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Serum adiponectin and leptin in relation to risk for preeclampsia: results from a large case-control study

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Abstract

OBJECTIVE—Conditions resulting in insulin resistance, as well as metabolic, immune and angiogenic perturbations, have been associated with an increased risk of preeclampsia (PE). Our purpose was to assess whether the adipose tissue secreted hormones: adiponectin, which has immune modulating, metabolic and angiogenic properties, and leptin, which reflects overall fat mass, are associated with PE risk.

METHODS—We performed a case-control design study within a hospital-based cohort of 368 pregnant women (106 with PE and 262 controls; mean age: 26.6 ± 6.8 years; mean gestational age at admission: 38.2 ± 2.8 weeks) between March 2005 and August 2007 at the Hospital of Pennsylvania University. Serum adiponectin and leptin were measured by radioimmunoassay. Statistical analysis of data was performed using simple and multiple regression analyses.

RESULTS—No significant differences in adiponectin or leptin levels between pre-eclamptic and control pregnant women emerged in univariate analyses ($p=0.57$ and $p=0.15$ respectively). Among pre-eclamptic women, there were also no differences in adipokines between those with mild and severe disease. Serum adiponectin and leptin were not associated with higher risk of PE before and after adjustment for maternal age, race, primigravida, smoking status, body mass index at

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Author contributions

MD analyzed data, wrote and revised/edited manuscript; SKS provided patient care and samples, collected data, compiled database, and revised manuscript; MAE supervised the overall study with SKS, provided patient care and samples, and revised manuscript; JC performed the experiments and provided technical support; CSM designed the study, revised/edited manuscript and supervised the whole project.

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screening, gestational age at admission, history of preeclampsia, chronic hypertension and gestational diabetes (OR: 0.93, 95% C.I.: 0.83–1.04 and OR: 1, 95% C.I.0.97–1.03, respectively).

CONCLUSION—Maternal serum adiponectin and leptin levels, drawn at the time of PE diagnosis, were not associated with PE.

Keywords

Adiponectin; Adipokine; Hypertension; Leptin; Preeclampsia

INTRODUCTION

Preeclampsia (PE) is characterized by the onset of high blood pressure and proteinuria after 20 weeks gestation [1]. It occurs in about 5–10% of all pregnancies and results in substantial maternal and neonatal morbidity and mortality [1–2]. Pre-eclamptic women are at increased risk for developing coagulation defects, pulmonary edema, cerebral hemorrhage, blindness, seizures, hepatic and/or renal failure and cardiovascular disease later in life [1–2] while infants born to pre-eclamptic women are prone to prematurity and more likely to be small for gestational age [1–2].

The etiology of the disease remains obscure. Several genetic, placental, metabolic and immune factors giving rise to abnormal remodeling of the placental vasculature, ischemia and endothelial cell dysfunction have been implicated in the etiopathogenesis of PE including insulin resistance [2–4]. Several conditions associated with insulin resistance such as hyperinsulinemia, glucose intolerance, gestational diabetes, polycystic ovary syndrome, maternal obesity as well as excessive weight gain during pregnancy may predispose pregnant women to a substantially augmented risk of PE [5–8].

Adipose tissue is now broadly recognized as a functioning endocrine and paracrine organ secreting several bioactive adipokines, which regulate physiological and pathological processes, such as appetite, insulin sensitivity and resistance, inflammation, immunity, hematopoiesis and angiogenesis [9]. The two best studied adipocyte secreted hormones that circulate in the highest concentrations in the blood stream are leptin and adiponectin. Leptin has multiple physiologic functions, mainly in states of energy deficiency, in modulating satiety and energy homeostasis, but also in reproductive biology, ranging from placental angiogenesis to regulation of fetal development and growth [5, 10–14]. Adiponectin is a pleiotropic, insulin-sensitizing, anti-inflammatory and anti-atherogenic adipokine, and hypoadiponectinemia is associated with obesity, insulin resistance, type II diabetes, hypertension [15] and obesity-related malignancies [6, 16–17].

