Paradoxical Elevation in Adiponectin Concentrations in Women With Preeclampsia

Jane E. Ramsay, Nigel Jamieson, Ian A. Greer, Naveed Sattar

Abstract—Adiponectin is a recently identified, insulin-sensitizing and anti-inflammatory protein released by adipocytes, which is paradoxically reduced in obesity. It suppresses endothelial activation. Physiological insulin resistance occurs in normal pregnancy and is exaggerated in women with preeclampsia (PE), together with enhanced inflammatory and endothelial activation. Women with increased body mass index (BMI) and insulin resistance are predisposed to PE. We hypothesized that adiponectin concentrations are reduced in normal pregnancy compared with postpartum values and further reduced in women with PE. Fifteen women with PE and 30 control subjects with similar first trimester BMI had adiponectin concentrations measured in the third trimester; postpartum measurements were repeated in 16 control subjects. Adiponectin concentration in healthy pregnant women correlated inversely with early pregnancy BMI ($r = -0.47$, $P = 0.01$) and fasting insulin concentrations ($r = -0.58$, $P = 0.001$). However, adiponectin concentrations did not differ significantly in pregnancy and postpartum samples (mean change, $-0.15$ g/mL; 95% CI, $-2.28$ to $1.98$, $P = 0.88$). Plasma adiponectin concentrations were markedly elevated ($P = 0.01$) in women with PE (mean, $21.6$ g/mL; SD, $8.18$ g/mL) compared with control subjects (mean, $14.7$ g/mL; SD, $7.06$ g/mL). Moreover, in PE, adiponectin concentrations did not correlate with first trimester BMI or insulin or with serum urate or creatinine concentrations or urinary protein levels. We conclude that plasma adiponectin concentrations are not elevated in normal human pregnancy and paradoxically elevated (by 47%) in women with PE. This may be secondary to exaggerated nonspecific adipocyte lipolysis or as a physiological response to enhance fat utilization and attenuate endothelial damage. Future studies should determine whether adiponectin concentrations help improve prediction of PE. (Hypertension. 2003;42:891-894.)

Key Words: adipose tissue  ■  insulin resistance  ■  pregnancy  ■  endothelium  ■  preeclampsia

Preeclampsia (PE) is characterized by widespread endothelial damage and dysfunction throughout the maternal circulation, resulting in the classic manifestations of hypertension caused by vasoconstriction, proteinuria caused by glomerular damage, and edema caused by increased vascular permeability.$^1$ It accounts for the majority of referrals to obstetric day care units$^2$ and is a major cause of hospital admission.$^3$ Placental damage associated with the condition can result in intrauterine growth restriction. Delivery is the only known cure for PE and often results in preterm delivery$^4$ and low birth weight.$^3$

The pathogenesis of PE continues to be elusive. Endothelial dysfunction may be the final common pathway linking upstream metabolic perturbations to the clinical manifestations.$^6$ However, the nature of the perturbances leading to endothelial activation is unclear, although the placental release of toxic factors with subsequent inflammatory upregulation$^7$ and adipocyte lipolysis probably are involved.$^1$

Adiponectin is a novel 244–amino acid, adipose tissue–derived protein with important metabolic effects that circulates in human plasma at very high concentrations.$^8$ Despite being derived solely from adipose tissue, it is paradoxically reduced in obesity.$^9$ In line with this observation, high adiponectin concentrations are associated with better insulin sensitivity$^9$ and independently predict a reduced risk of type 2 diabetes.$^{10}$ Additional observations indicate that adiponectin is strongly anti-inflammatory, acting through the NF-$\kappa$B pathway,$^{11}$ and downregulates cell adhesion molecule expression on endothelial cells.$^{12}$ Thus, adiponectin is attracting considerable interest as a potential therapeutic modality to prevent vascular disease and diabetes. Indeed, in animal models, adiponectin prevents diabetes and atherogenesis.$^{13}$

The second half of normal gestation is a state of physiological insulin resistance, which is exacerbated in women with PE,$^{14}$ together with enhanced inflammatory$^7$ and endothelial pathway activation,$^6$ as discussed above. We therefore hypothesized that adiponectin concentrations would be reduced in normal pregnancy compared with postpartum values and markedly reduced in women with PE.

