured using a enzyme immunoassay (Diagnostic Systems Laboratory, Inc., Webster, Texas) with the intra- and inter-assay coefficients of variation both < 8%. All assays were performed without knowledge of case-control status.

Statistical Analysis - We examined frequency distributions of maternal sociodemographic characteristics and medical and reproductive histories according to case-control status. We defined a woman as overweight if her pre-pregnancy BMI was $\geq 25 kg/m^2$; lean women were those with a pre-pregnancy BMI of < 25 kg/m^2. We examined the correlation between BMI and leptin using the Spearman's correlation coefficient. Because of the rightward skew of the leptin distribution, we compared median leptin concentrations between cases and controls using the Mann-Whitney two-sample statistic. We categorized each subject according to tertiles determined by the distribution of leptin among normotensive control subjects. We used logistic regression with preeclampsia as the binary outcome variable to derive relative risk estimates (i.e., odds ratios [OR] and 95% confidence intervals [CI]). To assess confounding, we added additional covariates into the logistic regression model with leptin, one at a time, and we compared the adjusted and unadjusted ORs. Multivariate logistic regression models included covariates that altered unadjusted odds ratios by at least 10%, as well as maternal first-degree family history of chronic hypertension, pre-pregnancy BMI and parity. We explored the possibility of a nonlinear relation between serum leptin concentrations and preeclampsia risk using generalized additive modeling (GAM) procedures.

Results

Preeclampsia cases and normotensive control subjects were similar with respect to maternal age, race/ethnicity, marital status, annual household income, and gestational age at blood collection. Compared with controls, cases tended to be less well educated, nulliparous and overweight. Maternal plasma leptin concentrations were highly correlated with pre-pregnancy body mass index among normotensive women (Spearman's $r = 0.5314$, $p < 0.001$) and among preeclampsia cases ($r = 0.6678$, $p < 0.001$). The median concentration of leptin was higher in cases (34.6 ng/ml) as compared with controls (19.5 ng/ml, $p < 0.001$). Among lean subjects, maternal leptin

concentrations were approximately 30% higher in cases than controls ($p = 0.20$). Among overweight subjects, median leptin concentrations were 57% higher in cases compared with controls ($p < 0.05$).

Relative to women in the lower 2 tertiles of the control distribution of maternal leptin concentration (< 27.4 ng/ml), women with leptin values in the upper tertile (≥ 27.4 ng/ml) experienced a 3.5-fold increased risk of preeclampsia (OR = 3.5; 95% CI 2.0 - 6.3). After adjustment for potential confounding by maternal age, race/ethnicity, first degree family history of hypertension, and pre-pregnancy BMI the association was attenuated (adjusted OR = 2.3; 95% CI 1.1 - 4.6). Among lean women, elevated leptin was associated with a 2-fold increased risk of preeclampsia (adjusted OR = 2.0; 95% CI 0.8 - 5.0), though the association did not reach statistical significance. The corresponding adjusted OR for overweight women was 2.9 (95% CI 0.8 - 9.7) and again the results of this stratified analysis did not reach statistical significance.

We next modeled the risk of preeclampsia in relation to maternal plasma leptin concentrations expressed as a continuous variable using a generalized additive model (GAM). From these analyses, we noted a linear relationship between preeclampsia risk and plasma leptin. On the basis of this observation, we modeled plasma leptin concentrations expressed as a continuous variable. From this analysis, we noted that a 10 ng/ml increase in plasma leptin concentration was associated with a 30% increase in preeclampsia risk (adjusted OR = 1.3; 95% CI 1.1 - 1.5), after adjusting for maternal age, race/ethnicity, nulliparity, first-degree family history of chronic hypertension and pre-pregnancy BMI.

Discussion

In this prospective, nested case-control study, elevated maternal leptin concentrations, measured in early pregnancy, was associated with a more than doubling in risk of preeclampsia in lean and overweight women, respectively. Women who were overweight and who had elevated leptin concentrations experienced a 6.4-fold increased risk of preeclampsia as compared with lean women without leptin elevations. Additionally, we noted that the risk of preeclampsia increased by 30% for each 10 ng/ml increase in maternal plasma leptin concentration.

Physical Activity and Leptin (Ning, et al 2005)

Introduction

Our results and those of others indicate that plasma leptin is predictive of subsequent preeclampsia risk. Given these observations, we are now evaluating behavioral factors that may be manipulated to alter leptin concentrations in pregnancy. The first behavioral factor that we have evaluated is physical activity.

Two independent groups of investigators have reported that recreational physical activity during pregnancy is associated with a reduced risk of preeclampsia (Sorensen, 2003). Physical activity, because of its role in long-term regulation of body weight, fat mass, and capacity to increase resting metabolic rate, was postulated to be a determinant of leptin concentrations. This thesis is supported by results from animal studies and short-term exercise training studies in humans. To date, only a few investigators have studied the effects of habitual physical activity on leptin concentrations, and results have been inconsistent. We are unaware of published studies that

have assessed the influence of habitual physical activity on plasma leptin concentrations in pregnant women.

In light of this gap in knowledge, and given the fact that leptin concentrations are profoundly altered in pregnant women, particularly women with gestational diabetes and preeclampsia (disorders that have been shown to be reduced in physically active inactive women), we conducted the present study. We sought to assess the extent to which, if at all, maternal plasma leptin concentrations in early pregnancy are reduced in women who regularly engage in recreational physical activity as compared to their less active counterparts. Detailed assessments of maternal physical activity during early pregnancy allowed us to determine whether the amount and intensity of recreational physical activity are independent determinants of plasma leptin concentrations in early pregnancy.