Until recently, few studies, mainly cross-sectional in their design without adjustment for known risk factors of PE, and with limited number of participants (i.e. ranging from 37 to 200) in different trimesters of pregnancy have evaluated changes in serum adiponectin and leptin in pre-eclamptic women and gave rise to conflicting results [18–22]. Since no previous large study has jointly evaluated adiponectin and leptin in relation to PE taking into account other known risk factors of PE, we attempted to explore whether these adipose tissue secreted hormones are associated with PE risk. We hypothesized that hypoadiponectinemia might be present in PE, because lower adiponectin levels are linked to insulin resistance, impaired endothelium-dependent vasodilatation and reduced blood flow, and predict risk for hypertension [15]. As a matter of fact, previous evidence from a nested-case control study carried out on a large cohort of pregnant women, revealed a strong association between first-trimester hypoadiponectinemia and subsequent risk of hypertensive disorders including PE [23]. In this case-control study, we investigated the role of serum adiponectin and leptin levels in the etiopathogenesis of PE utilizing a multivariate

model adjusting for maternal age, race, primigravida, smoking status, body mass index, gestational age at admission, history of preeclampsia, chronic hypertension and gestational diabetes.

MATERIAL AND METHODS

We performed a case-control design study within a hospital-based cohort of 368 pregnant women between March 2005 and August 2007 at the Hospital of the University of Pennsylvania. Cases were pregnant women with PE. Controls were women presenting for delivery at term (≥ 37 weeks) without PE.

All women admitted to Labor and Delivery with PE were eligible for enrollment and invited to participate in the study. Women with available serum, drawn at the time of diagnosis on labor and delivery, were included in this study, nested in the overall study. Cases were identified based on maternal criteria for PE. Mild preeclampsia was defined as elevated blood pressure (140/90 mmHg or greater on two measurements that were obtained six or more hours apart, or 160/105 mmHg or greater at time of admission) with proteinuria equal +1 on urine dip [1, 24]. Severe preeclampsia was defined as blood pressure 160/105 mmHg with greater than +1 on urine dip or $\geq 140/90$ mmHg on two occasions 6 hours apart and any one of the following: platelets $< 120,000/\text{mL}$, aspartate aminotransferase (AST) > 45 U/L, alanine aminotransferase (ALT) > 60 U/L, and/or creatinine ≥ 1 mg/dL [1, 24]. Severe disease also included women diagnosed with HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome or eclampsia, women who required intravenous antihypertensive medications prior to delivery, as a surrogate for blood pressure values persistently in the severe range, or iatrogenic preterm delivery (< 37 weeks) due to the severity of their disease [1, 24].

We identified 106 cases during the study period who met all the inclusion and exclusion criteria. 262 pregnant women (controls) were prospectively enrolled during the same time period from women presenting for delivery at term (≥ 37 weeks) for scheduled induction of labor, scheduled cesarean section, spontaneous rupture of membranes or term labor. It is important to note that all patients were enrolled at the time of PE diagnosis which coincides with the time of delivery for the majority of them. If PE diagnosis was established preterm then pregnant women were followed to their delivery. There were no exclusion criteria for either cases or controls in the overall study. Patients with multiple gestations or gestational hypertension (blood pressure $\geq 140/90$ mmHg on two measurements ≥ 6 hours apart without proteinuria) or not available serum were excluded from this case-control study. All study participants were fully informed and gave written consent for their participation. University of Pennsylvania Institutional Review Board approval was obtained prior to enrollment.

Trained research nurses collected information on height, race, ethnicity, history of chronic hypertension (CHTN) and family history by patient interview at the time of enrollment. Other history including obstetric, demographic, prenatal delivery and neonatal information were collected from prenatal and hospital chart abstraction by trained research nurse abstractors. A separate individual performed data entry. The primary investigator (SKS) reviewed all data sheets for completeness, consistency, and accuracy. Small for gestational age was defined using actual birth weight and the Alexander growth curve to determine percentile fetal growth for gestational age [25].

Maternal whole blood was collected from each subject within 24 hours of enrollment. After centrifugation, serum samples were aliquoted and placed at -80°C . For each subject, commercially available assays were used to measure levels of adiponectin and leptin by personnel who were blinded to the case-control status. Serum adiponectin was determined

by radioimmunoassay (LINCO Research, St. Charles, MO) with a sensitivity of 1 ng/mL, an intra-assay coefficient of variation of 1.8% to 6.2%, an inter-assay coefficient of variation of 6.9% to 9.3% and a recovery rate of 99–103% for adiponectin. Serum leptin levels were measured using radioimmunoassay (LINCO Research, St. Charles, MO). For leptin, the sensitivity of the assay was 0.5 ng/mL, with an intra-assay coefficient of variation of 3.4% to 8.3% and an inter-assay coefficient of variation of 7.0% to 9.3%.

