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Maternal Serum Adiponectin at 11–13 Weeks of Gestation in Preeclampsia

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Key Words
Adiponectin · First trimester · Preeclampsia · Pregnancy-associated plasma protein-A · Uterine artery Doppler

Abstract
Objective: To determine whether the maternal serum levels of adiponectin in the first trimester of pregnancy are altered in cases that develop preeclampsia (PE) and whether the levels are related to pregnancy-associated plasma protein-A (PAPP-A) and uterine artery pulsatility index (PI). ***Methods:*** Serum adiponectin, PAPP-A and uterine artery PI were measured at 11–13 weeks in 90 cases that developed PE, including 30 that required delivery before 34 weeks (early PE) and 300 unaffected controls. The median adiponectin, PAPP-A and uterine artery PI multiple of the unaffected median (MoM) in the outcome groups were compared. ***Results:*** In both early PE and late PE, compared to controls, uterine artery PI MoM was increased (1.32 and 1.05 vs. 1.02) and PAPP-A MoM was decreased (0.61 and 0.84 vs. 1.00), whereas adiponectin MoM was increased in early PE but not in late PE (1.32 and 1.05 vs. 1.02). In the PE group, there was no significant association between adiponectin and PAPP-A or uterine artery PI. Serum adiponectin did not improve the performance of screening for PE provided by a combination of the maternal factors, uterine artery PI and serum PAPP-A. ***Conclusion:*** Serum adiponectin levels at 11–13 weeks are increased in women that develop early PE by a mechanism unrelated to impaired placentation.

Introduction

Adiponectin, an adipocyte-derived protein, is thought to play an important role in the regulation of insulin resistance, atherosclerosis and inflammatory responses and angiogenesis [1, 2]. Serum adiponectin concentration is inversely correlated with insulin resistance and is consequently reduced in obesity and type 2 diabetes mellitus [3–5]. There is some conflicting evidence that in pregnancy insulin resistance may be associated with increased risk for development of preeclampsia (PE) [6–8]. Studies examining maternal serum or plasma adiponectin in women with PE reported that the levels are usually increased, but in some studies the levels were decreased or not different from normal (see literature review below). In a longitudinal study of women who developed PE,

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plasma adiponectin levels at 9–13 weeks' gestation were decreased but during the clinical phase of the disease the levels were increased [9]. Another study investigating first-trimester adiponectin levels reported no significant differences between those that subsequently developed PE and controls [10].

There is extensive evidence that in some cases of PE, particularly those with early-onset severe disease requiring delivery before 34 weeks (early PE), there is impaired placental perfusion and function, manifested with increased pulsatility index (PI) in the uterine arteries and reduced maternal serum concentration of pregnancy-associated plasma protein-A (PAPP-A) [11–13].

The aim of this study is to investigate further whether in the first trimester of pregnancy maternal serum levels of adiponectin are altered in pregnancies that subsequently develop early and late PE and whether such changes are related to alterations in placental perfusion and function, reflected in uterine artery PI and serum levels of PAPP-A.

Methods

Study Population

This was a case-control study drawn from a large prospective observational study for early prediction of pregnancy complications in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. At this visit, which takes place at 11^{+0} to 13^{+6} weeks of gestation, we record maternal characteristics and medical history and perform combined screening for aneuploidies by measurement of the fetal crown-rump length and nuchal translucency thickness and maternal serum PAPP-A and free β-hCG [14, 15]. We also measure the uterine artery PI by transabdominal pulsed Doppler [12] and store serum and plasma at –80°C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital ethics committee.

In this study we measured maternal serum adiponectin in 90 cases that developed PE, including 30 that required delivery before 34 weeks (early PE) and 60 with late PE, and 300 unaffected controls who did not develop any hypertensive disorder of pregnancy and delivered a phenotypically normal neonate at term with weight appropriate for gestational age. Cases and controls were selected at random from our database of stored samples. None of the samples in this study were previously thawed and refrozen.

Outcome Measures

Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were recorded in our database. The obstetric records of all women with preexisting or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or gestational hypertension. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [16]. The systolic blood pressure should be 140 mm Hg or more and/or the diastolic blood pressure should be 90 mm Hg or more on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women and there should be proteinuria of 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).