Given that habitual exercise during pregnancy is associated with improved insulin sensitivity, reduced blood pressure, and improved plasma lipid and lipoprotein concentrations, we hypothesized that similar benefits would be found when leptin was assessed.

Methods

The study population included 879 normotensive, non-diabetic pregnant women who reported physical activity type, frequency, and duration in early pregnancy. Plasma leptin, measured in blood samples collected at 13 weeks gestation, on average, were determined using enzyme immunoassays. Weekly duration (hours/week) and energy expended on recreational physical activity (metabolic equivalent score [MET]-hours/week) were categorized by tertiles among active women. Physical activity intensity was categorized as none, moderate (<6 METs), and vigorous (≥6 METs). Differences in leptin concentrations across categories were estimated using linear regression procedures.

Results

Mean leptin concentrations decreased across levels of physical activity during pregnancy. Mean leptin was 25.6±0.7 ng/ml among women who reported participating in any recreational physical activity, compared to 34.1±1.8 ng/ml among inactive women ($p < 0.001$). Among active women, mean leptin concentrations decreased across categories of increasing hours/week engaged in physical activity. For women who exercised ≤4.8, 4.9-12.8, and >12.9 hours per week, mean leptin concentrations were 27.6±1.2, 25.4±1.2 and 23.7±1.3 ng/ml, respectively. Similar patterns were observed across categories of maximum intensity and energy expended performing physical activity.

We also evaluated leptin concentration in women according to whether they were active during one or both periods of observations. When women were classified according to physical activity status during the periods of before and during pregnancy, those reporting activity during both periods had the lowest mean leptin concentrations compared with inactive women (25.2±0.7 vs. 29.9±4.0 ng/ml). Mean leptin concentrations were higher among those performing physical activity only in the year before pregnancy (35.1±2.0 ng/ml) and among those performing physical activity only during the study pregnancy (30.9±3.3 ng/ml). These differences, however, did not reach statistical significance. A larger more powerful study is needed to evaluate maternal leptin concentrations in relation to her activity level over the two time periods.

Associations between leptin concentration and measures of physical activity remained after adjustment for potential confounding by maternal age, race/ethnicity, parity, and smoking status (Model 2). Notably, the associations remained statistically significant, though somewhat attenuated, after maternal early pregnancy BMI was included in the multivariable model (Model 3). After controlling for confounders, any physical activity during pregnancy was associated with lower plasma concentrations on average (6.0±1.6 ng/ml, p=0.001). The model explained 42% of the variance in leptin concentration (adjusted R^2=0.42). Active women reporting the lowest level of energy expended on recreational physical activity (<20.9 MET-hours/week) had leptin concentrations that were 3.5±1.7 ng/ml lower, on average, compared with concentrations observed among inactive women (p=0.040). Mean leptin concentrations were 6.1±1.7 ng/ml lower among women in the middle level (21.0-70.4 MET-hours/week) (p <0.001), and 8.5±1.8 ng/ml lower among women in the highest level of expended energy category (p <0.001). Similar relationships were observed between plasma leptin concentrations and both the amount of time spent performing physical activity and maximum intensity after adjustment for confounders.

We next evaluated the association between leptin concentration and physical activity according to maternal early pregnancy BMI. We fitted linear models with interaction terms between physical activity energy expenditure and BMI categories. The results from these analyses are summarized in Figure 1. The figure shows maternal mean leptin concentrations across levels of energy expenditure, within groups defined by early pregnancy BMI. Values are representative of nulliparous, white, nonsmokers less than 35 years of age. As seen in Figure 1, leptin concentrations tended to be inversely associated with physical activity energy expenditure in lean, normal weight, overweight and obese women, alike.

Discussion

In this cross sectional study of recreational physical activity and leptin, we observed statistically significant inverse associations between multiple measures of maternal physical activity during pregnancy (e.g., duration, intensity and energy expenditure on recreational physical activity) and plasma leptin concentrations. The associations were independent of maternal early pregnancy BMI and other potential confounders. In this population, physically active lean women had the lowest plasma leptin concentrations in early pregnancy.

There are several postulated biological mechanisms for the observed inverse association between physical activity and plasma leptin concentrations. Some investigators have noted that exercise-induced modifications of the sympathetic nervous system results in increased concentrations of catecholamines which may attenuate leptin synthesis and release. This thesis is supported by data which indicate that plasma leptin is reduced after an epinephrine infusion in lean and obese women. Alternatively, physical activity may influence plasma leptin concentrations directly through its impact on leptin synthesis. Leptin mRNA expression was reduced in genetically obese rats after exercise training. Others have noted that moderate-intensity physical activity resulted in a reduction in abdominal fat leptin synthesis in humans. Lastly, some investigators postulate that improved insulin sensitivity, secondary to physical activity, may influence leptin synthesis and concentrations in circulation, independent of adipose tissue mass. Whatever the mechanism, results from animal and human studies using diverse methodologies suggest that physical activity is an independent determinant of leptin concentrations in peripheral circulation.

Our results extend this growing literature to include pregnant women. Given the central role leptin plays in regulating energy homeostasis through central and peripheral mechanisms; and that pregnancy represents a period of profound alterations in glucose homeostasis and lipid metabolism, it stands to reason that factors that influence leptin synthesis and release in the non-pregnant state may also play a role during pregnancy. Our findings suggest that alterations in maternal leptin concentrations may be achieved with habitual physical activity during pregnancy.

Our findings suggest that physical activity, a modifiable factor, influences leptin synthesis and release in pregnancy. If confirmed, physical activity during pregnancy may well be one important component in lifestyle programs and strategies aimed towards disease prevention and health promotion in all populations, including pregnant women.

References

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

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