Statistical analysis

Statistical analysis of the data was performed using SPSS® version 17 for Windows statistical software package. Initial data were assessed through simple cross-tabulations and by using chi-square test and Fisher's exact test for categorical variables, t-test for normally distributed variables and Mann-Whitney U test for not normally distributed variables. The normality hypothesis was tested by Kolmogorov-Smirnov test, measures of asymmetry and Shapiro-Wilk test. In order to compare means of cases amongst different subgroups, one-way ANOVA test for normally distributed variables or Kruskal-Wallis test for not normally distributed variables were conducted. Post hoc pairwise comparisons were performed using the Bonferroni method. Analysis of covariance was used in order to determine if cases and controls differ in serum leptin or adiponectin levels after accounting for gestational age and/or weight gain during pregnancy. The Pearson or Spearman correlation coefficients (r) were used as measurements of correlation for continuous normally or not normally distributed variables respectively. Multivariable logistic regression analysis was performed in order to evaluate independent predictors of preeclampsia (mainly adiponectin or leptin), with results reported as odds ratios (ORs) with 95% confidence intervals (CIs). For all tests performed, a two-sided P value of less than 0.05 was considered as significant.

RESULTS

Clinical and demographic characteristics of 106 preeclampsia patients and 262 controls are depicted in Table 1. Maternal age and the proportion of African American race were similar between cases and controls. There were fewer primigravida women with preeclampsia than controls ($p=0.009$). Cases had significantly higher systolic blood pressure at first visit (prenatal care-screening visit) than controls ($p=0.03$), but there were no significant differences in diastolic blood pressure and mean blood pressure. BMI, body height, body weight as well as body weight gain during pregnancy did not differ between cases and controls (>0.05). Women in the PE group had a lower mean gestational age at delivery and therefore, gave birth to smaller for gestational age and smaller birth weight infants when compared with control pregnant women ($p<0.001$, $p=0.027$ and $p<0.001$ respectively). Pre-eclamptic women were more likely to have a history of preeclampsia ($p=0.001$), gestational diabetes ($p=0.02$) and renal disease ($p=0.03$) compared to controls.

Serum concentrations of leptin and adiponectin in the PE group and in the control group did not differ significantly (9.3 ± 4.4 versus 9.6 ± 5.2 $\mu\text{g/mL}$ for adiponectin, $p=0.57$; 21 ± 15.9 versus 23.8 ± 18.1 ng/mL for leptin, $p=0.15$). Serum leptin and adiponectin were similar in both groups after adjusting for gestational age (for leptin: estimated marginal means (EMM) $\pm$ standard error (SE): 21.4 ± 1.9 in cases versus 23.6 ± 2.16 ng/mL in controls, $F=0.92$, $p=0.34$ and for adiponectin: EMM $\pm$ SE: 9.11 ± 0.55 in cases versus 9.6 ± 0.32 $\mu\text{g/mL}$ in controls, $F=0.65$, $p=0.42$). Serum leptin and adiponectin did not differ significantly between cases and controls after adjusting for gestational age and weight gain during pregnancy (for leptin: EMM $\pm$ SE: 21.25 ± 2.04 in cases versus 23.9 ± 1.21 ng/mL in controls, $F=1.16$, $p=0.28$ and for adiponectin: EMM $\pm$ SE: 9.06 ± 0.55 in cases versus 9.53 ± 0.31 $\mu\text{g/mL}$ in controls, $F=0.51$, $p=0.48$). When categorizing pre-eclamptic women into those with mild ($n=23$) and severe ($n=83$) disease, there were not any significant differences in serum adiponectin or leptin (9.7 ± 4.7 in mild PE versus 9.2 ± 4.3 $\mu\text{g/mL}$ in severe PE for