Sample Analysis

Maternal serum adiponectin concentration was measured by a quantitative enzyme-linked immunoassay (ELISA) technique using a Quantikine Human Adiponectin ELISA kit (R & D Systems Europe Ltd., Abingdon, UK). The lower limit of detection of the assay was 0.246 ng/ml. The intra-assay coefficient of variation (CV) ranged from 2.5% to 4.7% and the inter-assay CV ranged from 5.8% to 6.9%. All samples were analyzed in duplicate and those with a CV exceeding 10% were reanalyzed.

Literature Search

We searched MEDLINE and EMBASE from January 1995 to September 2010 to identify studies reporting on the relationship between maternal serum or plasma adiponectin concentration and PE.

Statistical Analysis

The distribution of serum adiponectin was made Gaussian by square root (sqrt) transformation and normality was confirmed using the Kolmogorov-Smirnov test ($D = 0.03$, $p = 0.20$). The distributions of PAPP-A and uterine artery PI were made Gaussian after logarithmic transformation. Multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of sqrt adiponectin in the unaffected group. Each value in the unaffected and PE group was then converted into multiple of the unaffected median (MoM) after adjustment for those characteristics found to be significant in the multiple regression analysis. In each case and control the measured PAPP-A and uterine artery PI were converted into MoMs after adjustment for gestation, maternal age, racial origin, maternal weight, smoking, parity, and method of conception as previously described [17, 18]. The Mann-Whitney U test was used to compare median MoM values of adiponectin, PAPP-A and uterine artery PI between the outcome groups. Regression analysis was used to determine the significance of association of maternal serum adiponectin with PAPP-A and uterine artery PI in the outcome groups. Maternal factor-derived a priori risks for PE were determined as previously described and were then logarithmically transformed [17]. Logistic regression analysis was used to determine if the log-transformed maternal factor-derived a priori risks, sqrt adiponectin MoM, $\log_{10}$ PAPP-A MoM and $\log_{10}$ uterine artery PI MoM had a significant contribution in predicting PE. The detection and false-positive rates were calculated as the respective proportions of PE

Table 1. Maternal and pregnancy characteristics in the outcome groups

Maternal characteristics	Unaffected controls (n = 300)	Early PE (n = 30)	Late PE (n = 60)
Maternal age[1], years	32.2 (26.9–35.6)	31.6 (25.5–36.5)	32.2 (27.1–36.9)
Maternal weight[1], kg	63.3 (57.0–70.0)	76.5 (62.8–92.8)*	74.0 (63.3–84.8)*
Maternal BMI[1]	23.1 (21.3–26.3)	28.8 (24.2–34.0)*	26.9 (23.2–31.6)*
Crown-rump length[1], mm	64.0 (58.7–69.6)	62.5 (56.3–69.6)	61.3 (58.0–68.9)
Gestation at sampling[1], weeks	12.4 (12.1–12.9)	12.5 (12.1–12.9)	12.4 (12.1–12.9)
Racial origin, n (%)			
Caucasian	189 (63.0)	10 (33.3)	30 (50.0)
African	86 (28.7)	15 (50.0)*	21 (35.0)
South Asian	10 (3.3)	4 (13.3)*	6 (10.0)*
East Asian	6 (2.0)	0 (0)	1 (1.7)
Mixed	9 (3.0)	1 (3.3)	2 (3.3)
Parity, n (%)			
Nulliparous	148 (49.3)	16 (53.3)	36 (60.0)
Parous – no previous PE	145 (48.4)	11 (36.7)	17 (28.3)*
Parous – previous PE	7 (2.3)	3 (10.0)*	7 (11.7)*
Family history of PE, n (%)	17 (5.7)	4 (13.3)*	6 (10.0)
Cigarette smokers, n (%)	28 (9.3)	1 (3.3)	4 (6.7)
Conception, n (%)			
Spontaneous	296 (98.7)	28 (93.3)	55 (91.7)
Assisted	4 (1.3)	2 (6.7)*	5 (8.3)*
History of chronic hypertension, n (%)	0	4 (13.3)*	4 (6.7)*
Birth weight[1], kg	3.4 (3.2–3.7)	1.2 (1.1–1.6)*	3.1 (2.5–3.5)*

Comparisons between outcome groups (χ^2 and Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables): * $p < 0.05$. IQR = Interquartile range.

