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Circulating levels of adiponectin and leptin at 23-25 weeks of pregnancy in women with impaired placentation and in those with established fetal growth restriction

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Short title: Adiponectin and leptin in impaired placentation

Key Words: adiponectin, leptin, Doppler, pre-eclampsia, fetal growth restriction, maternal

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Abstract

Adiponectin and leptin, two adipose tissue-derived proteins, have been reported to be elevated in women with established pre-eclampsia (PE). The aim of the current study was to investigate whether alterations of adiponectin and leptin levels predate the development of PE and fetal growth restriction (FGR) in women at increased risk of these complications, as assessed by Doppler examination of the uterine arteries during the second trimester of pregnancy. We also sought to investigate the circulating levels of adiponectin and leptin in women with established severe, early onset FGR. The study included three groups of pregnant women at 23-25 weeks: Group A (n=44) with normal uterine artery Doppler waveforms, Group B (n=49) with abnormal Doppler waveforms and normal fetal growth at the time of the examination and Group C (n=15) with established, severe FGR and abnormal Doppler. All women had plasma adiponectin and leptin measured by sensitive immunoassays. In Group B, 19 women had normal outcome, 17 delivered FGR infants and 13 developed PE. The women who developed PE delivered smaller babies earlier compared to women with normal outcome ($p<0.001$). There were no significant differences in adiponectin levels between any of the groups (overall $p=0.3$). Leptin concentrations, expressed as multiples of the median (MoM) of Group A, were higher in women of Group C i.e. established severe FGR at 2.5 (1.2-2.7) MoM's (overall $p<0.001$) compared to all the other groups and subgroups. In summary, we found that in pregnancies complicated by severe, early onset FGR maternal plasma concentration of leptin is twice as high as in normal pregnancies. However, the second trimester levels of maternal plasma adiponectin and leptin in pregnancies that subsequently develop PE and/or FGR are not significantly different from normal and consequently it is unlikely that these markers will be useful as predictors of these pregnancy complications.

Introduction

Pre-eclampsia (PE) is a major cause of maternal and perinatal mortality and morbidity [1]. Although its exact pathophysiology remains elusive, the widely accepted model is that of a hypoxic placenta, which releases factor(s) in the maternal circulation that cause endothelial dysfunction, which results in hypertension and proteinuria [2]. Inflammatory upregulation and adipocyte lipolysis are also probably involved [3-7]. Fetal growth restriction (FGR), another major cause of perinatal morbidity and mortality, seems to share the same pathophysiology with PE. In both conditions there is histological evidence of impaired trophoblastic invasion of the uterine spiral arteries, and Doppler evidence of increased impedance to flow in the uterine arteries [8,9].

Adiponectin and leptin are two adipose tissue-derived proteins with important metabolic effects. The plasma concentration of adiponectin, which is derived mainly from adipose tissue and possibly from placenta, is inversely correlated with insulin resistance and is consequently reduced in obesity and in type 2 diabetes but it is paradoxically increased in PE [10-16].

Leptin, a protein regulating body weight, is produced in large amounts by adipocytes and human placental trophoblasts [17]. Leptin gene expression in the placenta is augmented in severe PE and it has been suggested that placental hypoxia may play a role in this augmentation [18]. Maternal leptin levels have also been reported to be elevated in women with established severe PE, and in women destined to develop the condition but not in women who subsequently delivered FGR infants [6,19].

The aim of the current study was to investigate whether alterations of adiponectin and leptin levels predate the development of PE and fetal growth restriction (FGR) in women at increased risk of these complications, as assessed by Doppler examination of the uterine arteries during the second trimester of pregnancy. We also sought to investigate the circulating levels of adiponectin and leptin in women with established severe, early onset FGR.

Methods

Study Participants

This was a retrospective study, which included three groups of healthy women with singleton pregnancies at 23-25 weeks of gestation. They were all recruited

consecutively from the Ultrasound Department of King's College Hospital, where color Doppler examination of the uterine arteries is routinely performed, as previously described [9]. Group A included 44 women with normal uterine artery Doppler waveforms and normally grown fetuses. Group B, included 49 with abnormal uterine artery Doppler waveforms (presence of early diastolic notch bilaterally) and normally grown fetuses at the time of the examination, and Group C included 15 women with estimated fetal weight <5th centile for the gestation at the time of the examination; all of them had abnormal uterine artery Doppler waveforms, 11 of these fetuses had absent or reversed end-diastolic flow in the umbilical artery and 8 of these fetuses had reduced amniotic fluid. The fetal weight was estimated from the sonographic measurements of head circumference, abdominal circumference and femur length [20].

