J. Perinat. Med. 35 (2007) 503–512 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/JPM.2007.121

Adiponectin in severe preeclampsia

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Abstract

Aims: Adiponectin is an adipokine with insulin-sensitizing, anti-atherogenic, anti-inflammatory and angiogenic properties. The aims of this study were to determine whether maternal plasma adiponectin concentrations differ between patients with severe preeclampsia and those with normal pregnancies, and to explore the relationship between plasma adiponectin and the results of Doppler velocimetry of the uterine arteries.

Methods: This case-control study included two groups: (1) patients with severe preeclampsia (n = 50) and (2) patients with normal pregnancies (n = 150). Pulsed-wave and color Doppler ultrasound examination of the uterine arteries were performed. Plasma adiponectin concentrations were determined by ELISA. Non-parametric statistics were used for analysis.

Results: (1) Patients with severe preeclampsia had a higher median plasma concentration of adiponectin than that of normal pregnant women. (2) The median plasma adiponectin concentration did not differ between women with severe preeclampsia who had a high impedance to blood flow in the uterine arteries and those with normal impedance to blood flow. (3) Among patients with normal pregnancies, plasma adiponectin concentrations were negatively correlated with BMI in the first trimester and at sampling.

Conclusions: Women with severe preeclampsia have a higher median plasma concentration of adiponectin than that of normal pregnant women. This may reflect a compensatory feedback mechanism to the metabolically-altered, anti-angiogenic and pro-atherogenic state of severe preeclampsia.

Keywords: Adiponectin; Doppler; obesity; preeclampsia; pregnancy; uterine artery.

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Introduction

Adiponectin is a hormone produced abundantly by adipose tissue [35, 88]. A large body of evidence from experimental and epidemiological studies supports a role of adiponectin in the regulation of insulin resistance, atherosclerosis, inflammatory responses and angiogenesis. In contrast to other hormones produced by adipose tissue (collectively known as adipokines), adiponectin concentrations are negatively correlated with insulin resistance [99, 102], obesity [4, 74], dyslipidemia [53] and hypertension [67]. Low concentrations of adiponectin are also associated with gestational diabetes [14, 44, 71, 73, 97].

In addition to the insulin-sensitizing property of adiponectin, this adipokine has a protective effect against atherosclerosis. Adiponectin suppresses the macrophage-to-foam cell transformation [64] and inhibits the expression and the activity of the class A macrophage scavenger receptor [66]. Furthermore, atherosclerosis that develops in apolipoprotein-E knockout mice can be prevented in 30% of cases by treatment with a vector expressing human adiponectin [63]. Several reports have highlighted the anti-inflammatory properties of adiponectin, including the suppression of macrophage production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), [98, 103] interferon-gamma (IFN-γ) [96] and interleukin-6 (IL-6). Adiponectin can also exert its anti-inflammatory effects by preventing activation of the

nuclear transcription factor NF-κB [65]. Recently, it has been demonstrated that adiponectin stimulates angiogenesis *in vivo* and *in vitro* [68, 80].

Preeclampsia is a leading cause of maternal death. The maternal mortality rate associated with this complication is 1.5/100,000 live births [47]. Most maternal deaths are associated with complications of severe preeclampsia, such as cerebrovascular hemorrhage, renal or hepatic failure, and HELLP syndrome [47]. Thus, the understanding of severe preeclampsia is of major clinical importance. A growing body of evidence indicates that reduced uteroplacental blood flow in the mid-trimester and/or at the time of the onset of disease may play a role in the pathophysiology of preeclampsia [49, 75, 91]. Preeclampsia is also associated with insulin resistance [34, 85, 95], obesity [19, 82], hyperlipidemia [24, 45] and an exaggerated intravascular inflammatory response [8, 76, 78]. Moreover, patients with a history of preeclampsia are at increased risk for the development of several components of the metabolic syndrome later in life [23, 33, 81, 84]. Because low serum concentrations of adiponectin are strongly associated with these metabolic manifestations, it is tempting to hypothesize that adiponectin plays a role in the pathogenesis of preeclampsia, and specifically, in the metabolic derangements observed in this syndrome.

