Intraabdominal fat, insulin sensitivity, and cardiovascular risk factors in postpartum women with a history of preeclampsia

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OBJECTIVE: Women who develop preeclampsia have a higher risk of future cardiovascular disease and diabetes compared to women who have uncomplicated pregnancies. We hypothesized that women with prior preeclampsia would have increased visceral adiposity that would be a major determinant of their metabolic and cardiovascular risk factors.

STUDY DESIGN: We compared intraabdominal fat (IAF) area, insulin sensitivity index (S_I), fasting lipids, low-density lipoprotein relative flotation rate, and brachial artery flow-mediated dilatation in 49 women with prior preeclampsia and 22 controls who were at least 8 months postpartum and matched for age, parity, body mass index, and months postpartum. Women were eligible if they did not smoke tobacco, use hormonal contraception, have chronic hypertension, or have a history of gestational diabetes.

RESULTS: The groups were similar for age (mean ± SD: prior preeclampsia 33.4 ± 6.6 vs control 34.6 ± 4.3 years), parity (median: 1 for both), body mass index (26.7 ± 5.9 vs 24.0 ± 7.3 kg/m^2), and months postpartum (median [25th-75th percentile]: 16 [13-38] vs 16.5 [13-25]). There were no significant differences in IAF area and S_I. Despite this, women with preeclampsia had lower high-density lipoprotein (46.0 ± 10.7 vs 51.3 ± 9.3 mg/dL; $P < .05$), smaller/denser low-density lipoprotein relative flotation rate (0.276 ± 0.022 vs 0.289 ± 0.016; $P = .02$), higher systolic (114.6 ± 10.9 vs 102.3 ± 7.5 mm Hg) and diastolic (67.6 ± 7.5 vs 60.9 ± 3.6 mm Hg; $P < .001$) blood pressures, and impaired flow-mediated dilatation (4.5 [2-6.7] vs 8.8 [4.5-9.1] percent change, $P < .05$) compared to controls. In a subgroup analysis, women with nonsevere preeclampsia (n = 17) had increased IAF (98.3 [60.1-122.2]) vs 63.1 [40.1-70.7] cm^2; $P = .02$) and decreased S_I (4.18 [2.43-5.25] vs 5.5 [3.9-8.3] × 10^{-5} min^{-1}/pmol/L; $P = .035$) compared to the controls, whereas women with severe preeclampsia (n = 32) were not different for IAF and S_I. IAF was negatively associated with S_I and positively associated with cardiovascular risk factors even after adjusting for the matching variables and total body fat.

CONCLUSION: Women with prior preeclampsia have an atherogenic lipid profile and endothelial dysfunction compared to matched control subjects despite having similar adiposity and insulin sensitivity, suggesting that there are mechanisms separate from obesity and insulin resistance that lead to their cardiovascular risk factors. Visceral adiposity may have a role in contributing to these risk factors in the subgroup of women who have preeclampsia without severe features.

Key words: body fat distribution, cardiovascular risk factors, endothelial dysfunction, insulin resistance, preeclampsia

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Women who develop preeclampsia are more likely to be obese,[1-5] be insulin resistant,[6-10] have an atherogenic lipoprotein phenotype,[5,11,12] and have markers of endothelial dysfunction.[13,14] Although the clinical manifestations of preeclampsia resolve postpartum, women have abnormalities remote from delivery including lower insulin sensitivity,[7] higher blood pressures,[15-19] an atherogenic lipoprotein phenotype,[15] and endothelial dysfunction.[20] The persistence of these

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abnormalities suggests that they have an underlying condition, presumably the metabolic syndrome.[21] Indeed, recent studies have shown that the metabolic syndrome is more common in women with a history of preeclampsia[22-24] and that they have an increased risk of developing complications associated with the metabolic syndrome such as cardiovascular disease[25-31] and diabetes mellitus.[32-34]

We and other investigators have demonstrated in other populations that visceral adiposity is a significant determinant of the metabolic syndrome[35] and its features including decreased insulin sensitivity[36-39] and ß-cell function,[39,40] impaired glucose tolerance,[41] elevated blood pressure,[35,42] and dyslipidemia.[35,38,43] Visceral fat is metabolically active as a source of free fatty acids[44,45] and adipokines, such as adiponectin,[46,47] tumor necrosis factor (TNF)-α,[45,48,49] and plasminogen activator inhibitor (PAI)-1[50,51]; many of these factors have been shown to be elevated in women with preeclampsia,[11,52-54] but the studies that measured these factors in women with preeclampsia did not quantify visceral adiposity. Our group was specifically interested in evaluating the role that visceral adiposity and insulin resistance play in contributing to cardiovascular risk factors in women with a history of preeclampsia. We hypothesized that visceral adiposity would be a major determinant of their metabolic and cardiovascular risk factors.