Methods

Subjects

Fifteen women with PE were recruited consecutively. PE was defined as blood pressure $>$140/90 mm Hg on 2 separate occasions
4 hours apart or a single recording of a diastolic pressure of 110 mm Hg, in association with proteinuria ≥2+ on dipstick testing, as defined by the International Society for the Study of Hypertension in Pregnancy. Thirty normotensive control subjects with body mass index (BMI) similar to the group with PE were recruited. The study was performed according to the Declaration of Helsinki, approval was granted by the institutional ethics committee, and all patients gave written informed consent.

The control group was invited to return at least 4 months after delivery. Of the original 30 control women, 16 women attended for postpartum determination of adiponectin concentration. The same protocol was followed at the postpartum and antenatal assessments.

Clinical and Laboratory Measurements

All patients attended for participation in the study after an overnight fast and underwent testing between 9 and 11 AM. Blood pressure was recorded by the same operator, using a standard mercury sphygmomanometer and appropriately sized cuff. Diastolic pressure was recorded as Korotkoff phase V. Blood was withdrawn for adiponectin and insulin determination and stored at −70°C until analyses.

Plasma adiponectin concentration was determined by radioimmunoassay (LINCO Research Inc). Serum samples were diluted 1:400. The lower limit of sensitivity was 1 ng/mL. The interassay and intra-assay coefficients of variation were <10% across the range of measured results. Fasting insulin was measured by a Microparticle Enzyme Immunoassay (Abbott Laboratories) assay with coefficient of variation <8% and sensitivity of 0.8 mU/L. The assay did not cross-react with proinsulin.

Statistical Analyses

Case-control differences in all descriptive demographic parameters were compared by means of the Mann-Whitney U or χ² tests. Adiponectin concentrations were normally distributed, and case-control differences were examined by unpaired t test. Antepartum and postpartum adiponectin concentrations were compared by paired t tests. Mean values and standard deviations are presented together with the mean difference and 95% confidence intervals. Correlations between parameters were examined by means of Pearson correlation coefficients, using, where required, log-transformed parameters. We elected to correlate first trimester BMI to third-trimester adiponectin concentrations, since BMI in latter half of pregnancy is complicated by the weight of the fetoplacental unit, whereas first trimester BMI is the most robust anthropometric predictor of PE, as indicated in recent systematic review. In addition, elevated first trimester BMI has been established by our group to predict perturbations in numerous metabolic, vascular, and inflammatory indexes in the third trimester of normal pregnancy.

Results

Demographic characteristics of the cases and control subjects are shown in the Table. There was no significant difference in BMI, age, smoking history, parity or gestation at examination, and sampling between PE and control subjects. Gestation of delivery was significantly earlier in the PE group compared with control subjects. Birth weight centile of babies born to mothers with PE was significantly less than in control subjects (25 versus 50, P = 0.024). Only 50% of women with PE achieved vaginal deliveries, which was significantly less than that seen in control subjects (80%). Fasting insulin concentrations were higher in women with PE, but this difference did not reach significance (PE median, 14.5 interquartile range, 9.5 to 35) mU/L versus control subjects, 9.8 (5.6 to 21.2) mU/L, P = 0.09).