Both low [13, 15, 86] and high [27, 29, 37, 46, 59, 70] serum concentrations of adiponectin have been reported in preeclampsia. The results of a longitudinal study may explain these conflicting results. Patients destined to develop preeclampsia are characterized by first trimester low serum concentrations of adiponectin and high serum concentrations of this adipokine after diagnosis, during labor [16]. Similarly, there are limited data and inconsistent findings regarding the association between plasma adiponectin and the metabolic manifestations of preeclampsia, e.g., insulin resistance [16, 37], maternal weight and body mass index (BMI – a proxy of adipose tissue content) [13, 15, 59, 70, 86], and maternal mean blood pressure [15, 59, 61].

This study investigated the association between maternal plasma adiponectin concentrations and Doppler velocimetry of the uterine arteries in patients with severe preeclampsia. We chose to focus on patients with severe preeclampsia, because pathological alterations are more likely to be present in this subset of patients.

Materials and methods

Study design and population

A case-control study was conducted including patients with severe preeclampsia (n = 50) and women with normal pregnancies (n = 150). The inclusion criteria for normal pregnant women were: (1) singleton pregnancies; (2) no prior abnormal metabolic or medical conditions; (3) no obstetrical, maternal, or fetal complications during pregnancy and (4) delivery of a healthy neonate at term with a birthweight appropriate for gestational age ($>10^{th}$ and $<90^{th}$ percentile).

Definitions

Severe preeclampsia was defined as severe hypertension (diastolic blood pressure >110 mm Hg) plus mild proteinuria, or mild hypertension and severe proteinuria (a 24-h urine sample containing >3.5 g of protein or a urine specimen with >3+ protein by dipstick measurement on two occasions), or severe hypertension plus severe proteinuria [83]. Patients with an abnormal liver function test (aspartate aminotransferase >70 IU/L) plus thrombocytopenia (platelet count $<100{,}000/cm^3$) were also classified as having severe preeclampsia [2]. Normal pregnant women were matched by gestational age at enrollment with those of preeclampsia, in a proportion of 3:1.

Overweight women have a high risk of developing glucose intolerance, dyslipidemia and coronary heart disease [1, 72]. Thus, we subdivided our study groups using the first trimester BMI according to the definitions of the World Health Organization (Normal weight: BMI ≥18.5 to <25, and Overweight: BMI ≥25) [17].

Upon enrollment, pulsed-wave and color Doppler ultrasound examination of the uterine arteries was performed in 28 women with preeclampsia with a real-time scanner (ACUSON Corporation, Mountain View, CA, USA) equipped with a 3.5 MHz or a 5 MHz curvilinear probe. Abnormal uterine artery Doppler velocimetry was defined in the presence of a mean pulsatility index from both the left and the right uterine arteries above the 95^{th} percentile for gestational age and/or in the presence of bilateral diastolic notches in the Doppler waveforms of the uterine arteries [3].

Written informed consent was obtained from all participants prior to the collection of maternal blood samples. The utilization of samples for research purposes was approved by the Institutional Review Board. Many of these samples have been employed to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concentrations in non-pregnant women, normal pregnant women and those with pregnancy complications.

Sample collection and adiponectin immunoassay

Blood samples were collected during the third trimester into vials containing ethylenediaminetetra-acetic acid, centrifuged at $1300 \times g$ for 10 min at 4°C. The plasma obtained was stored at −70°C until analysis. Plasma adiponectin concentrations were determined with the Human Adiponectin ELISA (LINCO Research Inc, St Charles, MO, USA) according to the manufacturer's guidelines. The sensitivity of the assay was 0.91 ng/mL and the coefficients of intra- and inter-assay variation were 4.6% and 6.6%, respectively.

Statistical analysis

The body mass index (BMI) was calculated for every patient using the weight and height in the first trimester and at the time of sample collection according to the following formula: BMI = Weight (kg)/ [Height (m)]^2. Normality of the data distribu-

tion was determined by the Shapiro-Wilk test. Data were presented as mean ± SD for those parameters which were normally distributed and parametric tests were used for analysis. The plasma adiponectin concentrations were not normally distributed. Thus, non-parametric tests were used for analysis. The Mann-Whitney *U*-test was used to compare medians for continuous variables between two groups and the χ^2-test was used to test differences in proportions. The statistical software package SPSS 12 (SPSS Inc., Chicago, IL) was used. A P-value <0.05 was considered significant.

Results

Plasma adiponectin was detectable in all subjects. Table 1 displays the demographic and clinical characteristics of the study groups. No significant differences were observed in mean maternal age, first trimester BMI, and gestational age at sample collection between patients with severe preeclampsia and normal pregnant women. As expected, patients with severe preeclampsia delivered earlier than normal pregnant women (Table 1).