Maternal age, ethnic group, smoking status, parity, body mass index (BMI) and blood pressure (BP) were recorded. BP was measured in the right arm with the subject seated using an ambulatory blood pressure monitor (SpaceLabs Medical 90207, WA, US). Three measurements were taken and averaged. The study was approved by the Local Research Ethics Committee and all women gave written informed consent.

Analysis of adiponectin and leptin

All women had a venous blood sample taken and plasma was separated by centrifugation, frozen and stored at -80°C. Plasma adiponectin concentration was determined using ELISA (R&D systems, Minneapolis, US). The intra-assay and the interassay coefficients of variability were each 7.5%. The minimal detectable concentration was 0.01 µg/ml. Leptin was measured by an in-house radioimmunoassay that was validated thoroughly against the commercially available Linco assay [21]. In this case the intra-assay and inter-assay coefficients of variation were <7% and <10%, respectively, over the sample concentration range and the detection limit of the assay was 0.5 ng/ml.

Definition of Clinical Outcome

Information on pregnancy outcome, including gestation at delivery, birth weight (BW) and sex were obtained from examination of individual patient hospital records.

The diagnosis of PE was made according to the criteria of the International Society for the Study of Hypertension in Pregnancy. Under this classification, PE is defined as diastolic BP of at least 110 mm Hg on one occasion or diastolic BP of at least 90 mmHg on two consecutive occasions more than four hours apart, in combination with proteinuria (≥ 300 mg total protein in a 24-hour urine collection or, if this was not available, $\geq +2$ proteinuria by dipstick on two consecutive occasions at least four hours apart) developing after 20 weeks of gestation in previously normotensive women [22]. The diagnosis of FGR was based on the delivery of an infant with BW below the 5th percentile for gestation and sex [23].

Statistical analysis

Normality of the distribution of continuous data was examined with the Shapiro-Wilk test. Logarithmic transformation was performed for non-normally-distributed data. Descriptive data were expressed as mean \pm SD or as median (interquartile range) for normally and non-normally distributed data respectively. Comparisons between groups were performed using one-way analysis of variance followed by the Bonferroni post-hoc test, Kruskal-Wallis or Mann-Whitney as appropriate. The chi-square (χ^2) test was used to compare categorical variables among groups. In order to compare the levels of adiponectin and leptin in the different groups of women, adjusting for BMI, smoking and ethnic group, variables that are known determinants of both adiponectin and leptin [10,21,24-26], the following steps were taken:

1. The patients were subdivided into five groups according to the outcome of pregnancy: Group A: normal Doppler-normal outcome, Group B: abnormal Doppler-normal outcome, abnormal Doppler-development of FGR, abnormal Doppler-development of PE and Group C: abnormal Doppler-established FGR.
2. Linear regression analysis was used to determine which factors among the maternal demographic and clinical characteristics were significant predictors of the adiponectin and leptin levels in Group A.
3. The distribution of adiponectin and leptin levels, expressed as multiples of the median (MoM) of Group A, were determined for all the subgroups of Group B and Group C.

4. Due to the small number of patients, a non-parametric test, followed by post-hoc tests, was used to compare the MoM's of adiponectin and leptin in the different groups.

Power analysis indicated that a sample of 13 cases of PE and 44 controls would have a power over 80%, with an alpha .05 (2-tails), for the detection of a mean difference of 6.9µg/ml in the plasma adiponectin concentration and a mean difference of 11.6 ng/ml in the plasma leptin concentration between the two groups. The effect size was estimated from previous publications [12,19].

Results

Characteristics of the study participants

In Group A (normal Doppler findings, n=44), none of the women developed PE and all of them delivered babies of appropriate size. The women in Group B (abnormal Doppler findings and normal fetal growth at presentation, n=49) were sub-classified into three groups according to the outcome of pregnancy; those with no complications (n=19, 39%), those who delivered FGR infants (n=17, 35%) and those who developed PE (n=13, 26%). In Group C (abnormal Doppler findings and FGR at presentation, n=15), three women had PE and in nine cases there was intra-uterine or early neonatal death. The demographic and clinical characteristics of the groups, obtained at study entry, are presented in Table I. Systolic and diastolic BP's were significantly higher in women who eventually developed PE and in women with established FGR. This was the case even after exclusion of the three women in Group C that developed PE (data not shown).