Postpartum samples were taken a median of 32 weeks after delivery, and only 3 women were still breast-feeding. Plasma adiponectin concentration did not differ significantly in the antenatal and postpartum periods in the 16 women with

Demographic Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n=30)</th>
<th>PE (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT BMI, kg/m²</td>
<td>26.8 (21.8–30.2)</td>
<td>26. (24–27.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>29 (25–32)</td>
<td>27 (22–29)†</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>5 (16.7)</td>
<td>5 (33.3)†</td>
</tr>
<tr>
<td>Parity (primigravidae), n (%)</td>
<td>21 (70)</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Gestation, wk</td>
<td>35 (34–37)</td>
<td>36 (32–37)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>120 (110–130)</td>
<td>160 (150–169)‡</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75 (70–80)</td>
<td>100 (95–105)‡</td>
</tr>
<tr>
<td>FT systolic, mm Hg</td>
<td>120 (112–126)</td>
<td>117 (102–126)</td>
</tr>
<tr>
<td>FT diastolic, mm Hg</td>
<td>71 (66.2–77.2)</td>
<td>70 (66–76.5)</td>
</tr>
<tr>
<td>Gestation of delivery, wk</td>
<td>39 (38–40)</td>
<td>36 (33.7–37)‡</td>
</tr>
<tr>
<td>Birthweight centile</td>
<td>50 (30–75)</td>
<td>25 (8.25–50)†</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>...</td>
<td>80 (70–85)</td>
</tr>
<tr>
<td>Urate, μmol/L</td>
<td>...</td>
<td>335 (298–420)</td>
</tr>
<tr>
<td>Protein urinalysis, pluses</td>
<td>...</td>
<td>2 (2–3)</td>
</tr>
<tr>
<td>Cesarean section, %</td>
<td>20</td>
<td>50†</td>
</tr>
</tbody>
</table>

Values are medians (interquartile ranges) except where otherwise indicated. PE indicates preeclampsia; BMI, body mass index; BP, blood pressure; FT, first trimester.

*P<0.1, †P<0.05, ‡P<0.001 for PE vs control. Statistical analysis performed using Mann-Whitney U or χ² test.

Plasma adiponectin concentrations were markedly elevated (47%, P = 0.01) in women with PE (mean, 21.6; SD, 8.18 μg/mL) compared with control subjects (mean, 14.7; SD, 7.06 μg/mL; Figure). The mean difference was 6.9 μg/mL (95% CI, 1.7 to 12.0). After further adjusting for smoking status and age, both parameters different in cases and control subjects at baseline, the case-control significance was strengthened to P = 0.002. Plasma adiponectin concentration in healthy pregnant women correlated inversely with first trimester BMI (r = –0.47, P = 0.01) and fasting insulin concentrations (r = –0.58, P = 0.001). However, such correlations were reversed and nonsignificant in women with PE (adiponectin

Adiponectin concentrations in women with PE and in healthy pregnant women with similar first trimester BMI and gestational age at sampling. Horizontal lines represent mean concentrations in each group. *Probability value strengthened to P = 0.002 with additional adjustment for age and smoking status.
versus BMI, $r=0.38$, $P=0.16$; adiponectin versus fasting insulin $r=0.36$, $P=0.21$). Adiponectin concentrations did not correlate with serum creatinine and urate concentrations or with urinary protein levels (all $P>0.25$, data not shown) in women with PE.

**Discussion**

In contrast to our hypotheses, adiponectin concentrations were not reduced in normal pregnancy despite strong inverse correlations with fasting insulin and BMI. Moreover, adiponectin concentrations were also not reduced in women with PE despite PE being associated with insulin-resistant phenotypes, including increased BMI and waist circumference, both of which predict increased risk.\(^{17}\) Although in this study fasting insulin levels were not statistically elevated in cases. By contrast, adiponectin concentrations in women with PE were markedly elevated such that the mean level was 47% higher than in women with normal healthy pregnancies. These counterintuitive data are novel, since, to date, only a few other disease states (renal failure, type 1 diabetes, anorexia nervosa) are known to be associated with increased plasma adiponectin concentrations.\(^{18,19}\) Moreover, as far as we are aware, these data represent the first reports on adiponectin concentrations in normal human pregnancy and in women with PE.

Why should adiponectin concentrations be elevated in PE? One possibility is clearly renal dysfunction in PE leading to elevated levels. However, this is unlikely in the patients studied because creatinine levels were all within normal levels in women with PE; associations between adiponectin concentrations and serum creatinine or urate or degree of proteinuria were absent (all $P>0.25$). Furthermore, although the inverse correlation between adiponectin and BMI and insulin measures in patients with renal failure persists,\(^{18}\) such relations were absent in women with PE. Indeed, there were no significant correlations between adiponectin and any metabolic parameters in women with PE.