Adiponectin concentrations in patients with preeclampsia and normal pregnancies

Plasma adiponectin concentrations of normal pregnant women showed a significant negative correlation with the BMI at sample collection (Spearman's rho = –0.27, P = 0.001), and with first trimester BMI (Spearman's rho = –0.25, P = 0.001). This relationship was not observed in the group of patients with severe preeclampsia. Likewise, when the analysis included only overweight patients, there was no correlation between plasma adiponectin and BMI.

When all pregnant women were pooled together, those with severe preeclampsia had a higher median plasma concentration of adiponectin than that of normal pregnant women (median: 9978 ng/mL, range: 3989–23,220 vs. median: 7629 ng/mL, range: 2772–16,340, respectively; P < 0.001) (Figure 1).

Among women with uncomplicated pregnancies, those who were overweight had a lower median adiponectin concentration than those of normal weight (median: 6469 ng/mL, range: 2820–11,570 vs. median: 8480 ng/mL, range: 2772–16,340, respectively; P < 0.001) (Figure 2). In contrast, among patients with severe preeclampsia, overweight and normal weight women had similar median plasma adiponectin concentrations (median: 9632 ng/mL, range: 3989–23,220 vs. median: 10,315 ng/mL, range: 4098–21,560, respectively; P = 0.7) (Figure 2).

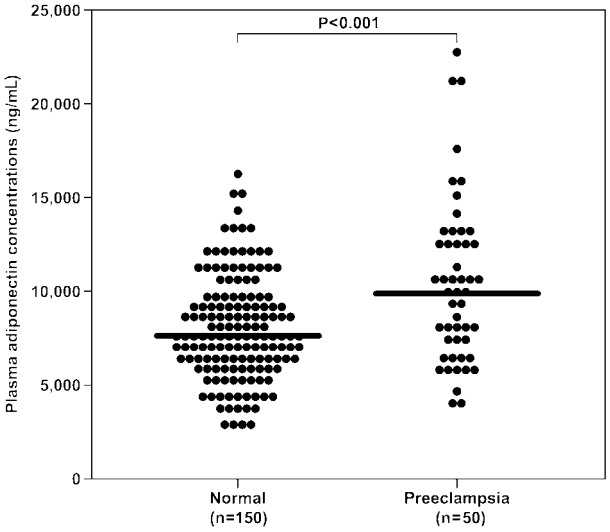

Figure 1 Adiponectin concentrations in normal pregnant women and patients with preeclampsia. Plasma adiponectin concentrations of women with preeclampsia showed increased concentrations compared to normal pregnant women.

Adiponectin concentrations in normal weight and overweight patients

Among normal weight women, there was no significant difference in the median plasma adiponectin concentration between those with severe preeclampsia and those with a normal pregnancy (median: 10,315 ng/mL, range: 4098–21,560 vs. median: 8480 ng/mL, range: 2772–16,340, respectively; P = 0.07) (Figure 2). However, when the analysis was confined to overweight women, the median plasma adiponectin concentration was significantly higher in patients with severe preeclampsia than in patients with normal pregnancy (median: 9632 ng/mL, range: 3989–23,220 vs. median: 6496 ng/mL, range: 2820–11,570, respectively; P = 0.001) (Figure 2).

Table 1 Demographics and clinical characteristics of the study groups.

	Control (n = 150)	Preeclampsia (n = 50)	P-value
Maternal age (mean ± SD, years)	20 ± 12	24 ± 9.9	NS
First trimester BMI (kg/m^2)	23.7 ± 3.7	24.9 ± 4.2	NS
Nulliparity (%, n)	36% (54/150)	62% (31/50)	< 0.001
Gestational age at sample collection (mean ± SD, weeks)	32 ± 3.6	32 ± 3.5	NS
Gestational age at delivery (mean ± SD, weeks)	39 ± 1.1	33 ± 3.1	< 0.001

Values are expressed as mean ± SD or percentage (proportion).
BMI: body mass index; SD: standard deviation; NS: not significant.