Levels of adiponectin and leptin

The multiple regression equations for adiponectin and leptin levels in Group A are:

Adiponectin= 17.008- 0.264 X BMI (kg/m²) + (3.434 if smokers, 0 if non-smokers) + (1.599 if Caucasian, -0.910 if Afro-Caribbean, 0 if any other ethnic group); R² =0.305, p=0.006.

Leptin= -27.915 + 2.744 X BMI (kg/m²) – (4.626 if smokers, 0 if non-smokers) – (15.699 if Caucasian, 18.472 if Afro-Caribbean, 0 if any other group); R²=0.665, p<0.001.

For each patient and using the formulas above, we calculated the expected adiponectin and leptin level and the ratio of the observed to expected value. The concentrations of

adiponectin and leptin (expressed as raw values and as MoM's of the unaffected Group A) in the different groups of women are shown in Table 2. All groups of women studied had similar adiponectin levels, expressed as MoM's of the unaffected Group A (overall $p=0.3$). Leptin concentrations, expressed as MoM's of the unaffected Group A, were higher in women with established, early onset FGR (Group C; overall $p<0.001$, Figure 1). Post-hoc analyses revealed that women of Group C had higher levels of leptin compared to all the other groups and subgroups. This was the case, even after exclusion of the three women in this group that developed PE.

Discussion

The study has demonstrated that maternal levels of adiponectin during the second trimester of pregnancy do not seem to predate the development of PE and/or FGR in women at risk of these complications, as assessed by Doppler examination of the uterine arteries. Furthermore, maternal adiponectin levels are not different between women with established, early onset, severe FGR and women with uncomplicated pregnancies.

We have previously shown that women who subsequently develop PE have evidence of endothelial dysfunction at 23-25 weeks, as assessed by flow-mediated dilatation of their brachial artery [27]. Adiponectin may be considered as a useful marker of endothelial function as it attenuates the excessive inflammatory response in the vascular wall [28] and it also increases nitric oxide production by activating and increasing the expression of the endothelial nitric oxide synthase enzyme [29].

In the current study, the lack of difference in the adiponectin levels between women who subsequently develop PE and/or FGR compared to those with uncomplicated pregnancies may suggest that either adiponectin does not play a fundamental role in the development of PE or that the second trimester of pregnancy is not a good time to use adiponectin as a marker of PE. Studies have demonstrated that adiponectin concentration decreases throughout normal pregnancy [30] and that its level, in women who subsequently develop PE, is lower in the first and higher in the third trimester compared to women with uncomplicated pregnancies [12,31]. Taken together these findings indicate that in women who develop PE later on in pregnancy, the adiponectin levels in mid-pregnancy may overlap with those of the women with uncomplicated pregnancies. Consequently, despite the fact that adiponectin may play a role in the development of PE, it is unlikely to be a useful

biomarker for it in mid-pregnancy. In line with this, we were not able to demonstrate a significant difference in the adiponectin concentration between women with established FGR and women with normal pregnancies. This was the case even after exclusion of the three women in this group that had PE developed.

Another finding of the current study is that maternal leptin concentrations do not seem to predate the development of PE and/or FGR. However, its levels were increased in women with established FGR.

Leptin is a peptide hormone, which was introduced as an adipocyte-derived messenger of energy metabolism [32]. Maternal leptin concentration has been reported to be elevated in women with established, severe PE and especially in those who delivered FGR infants as well [18,33]. Longitudinal studies have demonstrated that elevations of maternal leptin levels occur weeks prior to the clinical manifestation of PE [6,19]. However, these studies did not comprehensively adjust for potential differences in maternal weight, smoking and ethnic group, factors that are strongly linked to leptin levels [21,25,26]. In the current study, we expressed the levels of adiponectin and leptin as MoM's of the unaffected groups and consequently we were able to adjust for all the potential confounders. We were unable to detect any difference in maternal leptin levels between women that subsequently developed PE and those with uncomplicated pregnancies and this is in accordance with other studies [34].