An alternative possibility for the elevated adiponectin concentration is exaggerated adipocyte release, and there is evidence that other adipocyte-derived factors are present in elevated concentrations in women with PE. These include free fatty acids, inflammatory molecules such as IL-6 and TNF-α, metabolically active molecules such as leptin, and factors involved in thrombosis such as PAI-1.\(^{20}\) These candidate pathways are of particular interest because all have been linked to PE pathophysiology.\(^{21–23}\) There is evidence that circulating levels of free fatty acids, leptin, and PAI-1 are elevated in advance of PE.\(^{21–23}\)

If adipocyte lipolysis is indeed the culprit for enhanced adiponectin release, then is there any potential physiological benefit? Adiponectin increases insulin sensitivity by promoting β-oxidation of fatty acids in tissues, leading to reduced circulating fatty acid levels and reduced intracellular triglyceride content in liver and muscle.\(^{24}\) Interestingly, β-oxidation of fatty acids is impaired in PE,\(^{25}\) and there is certainly fat accumulation in liver in PE. Thus, adiponectin release could be a physiological feedback response acting to minimize the excess fat accumulation in tissues in women with PE. The elevated adiponectin concentrations may also suppress the expression of adhesion molecules in vascular endothelial cells and cytokine production from macrophages,\(^{11,12}\) thus inhibiting the inflammatory processes that are undoubtedly operating in PE to promote endothelial damage and dysfunction.\(^{7,22}\) A further possibility is that women with PE are adiponectin-resistant, a phenotype that would predispose to PE. Longitudinal studies in these women would be of interest.

Whatever the mechanism, our results are of significance because the magnitude of the elevation of adiponectin in PE beyond concentrations noted in normal pregnancy immediately suggests that like free-fatty acids and triglycerides, it could help predict PE when measured earlier in pregnancy or even in the nonpregnant state. It has advantages over lipid measurements in that it is not altered in the postprandial state.\(^{26}\) Moreover, the extent of the elevation in adiponectin suggests that it may be a particularly sensitive predictor of PE. This possibility requires direct examination.

Our data suggesting similar adiponectin concentrations in the third trimester of pregnancy and in the postpartum state perhaps argue against a placental source for this protein. Moreover, a recent study in mice also did not find elevated adiponectin in gestation. By contrast, this latter study noted near 50% lower adiponectin late in gestation compared with prepregnancy values, a finding at odds with our data in human pregnancy.\(^{27}\)

The strengths of our study include its strict criteria for inclusion of cases and control subjects, together with broad matching of BMI in the two groups. Given the critical role of obesity in increasing the risk for PE\(^{15}\) and in determining levels of a range of metabolic factors in normal pregnancy,\(^{16}\) consideration of BMI as a potential confounder in pregnancy metabolic studies is important. Many prior studies have not controlled for obesity. Our study also carefully matched cases and control subjects for gestational age at sampling. The limitations include its cross-sectional design and the measurement of proteinuria by dipstick testing only. We acknowledge that more precise quantitative techniques need to be used to confirm absence of correlation between proteinuria and adiponectin concentrations. Further studies also need to address adiponectin concentrations in early-onset PE and whether adiponectin concentrations return to control values in the postpartum period.

**Perspectives**

In conclusion, we showed for the first time that adiponectin concentration is markedly elevated (by nearly 50%) in women with PE, perhaps as the result of an exaggerated early adipocyte lipolysis. These data are of major interest, given the intense interest in the role of adiponectin in human metabolism. Elucidating the exact mechanism(s) for such elevation therefore will give further insight into the pathogenesis of this complex disease. Moreover, prospective studies are required to determine if plasma adiponectin determination in early pregnancy might improve prediction of PE.

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**References**


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