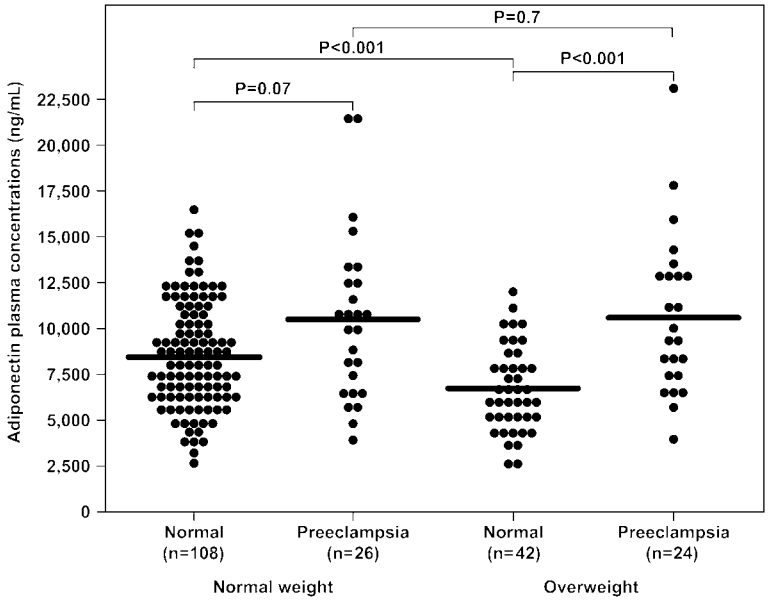

Figure 2 Comparison of adiponectin concentrations in normal and preeclamptic patients stratified by weight classification. Among women with uncomplicated pregnancies, those who were overweight had a lower median adiponectin concentration than those of normal weight. In contrast, among patients with severe preeclampsia, overweight and normal weight women had similar median plasma adiponectin concentrations.

Adiponectin and Doppler velocimetry studies in women with severe preeclampsia

Abnormal Doppler findings were detected in 22 of 28 patients with severe preeclampsia. There was no significant difference in the median maternal plasma adiponectin concentration between women with severe preeclampsia with high impedance to blood flow in the uterine arteries and those with normal impedance to blood flow.

Discussion

Principal findings of the study

(1) When all women were pooled together, those with severe preeclampsia had a higher median plasma adiponectin concentration than that of women with uncomplicated pregnancies; (2) Among women with uncomplicated pregnancies, those who were overweight had a lower median adiponectin concentration than those who were of normal weight. In contrast, among patients with severe preeclampsia, overweight and normal weight women, had similar adiponectin concentrations; (3) Abnormal Doppler studies in the uterine arteries were not associated with alterations in median adiponectin concentrations in patients with severe preeclampsia.

The physiological role of adiponectin

Adiponectin is a member of a growing group of proteins secreted by adipose tissue termed adipokines. Discovered in 1995–1996 [31, 50, 58, 77], adiponectin is a plasma protein produced abundantly by adipose tissue and which circulates at very high concentrations [31, 58, 77]. In contrast to other adipokines (e.g., leptin, TNF-α, and IL-6) adiponectin plasma concentrations are paradoxically lower in obese subjects than in normal weight. Moreover, weight reduction in obese individuals is accompanied by an increase in plasma adiponectin concentrations [20, 101], suggesting that adipose tissue inhibits adiponectin production.

Several lines of evidence indicate that adiponectin is an important regulator of insulin sensitivity and glucose homeostasis. Such evidence includes: (1) insulin resistance and plasma adiponectin concentrations are inversely correlated [30, 93]; (2) genetic variation in the adiponectin gene are associated with an increased risk of type 2 diabetes [26]; and (3) administration of recombinant adiponectin to both wild-type and insulin-resistant mice results in a significant decrease in plasma glucose concentrations [9, 22, 26]. The reduction in plasma glucose is independent of plasma insulin concentrations and has also been observed in mice with deficient insulin secretion, indicating that the effect of adiponectin is probably mediated by enhancing insulin function.

Adiponectin has anti-inflammatory effects, such as inhibition of endothelial nuclear factor-κB signaling [65],

phagocytic activity, and TNF-α production by macrophages [103]. Other studies have highlighted the antiatherogenic properties of adiponectin [62, 64, 65], as well as the angiogenic effect of this hormone [68, 80].