adiponectin, $p=0.51$; 20.3 ± 16 in mild preeclampsia versus 21.2 ± 15.9 ng/mL in severe preeclampsia for leptin, $p=0.72$). Among cases, no significant correlations were observed between adiponectin and leptin or other parameters such as BMI, body weight, height, screening SBP, DBP and MBP. Only serum adiponectin levels were negatively correlated with infant birth weight ($r=-0.2$, $p=0.04$). Among controls, serum leptin correlated positively with screening DBP ($r=0.21$, $p=0.001$) and MBP ($r=0.183$, $p=0.004$). Moreover, no significant differences in adiponectin and leptin levels emerged when we further categorized pre-eclamptic women as overweight/obese ($BMI \geq 25$) and non-overweight ($BMI < 25$). When categorizing all pregnant women as overweight/obese ($BMI \geq 25$) and non-overweight ($BMI < 25$) only leptin was significantly higher in overweight/obese women than in non-overweight pregnant women (24.7 ± 18.02 in overweight pregnant women versus 19.8 ± 17.07 ng/mL in non-overweight pregnant women, $p=0.016$).

Table 2 summarizes the odds ratios for PE risk by adiponectin and leptin concentrations, with and without covariate adjustment. Pregnant women with increasing leptin concentrations did not present significantly higher odds for preeclampsia before ($OR=0.99$, 95% CI 0.98–1, $p=0.18$) and after adjustment for maternal age, race, primigravida, smoking status, body mass index at screening, gestational age at admission, history of preeclampsia, chronic hypertension, gestational diabetes and serum adiponectin ($OR=1$, 95% CI 0.97–1.03, $p=0.96$). In contrast, subjects with higher adiponectin concentrations tended to present lower odds for preeclampsia risk (though not significant at 0.05) after adjustment for the aforementioned covariates including serum leptin ($OR=0.93$, 95% CI 0.83–1.04, $p=0.21$). Only history of preeclampsia and gestational age at admission were significant predictors of preeclampsia risk ($OR=3.6$, 95% CI 1.12–11.3, $p=0.03$ and $OR=0.53$, 95% CI 0.36–0.78, $p<0.001$, respectively).

DISCUSSION

We sought to determine whether serum adiponectin is associated with an increased risk of PE after adjusting for leptin levels which reflect body fat mass, maternal age, race, primigravida, smoking status, body mass index at screening, gestational age at admission, history of preeclampsia, CHTN and gestational diabetes. The results of the current investigation revealed no statistically significant associations between serum adiponectin and preeclampsia. Other important observations were that leptin was not associated with PE and that neither adiponectin nor leptin differed significantly between mild and severe cases. We have also found that history of PE and gestational age were significant predictors of PE risk in agreement with previous evidence demonstrating associations with PE [1–2, 7].

Increased risk of PE has been noted in relation to several conditions associated with insulin resistance, including gestational diabetes, polycystic ovary syndrome, maternal obesity and excessive weight gain during pregnancy [8]. The pathophysiology that links maternal obesity with PE and pregnancy-induced hypertension is a subject of intensive research with insulin resistance playing a pivotal role [26]. Although insulin resistance increases in the normal course of pregnancy in order to facilitate the diversion of glucose to the fetus and support the rapid fetal and placental growth [8], increase of insulin resistance beyond a certain point may become deleterious contributing to the development of gestational diabetes, pregnancy-induced hypertension and PE [26]. Recent reports have suggested that insulin signaling and angiogenesis are intimately related [27] and aberrations in angiogenesis and insulin resistance may lead to alterations in critical cellular functions, endothelial cell injury, and consequently augmented risk of developing PE [21]. Insulin resistance in pregnancy and pregnancy-complications is mainly attributed to placental hormones and increased maternal adiposity, but the underlying mechanisms remain to be fully elucidated [26].

Adiponectin, the most abundant adipose-tissue specific protein, is a pleiotropic, insulin-sensitizing, anti-inflammatory and anti-atherogenic adipokine [17]. Serum values of adiponectin are lower in insulin resistant states, including diabetes mellitus type 2, obesity, obesity-related cancers, and coronary artery disease [16–17]. Adiponectin plays an important role in angiogenesis and exhibits powerful anti-inflammatory properties: it inhibits the inflammatory cytokine network down-regulating TNF- α -induced expression of endothelial adhesion molecules, TNF- α expression in macrophages and adipose tissue, macrophage-to-foam cell transformation, and smooth muscle proliferation [28]. Moreover, it employs caspase-mediated endothelial cell apoptosis underscoring a possible role of adiponectin in PE which is generally linked to endothelial cell malfunction [6].