Maternal levels of leptin in women with established, early onset FGR were twice as high as in the other groups. Usually FGR is defined as a fetus below a certain weight percentile. This definition includes fetuses with a low genetic growth potential, that do not have a placental problem, and fetuses that do not reach their growth potential due to placental insufficiency. All the FGR pregnancies (Group C) included in our study were characterised by impaired placentation. However, it has to be mentioned that others did not find elevated maternal levels of leptin in FGR pregnancies [35,36]. The reason for this inconsistency could be the above mentioned difficulties to define FGR. Certainly, we cannot exclude that some of the FGR pregnancies would have had PE developed if they did not have their pregnancies terminated. The tendency of elevated maternal BP in FGR pregnancies when compared to controls, even after exclusion of those women who definitely developed PE, indicate that some of the FGR pregnancies were possibly close to the threshold of PE and this has to be considered in the interpretation of the data. Therefore, it could

be stated that although leptin may play a role in the clinical manifestation of established FGR, it is unlikely that this adipokine plays a fundamental role in the initiation of this condition and therefore it is unlikely that leptin alone would be a useful biochemical marker in screening for the development of either PE or FGR.

In summary, maternal levels of adiponectin and leptin during the second trimester of pregnancy do not seem to predate the development of PE and/or FGR and consequently it is unlikely that these biochemical markers will be useful to allow improved prediction of the above pregnancy disorders. However, elevated levels of maternal leptin, but not adiponectin, seem to characterise pregnancies complicated by severe, early onset FGR.

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Figure legends

Figure 1. Box and whisker plot comparing leptin levels, expressed as Multiples of the Median (MoM's) of the unaffected Group A, at 23-25 weeks of gestation between the different patient groups: Group A (n=44), women with normal Doppler and normal outcome, Group B (n=49), with abnormal Doppler and either normal outcome (n=19), or subsequent development of fetal growth restriction (FGR) (n=17), or subsequent development of pre-eclampsia (PE) (n=13), and Group C (n=15) with abnormal Doppler and established FGR. Boxes represent interquartile range, where the line represents the median. Whiskers at top and bottom of the box represent the highest and lowest values. Group C had the highest leptin levels compared to all the other groups (*P<0.001).

Table 1 Demographic, clinical maternal and neonatal characteristics in each group of women, according to the outcome of pregnancy. Group A: women with normal Doppler examination and normal outcome, Group B: women with abnormal Doppler examination, with subgroups according to the pregnancy outcome, Group C: women with established fetal growth restriction at 23-25 weeks of gestation. All statistical comparisons were performed with Group A.

Group	Group A		Group B		Group C
	Normal outcome (n=44)	Normal outcome (n=19)	Development of FGR (n=17)	Development of PE (n=13)	Established FGR (n=15)
Maternal age (years)	30 (25-33)	27 (21-31)	28 (21-34)	28 (23-32)	35 (25-37)
Smokers	9 (20%)	2 (10.5%)	3 (17.6%)	4 (31%)	6 (40%)
Nulliparity	24 (54%)	11 (58%)	14 (82.3%)	10 (77%)	11 (73%)
Body mass index (kg/m ²)	27 (24-30)	26.5 (23.5-31)	26 (22-26.5)	27 (25-32)	26 (23-28)
Ethnic group					
White (%)	23 (52)	9 (47.4)	8 (47.1)	8 (53.8)	10 (66.7)
Afro-Caribbean (%)	18 (41)	9 (47.4)	6 (35.3)	4 (30.8)	4 (26.7)
Others (%)	3 (7)	1 (5.3)	3 (17.6)	2 (15.4)	1 (6.7)
Systolic Blood Pressure (mmHg)	114±8	114±7	111±7	123.5±8*	127±9†
Diastolic Blood Pressure (mmHg)	66±6.6	65±16	64±4.5	75±8‡	79±6†
Gestation at delivery (wk)	39 (38.6-40.4)	41 (39-41)	40 (37-40.5)	36 (31.3-37) †	29 (27-29) †
Birth weight (gr)	3323±513	3254±407	2300±596†	2034±662 †	570±156†