Adiponectin and vascular dysfunction

Adiponectin has been consistently shown to have protective effects on the vasculature. The following experimental evidence supports a role of adiponectin in the prevention of atherosclerosis: (1) adiponectin, at physiological concentrations, inhibits TNF-α-induced monocyte adhesion to human aortic endothelial cells, which has been implicated in atherogenesis [64, 65]; (2) adiponectin reduces the expression of various adhesion molecules, including vascular cell adhesion molecule-1 and E-selectin [64], which endothelial cells express in the early stages of atherosclerosis; (3) *in vitro* studies have demonstrated that human adiponectin inhibits macrophage-to-foam cell transformation, and macrophages exposed to adiponectin have a reduced intracellular cholesteryl ester content [62]; (4) adiponectin can suppress the proliferation of smooth muscle cells, alterations of which are important for the formation of atherogenic lesions [5]; (5) adiponectin accumulates in lesions of injured large vessels, but not in intact vascular walls [62]; and (6) an injury to arteries in adiponectin-knockout mice, but not to wild-type mice, results in severe neointimal thickening and increased proliferation of vascular smooth muscle cells [52]. Moreover, treatment with adiponectin may prevent this pathological condition [52]. Taken together, these findings indicate that adiponectin has a role, either direct or indirectly, in the regulation and integrity of the vascular system.

Adiponectin and Doppler studies

Few studies have addressed the relationships between plasma/serum adiponectin concentrations and Doppler studies of blood vessels. Serum adiponectin concentrations are positively correlated with coronary flow velocity reserve in healthy young men [39]. Coronary flow velocity reserve is a measure of coronary artery integrity and cardiac microvascular function, and it is defined as the ratio between coronary blood flow velocities before and during pharmacologically-induced vasodilatation [7, 18].

One study investigated the association between maternal plasma adiponectin concentrations and Doppler studies of the uterine arteries in 24 pregnant patients during the second trimester (18–21 weeks of gestation) [21]. Six patients had normal Doppler findings, whereas 18 patients had abnormal Doppler results, defined as bilateral notching and/or the mean PI of both arteries greater than the 90th percentile (mean PI >1.45) of the reference group. Mean plasma adiponectin concentrations were significantly higher in patients with abnormal Doppler findings than in those with normal findings. Eleven of the 18 patients with abnormal Doppler studies developed preeclampsia or intrauterine growth restriction later in the pregnancy. Of note, the mean plasma adiponectin concentration did not differ between patients with abnormal uterine blood flow who developed complications and those who did not [21].

Why is severe preeclampsia characterized by high plasma concentrations of adiponectin?

The findings of the present study indicate that the median plasma adiponectin concentration is higher in patients with severe preeclampsia than in normal pregnant women. Our findings are in agreement with some previous reports [27, 29, 37, 46, 59, 70], but contrast other observations, in which serum adiponectin concentration is lower in patients with preeclampsia than in normal pregnant women [13, 15, 86]. Differences in study design and sample size may contribute to the discrepancies among studies. Our study includes the largest number of patients with severe preeclampsia in the third trimester and normal pregnant women reported thus far. Previous reports have included patients with both mild and severe preeclampsia [13, 15, 86] and only in one study were all patients studied in the third trimester [86].

Insulin resistance, obesity, hyperlipidemia, and an exaggerated inflammatory response are associated with low adiponectin concentrations in the non-pregnant state. Preeclampsia, a disease of pregnancy, is associated with these conditions with accompanying high serum concentrations of adiponectin. The mechanisms underlying the paradoxical increase in serum adiponectin in patients with preeclampsia have not been elucidated. Several hypotheses have been proposed to explain this finding in preeclampsia:

Impaired renal function in patients with severe preeclampsia Because adiponectin is secreted into the urine [41], renal dysfunction may increase its serum concentrations. Indeed, patients with end-stage renal failure have higher serum concentrations of adiponectin than do normal subjects [41, 104]. However, there is no evidence to support this association in patients with preeclampsia. Moreover, although the subjects included in our study had proteinuria associated with preeclampsia, none had renal failure.

Overproduction and/or exaggerated secretion of adiponectin by adipocytes Preeclampsia is associated with increased concentrations of adipocyte-derived metabolites such as free fatty acids [32, 57], TNF-α [28, 94], IL-6 [48, 87], leptin [55, 56] and others. Thus, high adiponectin concentrations in preeclampsia may be another manifestation of adipocyte activation.

Adiponectin resistance in patients with preeclampsia It has been suggested that serum concentrations of adiponectin are increased as part of a compensatory mechanism for decreased expression of adiponectin receptors in muscles and adipose tissue [35, 36, 89]. Of note, insulin resistance, a well-known characteristic of preeclampsia, has been associated with decreased expression of adiponectin receptors [35]. However, there are no data to suggest that muscles or adipose tissue obtained from patients with preeclampsia have low expression of adiponectin receptors.