In this investigation, we hypothesized that lower adiponectin might be present in PE, because hypoadiponectinemia is associated with impaired endothelium-dependent vasodilatation and reduced blood flow, and is an independent risk factor for hypertension [15]. In our study, although pre-eclamptic women showed a slightly lower adiponectin than the control group, we did not observe any statistically significant difference in serum adiponectin between cases and controls both in univariate analysis and after adjustment for possible confounders. This finding is in accordance with two previous smaller studies showing no change in adiponectin values [29–30]. But controversial data exist in the literature regarding adiponectin as predictive marker of PE. A decrease [18, 22–23], no change [29–30] and even an increase in maternal adiponectin levels have been reported [18–19, 31]. Also, in a small study with different women in different trimesters of pregnancy, Herse et al found that serum adiponectin increased throughout normal pregnancy but was lower in women with PE [32]. The results of our study may be attributable to: a) the case-control design nested within a hospital-based cohort study-the majority of previous studies are cross-sectional, b) the larger size of our study (N=368) while the other studies have a limited number of participants ranging from 37 to 200, and c) possibly, the greater percentage of African American pregnant women in our study compared to previous reports. However, the findings of this study suggest that adiponectin levels may not be an important contributor to the pathogenesis of PE. Whether or not placental adiponectin synthesis and secretion contribute to maternal serum adiponectin levels remains to be elucidated given that placental expression of mRNA adiponectin was found to be weaker than it was in adipose tissue [18]. Whether the relative amounts of adiponectin isoforms are altered in pregnancy-associated hypertensive disorders is not known and remains to be elucidated but we have shown no major differences in terms of insulin resistance [33].

We found no difference in serum leptin levels between pre-eclamptic women and controls both in univariate analysis and after controlling for potential confounders. This is in agreement with other studies which did not detect any significant differences [18, 34]. We also found similar leptin levels in pregnant women with mild or severe PE in accordance with a previous study [34]. Pre-eclamptic placentas are characterized by several vascular alterations and are associated with hypoxic stress [2]. It has been considered that leptin is upregulated in PE reflecting an induced compensatory response in order to augment nutrient delivery to an underperfused and hypoxic placenta [2]. However, it seems that there is no consensus regarding leptin levels in PE: some investigators found no change [18, 34] while others detected an increase [18, 32, 35–36] and even a reduction [37]. Nevertheless, in some of these cross-sectional studies, the results were not adjusted for maternal BMI and other important known risk factors for PE, or leptin levels were measured during early pregnancy. In particular, even if participants of some previous studies were matched for age and BMI, results on adipokines were not adjusted in multivariate models for important confounders such as gestational age, race, parity, history of PE, CHTN, gestational diabetes, etc.

Our findings must be interpreted in the context of the study design. When using a case-control design, there is potential for selection bias, particularly in the selection of controls. It is challenging to match for all covariates, and it is possible that uncontrolled differences between groups may mask an association of adipokines with PE. Our controls came from the same study base as our cases. This, as well as the random selection of controls, reduces selection bias. Furthermore, other methodological strengths of the present investigation include: 1) the larger sample size (N=368) compared to other studies of adipokines and PE, 2) the strict criteria for inclusion of cases and control subjects, and 3) the adjustment for many known potential risk factors for PE, which further reinforces the observed null associations. The assessment of adiponectin and leptin were made using state of the art technology and in a blinded fashion which also eliminates uncontrolled confounding from this source.

In summary, the results of our case-control study do not support an association between the two well-known adipokines: adiponectin and leptin, and risk for preeclampsia. Further research, including mechanistic, prospective and longitudinal studies, is required to determine exactly if and when adiponectin and leptin concentrations are altered in PE and whether adiponectin per se and/or any of its isoforms- and/or leptin may play a causal role in the pathogenesis of PE.

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List of abbreviations

PE	Preeclampsia
CHTN	chronic hypertension
HELLP	<u>H</u> emolysis, <u>E</u> levated <u>L</u> iver Enzymes <u>L</u> ow <u>P</u> latelets
BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure
MBP	mean blood pressure
AST	aspartate aminotransferase
ALT	alanine aminotransferase
TNF	tumor necrosis factor
OR	odds ratio
C.I.	Confidence interval

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Table 1

Clinical and demographic characteristics of preeclampsia (N=106) and control (N=262) patients. Data are expressed as percentage (number) or mean $\pm$ standard deviation.