[1] Values represent median with the IQR in parentheses.

(detection rate) and unaffected pregnancies (false-positive rate) with MoM values above given cutoffs. The performance of screening was determined by receiver-operating characteristic curve analysis.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

The maternal characteristics of each of the outcome groups are compared in table 1. In both the early- and late-PE groups, compared to controls, the median maternal weight was higher, more women had PE in their previous pregnancies, required assisted conception techniques and had chronic hypertension.

Unaffected Group

Multiple regression analysis in the unaffected group demonstrated that for sqrt adiponectin significant independent contribution was provided by maternal age, weight, smoking status, African and South Asian racial origin but not by fetal crown-rump length ($p = 0.459$), method of conception ($p = 0.637$) or parity (0.219):

sqrt adiponectin expected = 130.19 + 0.74 × maternal age in years + (–18.24 if the racial origin was African, –31.89 if South Asian, 0 if Caucasian, East Asian or Mixed) – 0.53 × maternal weight in kg – 10.38 if cigarette smoker; $R^2 = 0.223$, $p < 0.0001$.

In each patient we used this formula to derive the expected sqrt adiponectin and then expressed the observed value as a MoM of the expected. In the control group, there was no significant association between sqrt adiponectin MoM and $\log_{10}$ PAPP-A MoM ($p = 0.094$) or $\log_{10}$ uterine artery PI MoM ($p = 0.504$).

PE Group

In both the early- and late-PE groups, compared to unaffected controls, median uterine artery PI MoM was increased and PAPP-A MoM was decreased (table 2). In the early-PE group, but not in late PE, the median adipo-

Table 2. MoM (interquartile range) for maternal serum adiponectin, PAPP-A and uterine artery PI in the outcome groups

Variable	Unaffected controls (n = 300)	Early PE (n = 30)	Late PE (n = 60)
Adiponectin			
ng/ml	12,035 (8,595–17,085)	12,692 (7,688–16,350)	11,459 (7,748–15,798)
MoM	1.02 (0.70–1.29)	1.32 (0.91–1.72)*	1.05 (0.73–1.66)
PAPP-A			
mU/ml	3.07 (2.03–4.76)	1.51 (0.77–4.00)	2.18 (1.49–3.38)
MoM	1.00 (0.71–1.39)	0.61 (0.34–1.15)*	0.84 (0.55–1.13)*
Uterine artery PI			
Unit	1.65 (1.36–1.98)	2.10 (1.69–2.67)	1.85 (1.43–2.24)
MoM	1.02 (0.83–1.21)	1.32 (1.03–1.71)*	1.15 (0.86–1.35)*

Comparisons between outcome groups by Mann-Whitney U test. Significance level: * $p < 0.05$.

Table 3. Detection rates of early PE at fixed false-positive rates (FPR) of 5 and 10% and comparison of screening performance by receiver-operating characteristic curve analysis in screening by maternal factors, maternal serum adiponectin, PAPP-A, uterine artery PI and by their combination

Screening test	AUROC (95% CI)	FPR 5%	FPR 10%
Maternal factors	0.761 (0.672–0.850)	33.3	46.7
Maternal factors plus			
Adiponectin	0.768 (0.677–0.860)	43.3	46.7
PAPP-A	0.799 (0.709–0.888)	46.7	50.0
Uterine artery PI	0.855 (0.783–0.926)	56.7	63.3
Maternal factors, PAPP-A, uterine artery PI	0.872 (0.804–0.941)	53.3	66.7

AUROC = Area under receiver-operating characteristic curve.

nectin MoM was increased. In the PE group, there was no significant association between sqrt adiponectin MoM and $\log_{10}$ PAPP-A MoM ($p = 0.659$), $\log_{10}$ uterine artery PI MoM ($p = 0.583$), gestation at delivery ($p = 0.708$) or birth weight percentile ($p = 0.331$). In contrast, there was a significant association between both PAPP-A MoM and uterine artery PI MoM with gestation at delivery ($r = 0.298$, $p = 0.004$ and $r = -0.336$, $p = 0.001$, respectively) and birth weight percentile ($r = 0.224$, $p = 0.034$ and $r = -0.353$, $p = 0.001$, respectively).