A counter-regulatory response aimed at moderating endothelial damage and metabolic alterations in preeclampsia The insulin sensitizing, anti-inflammatory, anti-atherogenic and angiogenic properties of adiponectin have led to the conclusion that it has a protective effect. Preeclampsia is closely linked to various metabolic changes, altered inflammatory responses, endothelial dysfunction and, recently, to an anti-angiogenic state [10, 40, 43, 51, 54, 69, 90]. Thus, given the noticeable overlap between the physiological functions of adiponectin and the pathological alterations in preeclampsia, it is tempting to postulate that increased adiponectin concentrations in patients with preeclampsia may represent a compensatory mechanism. Teleologically, increased concentrations of adiponectin can be beneficial to the mother by preventing excessive fat accumulation [70, 100] and to the fetus since lipolysis can increase triglyceride and free fatty acid availability. Conversely, adiponectin can also decrease maternal glucose production by the inhibition of hepatic gluconeogenesis [12] and, thus, negatively affect the fetus through decreased glucose availability.

Why are abnormal Doppler findings not accompanied by alterations in maternal plasma adiponectin?

The finding that patients with severe preeclampsia and an abnormal uterine arteries Doppler velocimetry have comparable median maternal plasma concentrations of adiponectin with those with normal uterine artery Doppler is novel. Of note, in this study, patients with abnormal Doppler velocimetry did not have a more severe clinical form of preeclampsia. The mean systolic and diastolic blood pressure, proteinuria, platelets count and liver function test did not differ significantly between the two groups. We hypothesize that high concentrations of plasma adiponectin in patients with preeclampsia are a counter regulatory phenomena and, thus, a reflection of the severity of the disease.

Obesity, pregnancy and preeclampsia – is adiponectin the missing link?

The association between an overweight state, obesity and preeclampsia is well documented [6, 11, 83, 92]. A 2 to 4-fold higher incidence of preeclampsia is reported in obese pregnancies [42, 79]. A meta-analysis of maternal BMI and preeclampsia showed that the risk doubled with each 5–7 kg/m^2 increase in BMI [60]. The underlying mechanisms for this relationship are still not completely understood, however, several mechanisms have been proposed: (1) excess adipose tissue can produce a hypoxic state by increasing the concentrations of glycosylated hemoglobin and decreasing the affinity for oxygen. This relative hypoxemia can cause abnormal placentation [38], (2) subclinical inflammation is one of the hallmarks of obesity, since an increase in body fat is associated with elevated cytokine levels and subclinical inflammation [25]. An exaggerated inflammatory response is one of the characteristics of preeclampsia, thus those patients with an inflammatory response in early pregnancy are prone to develop preeclampsia; (3) obese pregnant women have a 3 to 10-fold higher risk of preexisting hypertension or diabetes compared to those of normal weight [79], and both conditions are associated with an increased risk for preeclampsia.

This study indicates that in patients with severe preeclampsia, the median plasma adiponectin concentration did not differ between overweight and normal weight women. On the other hand, among women with normal pregnancy, an overweight state was associated with lower median plasma adiponectin concentrations. Thus, while patients who were overweight had the anticipated association with low plasma adiponectin concentrations, in normal pregnant women, this relationship was disrupted in severe preeclampsia. These findings suggest that adiponectin may have a role in the pathophysiology of preeclampsia and that the alterations in its concentrations in pregnant women with severe preeclampsia are not just a reflection of metabolic changes. Otherwise, excess adipose tissue should have some effect on the concentrations of this hormone. Consistent with this hypothesis is that the median adiponectin concentrations are significantly higher in overweight patients with preeclampsia than in overweight women with normal pregnancy. This finding may indicate that plasma adiponectin regulation is altered in severe preeclampsia as compared with normal pregnancy.

In conclusion, the results reported herein demonstrate that women with severe preeclampsia have higher plasma concentrations of adiponectin than those with normal pregnancy. We propose that these changes in plasma adiponectin concentration may be part of the compensatory mechanisms of the adipose tissue to the metabolically-altered, anti-angiogenic, pro-atherogenic state of severe preeclampsia.

Acknowledgements

Supported by the Intramural Research Program of the National Institute of Child Health and Human Development, NIH, DHHS.

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Received July 16, 2007. Accepted August 9, 2007.
Previously published online October 8, 2007.