Variables	Pre-eclamptic patients	Control Patients	p value
Maternal Age (years)	26.2 $\pm$ 6.4	26.8 $\pm$ 6.9	0.5
Race (N, %)			
African American	84 (79.2)	201 (76.7)	0.53
White	19 (17.9)	45 (17.2)	
Asian	1 (0.9)	8 (3)	
Latino	0 (0)	4 (1.5)	
Other	2 (1.9)	4 (1.5)	
Primigravida (N, %)	38 (35.8)	58 (22.1)	0.009
Systolic Blood Pressure at first visit (mmHg)	114.8 $\pm$ 12.1	111.8 $\pm$ 12	0.03
Diastolic Blood Pressure at first visit (mmHg)	70.5 $\pm$ 9.6	69.7 $\pm$ 8.7	0.45
Mean Blood Pressure at first visit (mmHg)	85.2 $\pm$ 9.6	83.7 $\pm$ 8.9	0.15
Body Mass Index at first visit (kg/m ²)	29.3 $\pm$ 9.3	29.3 $\pm$ 8.2	0.95
Body Height (m)	1.63 $\pm$ 0.07	1.63 $\pm$ 0.08	0.55
Body Weight at first visit (kg)	76.7 $\pm$ 21.7	77.5 $\pm$ 20.5	0.75
Body Weight gain during pregnancy (kg)	10.9 $\pm$ 7.9	9.7 $\pm$ 7.8	0.23
Gestational age at admission (weeks)	36.1 $\pm$ 4.2	39 $\pm$ 1.3	<0.001
Gestational age at delivery (weeks)	36.5 $\pm$ 3.4	39.1 $\pm$ 1.3	<0.001
Infant Birth weight (g)	2671 $\pm$ 755	3296 $\pm$ 468	<0.001
Small for gestational age infants (n, %)	24 (22.6)	34 (12.9)	0.027
Mode of delivery n,%			0.07
Vaginal delivery	63 (59.4)	182 (69.5)	
Cesarian section	43 (40.6)	80 (30.5)	
Current smokers (n,%)	13 (12.3)	26 (9.9)	0.5
Adiponectin (μ g/mL)	9.3 $\pm$ 4.4	9.6 $\pm$ 5.2	0.57
Leptin (ng/mL)	21 $\pm$ 15.9	23.8 $\pm$ 18.1	0.15
One-hour glucose tolerance test (mg/dL)	104.3 $\pm$ 24.6	101.2 $\pm$ 25.6	0.33
Gestational age at one-hour glucose tolerance test (weeks)	26.1 $\pm$ 5.2	26.2 $\pm$ 5.3	0.87
Gestational diabetes diagnosed during pregnancy (n, %)	5 (4.7)	3 (1.1)	0.02
History of PE (n, %)	19 (17.9)	20 (7.6)	0.001
History of Pre- Pregnancy diabetes (n, %)	4 (3.8)	8 (3)	0.75
History of CHTN (n, %)	11 (10.4)	14 (5.3)	0.08
History of preterm delivery (n, %)	3 (2.8)	4 (1.5)	0.06

Mean Blood pressure=DBP+(SBP-DBP)/3

Table 2

Unadjusted and adjusted Odds Ratios (ORs) with 95% Confidence Intervals (C.I.) for preeclampsia risk according to serum adiponectin or leptin in 106 pre-eclamptic pregnant women and 262 controls.

Variables	Unadjusted ORs (95% C.I.)	p-value	Adjusted ORs (95% C.I.) [‡]	p-value
Adiponectin				
1 µg/mL more	0.99 (0.94–1.03)	0.61	0.93 (0.83–1.04)	0.21
Leptin				
1 ng/mL more	0.99 (0.98–1)	0.18	1 (0.97–1.03)	0.96

[‡] Adjusted for maternal age, race, primigravida, smoking status, body mass index at screening, gestational age at admission, history of preeclampsia, chronic hypertension, gestational diabetes and serum adiponectin or leptin.