Logistic regression analysis demonstrated that in the prediction of early PE there were significant contributions from $\log_{10}$-transformed maternal factor-derived a priori risk [odds ratio (OR) 11.6, 95% confidence interval (CI) 4.2–32.0, $p < 0.0001$], $\log_{10}$ uterine artery PI MoM (OR $7.0E^3$, 95% CI 109.8–$4.5E^5$; $p < 0.0001$) and $\log_{10}$ PAPP-A MoM (OR 0.10, 95% CI 0.02–0.55; $p = 0.008$).

The patient-specific risk for early PE was calculated from the formula: odds/(1 + odds), where odds = e^Y and Y was derived from multivariate logistic regression analysis of the disease-specific maternal factor-derived a priori risk, uterine artery PI MoM and PAPP-A MoM. The estimated detection rates of early PE at fixed false-positive rates of 5 and 10% and their respective areas under the receiver-operating characteristic curves in screening by maternal factor-derived a priori risk, and by the combination of maternal factors with adiponectin, PAPP-A, uterine artery PI are shown in table 3. The estimated detection rate of screening for early PE by serum adiponectin independently was 43.3 and 46.7% at respective false-positive rates of 5 and 10%. The addition of adiponectin

Table 4. Studies reporting on the association between maternal serum or plasma adiponectin concentration (mean or median) and PE

Author	Assay	Gestation weeks	PE		Controls		p value
			n	adiponectin μg/ml	n	adiponectin μg/ml	
Before PE							
D'Anna et al., 2005 [26]	ELISA	9–13	34	6.6	82	13.0	0.001
D'Anna et al., 2006 [9]	ELISA	9–13			36	14.8	
Early-onset PE			16	11.1			0.3
Late-onset PE			20	6.2			<0.001
Odden et al., 2006 [10]	RIA	8–13	43	13.4	86	15.1	0.22
During PE							
Ramsay et al., 2003 [34]	RIA	32–39	15	21.6	30	14.7	0.01
Haugen et al., 2006 [38]	RIA	31–39	15	18.3	23	12.2	0.011
Hendler et al., 2005 [39]	RIA	33–40	77	11.5	22	9.6	0.005
Kajantie et al., 2005 [40]	ELISA	29–39	22	10.3	15	7.9	0.04
Naruse et al., 2005 [41]	RIA	28–40	15	17.5	34	9.3	<0.01
D'Anna et al., 2006 [9]	ELISA	33–40	36	9.2	36	7.8	0.04
O'Sullivan et al., 2006 [42]	RIA	35–37	12	22.4	10	18.6	NS
Takemura et al., 2007 [43]	ELISA	31–39	14	11.2	14	6.8	0.04
Cortelazzi et al., 2007 [44]	ELISA	20–37	9	5.0	33	9.5	0.008
Nien et al., 2007 [36]	ELISA	>28	50	10.0	150	7.6	<0.001
Ouyang et al., 2007 [45]	ELISA	36–38	53	0.007	20	0.012	<0.01
Fasshauer et al., 2008 [46]	ELISA	22–35	16	12.2	20	6.8	<0.01
Savvidou et al., 2008 [35]	ELISA	23–25	13	8.8	44	10.8	0.3
Mazaki-Tovi et al., 2009 [47]	ELISA	29–38	111	5.0	225	6.4	<0.001
Herse et al., 2009 [48]	ELISA	30–36	32	0.033	30	0.038	<0.001
Avci et al., 2010 [49]	RIA	–	20	15.6	20	8.4	<0.001
Mori et al., 2010 [50]	ELISA	28–31	15	7.3	17	10.2	<0.01
Masuyama et al., 2010 [25]	ELISA						
Early-onset PE		25–29	17	14.0	17	10.5	0.13
Late-onset PE		34–39	38	36.8	38	12.5	0.003

RIA = Radioimmunoassay; ELISA = enzyme-linked immunosorbent assay.

did not improve the detection rate of early PE that was achieved by a combination of maternal factor-derived a priori risk, uterine artery PI and serum PAPP-A.