Materials and Methods

Study design

This was a cross-sectional study comparing body fat distribution, insulin sensitivity, β-cell function, fasting lipids, hepatic lipase activity, and endothelial function between postpartum women who had either an uncomplicated pregnancy (control group) or a history of preeclampsia (prior preeclampsia group). The study was approved by the University of Washington Institutional Review Board prior to initiation. All subjects provided written informed consent to participate.

Subjects

Subjects were recruited by advertisement in the greater Seattle area and underwent a screening visit that included a history and physical examination with a fasting blood draw. Women were eligible if they were at least 8 months postpartum and premenopausal. They were excluded if they smoked tobacco, used hormonal contraception or medications that would impact glucose metabolism or lipids/lipoproteins, were pregnant, or had a fasting plasma glucose $\geq$110 mg/dL, an abnormal complete blood cell count, liver transaminases $\geq$1.5 $\times$ normal, a serum creatinine $\geq$1.4 mg/dL, a history of chronic hypertension, diabetes, renal disease, autoimmune disease, fetal anomalies or aneuploidy, or multifetal gestation. All women underwent screening for gestational diabetes as a part of standard practice in our region and had normal results on either the 1-hour oral glucose challenge test or 3-hour oral glucose tolerance test. Women diagnosed with gestational diabetes in any pregnancy were excluded.

Women in the prior preeclampsia group had medical record documentation of the following criteria for preeclampsia: systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg on 2 occasions 6 hours apart and persistent 1+ proteinuria (between 30-100 mg/dL) on random urine samples or total protein $\geq$300 mg/24-hour urine collection.[55] Women in the prior preeclampsia group were further characterized by whether they had features of severe preeclampsia: elevated transaminases, thrombocytopenia, severe blood pressure elevation (systolic $\geq$160 mm Hg or diastolic blood pressure $\geq$110 mm Hg), renal insufficiency, and neurological symptoms.[55] Women in the control group delivered their babies at $\geq$39 weeks' gestation and had normal blood pressures documented throughout their prenatal course, labor and delivery, and postpartum. The 2 groups were matched for age (within 5 years), body mass index (BMI) (within 2.5 kg/m^2), time since delivery (within 4 weeks), and parity (within 1 delivery).

Measurements

Study procedures were performed on 2 consecutive days during the subjects' follicular phase of the menstrual cycle at the University of Washington General Clinical Research Center. Study participants were instructed to avoid exercise or strenuous activity 24 hours prior to the visit. Dietary assessments were not performed.

Anthropometrics and body fat distribution and composition

BMI (kg/m^2) was calculated from the average of 3 weight and height measurements. Waist circumference was measured in the standing position at the level midway between the lateral lower rib margin and the iliac crest. To determine total and regional body fat and lean content, dual-energy x-ray absorptiometry (DEXA) was performed on the general clinical research center.[56] A computed tomography (CT) scan was performed in the department of radiology to quantify intraabdominal fat (IAF) and subcutaneous fat (SCF) areas.[57,58] A single observer who was blinded to group assignment made the DEXA and CT measurements. The coefficient of variation (CV) for the DEXA scan measurement of total fat mass is 1.67% (personal communication with Danielle Yancey, Bachelor of Science in Exercise Science, Research Scientist and Exercise Physiologist in the Nutrition Research and Body Composition Core at the University of Washington Medical Center, March 4, 2014). The CV for the SCF and visceral fat areas for the same scan on 10 separate days is 1.5%.[48]

Frequently sampled intravenous glucose tolerance test

Following a 12-hour overnight fast, an insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT) was performed to quantify the insulin sensitivity index (S_I) using minimal model of glucose kinetics[59] of Bergman et al.[60] The acute insulin response to glucose was quantified as the incremental insulin response above baseline from 2-10 minutes following glucose administration. ß-cell function (the disposition index) was calculated by adjusting the acute insulin response to glucose for the prevailing S_I.[61]

Assays

All chemical analyses were performed on blood samples obtained after a 12-hour