*P=0.005, †P=<0.001, ‡P=0.02

FGR: fetal growth restriction, PE: pre-eclampsia

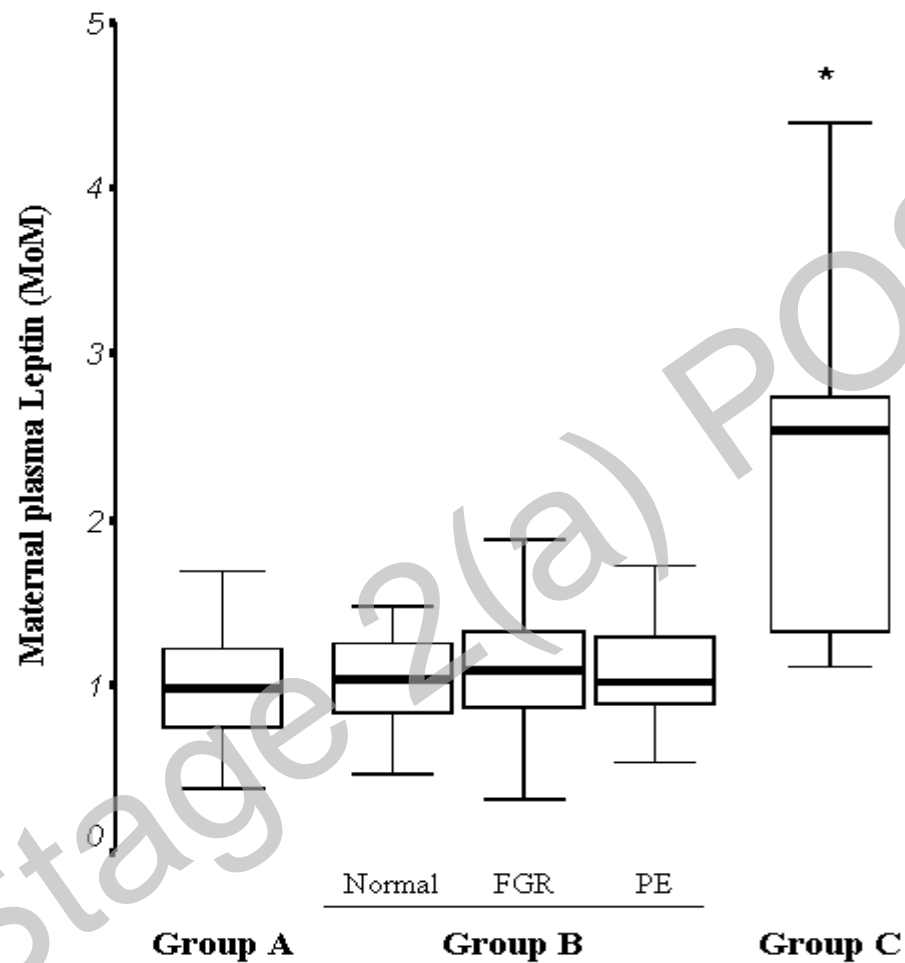
Table 2 Levels of adiponectin and leptin, expressed as raw values and as MoM's of the unaffected Group A, in each group of women according to the outcome of pregnancy. Group A: women with normal Doppler examination and normal outcome, Group B: women with abnormal Doppler examination and three subgroups according to outcome, Group C: women with abnormal Doppler examination and established FGR at 23-25 weeks of gestation.

<i>Group</i>	Group A		Group B		Group C
	Normal outcome (n=44)	Normal outcome (n=19)	Development of FGR (n=17)	Development of PE (n=13)	Established FGR (n=15)
Adiponectin(μ g/ml)	10.8 (4.8)	9 (3.9)	11.1 (4.3)	8 (2.3)	12.7 (5.8)
Adiponectin (MoM's of Group A)	0.9 (0.7-1.2)	0.8 (0.5-1)	0.9 (0.7-1.1)	0.9 (0.6-0.9)	0.9 (0.7-1.2)
Leptin (ng/ml)	31.4 (18.3)	28.9 (16.2)	27.2 (13.6)	4.9 (14.5)	52.2 (33.4) *
Leptin (MoM's of Group A)	0.9 (0.7-1.2)	1 (0.8-1.2)	1 (0.8-1.4)	1 (0.8-1.3)	2.5 (1.2-2.7)†

*P<0.01 (Group C vs Group A)
vs Group B/ normal outcome)
vs Group B/ development of FGR)

†P<0.001 (Group C vs Group A)
vs Group B/ normal outcome)
vs Group B/ development of FGR)
vs Group B/ development of PE)

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