Literature Search

The literature search identified 20 studies reporting on the association between maternal serum or plasma adiponectin concentration and PE (table 4). In 11 of the 18 studies investigating pregnancies with the clinical features of PE the levels of adiponectin were higher than in normotensive controls, in 5 studies they were lower and in 2 they were not significantly different. In 2 of the 3 studies reporting on first-trimester levels of adiponectin in women who subsequently developed PE the levels were decreased and in the 3rd the levels were not significantly different from normal controls. In some of the studies adiponectin was measured by radioimmunoassay but in most studies, especially after 2006, an ELISA technique was used.

Discussion

This study has demonstrated that maternal serum adiponectin concentration in the first trimester is significantly higher in women who develop early PE than in women who remain normotensive or develop late PE. The altered maternal serum levels were unrelated to the biophysical and biochemical markers of impaired placental

perfusion and function manifested in uterine artery PI and serum PAPP-A, respectively. There is emerging evidence that early PE is due to impaired placental perfusion and late PE is a consequence of a maternal metabolic disorder. In this respect we expected higher adiponectin levels in late PE rather than early PE [6–8, 11–13].

In unaffected pregnancies maternal serum adiponectin concentration increased with maternal age, decreased with weight and it was lower in women of African and South Asian racial origin than in Caucasians and in cigarette smokers than in nonsmokers. These findings are compatible with results of previous studies in nonpregnant individuals. A poor adipocytokine profile was observed in women of African and South Asian racial origin [19, 20] and in cigarette smokers [21, 22]. Studies in pregnancy have shown decreased adiponectin levels with smoking and in women of African, South Asian and East Asian racial origin [23, 24].

Our finding of high serum adiponectin in pregnancies that subsequently developed PE is compatible with the results of most previous studies examining women with established disease. However, only one of such previous studies distinguished between early and late PE and reported that the levels of adiponectin were increased only in late PE [25]. Three previous studies examined first-trimester maternal levels in women who subsequently developed PE and 1 reported no significant differences in adiponectin levels between cases and controls [10], whereas 2 studies demonstrated that in the PE group the levels were decreased [9, 26]. One of the studies examined differences between early and late PE and reported that significant reduction in plasma adiponectin was observed only in the cases that developed late PE [9].

In pregnancies that develop PE, impaired perfusion of the placenta is thought to cause hypoxia-related trophoblastic cell death and the release of inflammatory factors, which in turn cause endothelial dysfunction and the development of the clinical symptoms of the disease [27–31]. Adiponectin may be a useful marker of endothelial function as it attenuates the excessive inflammatory response in the vascular wall [32] and it also increases nitric oxide production by increasing the expression of endothelial nitric oxide synthase [33]. It has been suggested that the increased serum adiponectin in PE may be the consequence of a compensatory mechanism for decreased expression of adiponectin receptors in muscles and adipose tissue [34]. The elevated adiponectin concentrations may suppress the expression of adhesion molecules in vascular endothelial cells and cytokine production from macrophages, thus inhibiting the inflammatory processes that occur in PE. However, in our study there was no significant association between uterine artery PI and serum adiponectin in either the PE group or the controls. Similarly, 2 previous studies found no correlation between serum adiponectin concentration and uterine artery PI in the second trimester of pregnancy [35, 36]. In contrast, Fasshauer et al. [37] reported that in women with high impedance to flow in the uterine arteries at 18–23 weeks, serum adiponectin was increased, irrespective of whether the pregnancy outcome was normal or complicated by PE and/or fetal growth restriction.

Irrespective of the underlying mechanism for the observed increase in serum adiponectin at 11–13 weeks in pregnancies that subsequently develop early PE, measurement of this metabolite does not improve the prediction of PE provided by a combination of the maternal factors uterine artery PI and serum PAPP-A.

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