

# Maternal Serum Adiponectin at 11–13 Weeks of Gestation in Pregnancies Delivering Small for Gestation Neonates

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## Key Words

Adiponectin · Pregnancy-associated plasma protein A · First trimester · Small for gestational age · Fetal growth restriction

## Abstract

**Objective:** To investigate whether maternal serum levels of adiponectin in the first trimester are altered in pregnancies that subsequently deliver small for gestational age (SGA) neonates. **Methods:** Maternal serum adiponectin and pregnancy-associated plasma protein A (PAPP-A) were measured at 11–13 weeks' gestation in 50 singleton normotensive pregnancies that delivered SGA neonates and 300 non-SGA controls. The median adiponectin and PAPP-A levels in the SGA and non-SGA groups, expressed as multiple of the unaffected median (MoM), were compared. **Results:** The distribution of serum adiponectin was made gaussian by square root (sqrt) transformation. Regression analysis in the non-SGA group demonstrated that for sqrt adiponectin a significant independent contribution was provided by maternal age, weight, smoking status, African and South-Asian racial origin. Each value in the SGA and non-SGA group was then converted into a multiple of the non-SGA median (MoM) after

adjustment for maternal characteristics. In the SGA group, compared to the non-SGA controls, median maternal serum PAPP-A was decreased (0.79, interquartile range [IQR] 0.54–1.06 MoM vs. 1.00, IQR 0.71–1.39 MoM) but adiponectin MoM was not significantly different (0.89, IQR 0.65–1.31 MoM vs. 1.02, IQR 0.70–1.29 MoM). **Conclusion:** Maternal serum adiponectin is not a useful biochemical marker for early prediction of SGA.

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## 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, 4]. Adiponectin may also play a role in fetal growth, probably by enhancing the growth-promoting effect of insulin through its insulin-sensitizing action [5]. In small for gestational age (SGA) pregnancies there is reduced placental content and maternal serum or plasma concen-

tration of adiponectin [6, 7]. Additionally, adiponectin levels are reduced in cord blood of SGA neonates and in the blood of children that were SGA at birth [8, 9].

The aim of this study is to investigate whether the low maternal serum level of adiponectin observed in association with SGA fetuses precedes the onset of the fetal growth deficiency and is apparent from the first trimester of pregnancy. In addition, we investigate whether the serum level of adiponectin is related to alterations in placental function, reflected in the serum level of PAPP-A, which is known to be decreased in affected pregnancies [10].

## 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. In this visit, which is held between 11<sup>+0</sup> and 13<sup>+6</sup> weeks of gestation, we record maternal characteristics and medical history, and perform combined screening for aneuploidies by measurement of the fetal crown-rump length (CRL) and nuchal translucency thickness and maternal serum PAPP-A and free  $\beta$ -hCG [11, 12]. We stored serum and plasma at  $-80^{\circ}\text{C}$  for subsequent biochemical analysis from women agreeing to participate in the study. Written informed consent was obtained for the study, which was approved by King's College Hospital ethics committee.

In this study we measured maternal serum adiponectin in 50 cases that subsequently delivered SGA neonates in the absence of preeclampsia because we have previously reported that in this condition the levels are increased [13]. The levels were compared to 300 non-SGA controls who delivered a phenotypically normal neonate at term. 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 computerised records or the general medical practitioners of the women and were recorded in our database. The neonate was considered to be SGA if the birth weight was less than the 3rd percentile for gestation at delivery, using a reference range derived from our population [10]. Neonates with birth weight at or above the 5th percentile were classified as non-SGA.

### Sample Analysis

A duplicate serum sample of 250  $\mu\text{l}$  was used to measure adiponectin concentration by a quantitative enzyme-linked immunoassay (ELISA) technique using Quantikine Adiponectin ELISA kit (DRP300; R&D Systems Europe Ltd., Abingdon, UK). The lower limit of detection of the assay was 0.246 ng/ml and the between-batch coefficient of variation (CV) was 6.8% at an adiponectin concentration of 20.5 ng/ml, 5.8% at 74.4 ng/ml and 6.9% at 10.8 ng/ml. All samples were analyzed in duplicate and those with a CV exceeding 10% were re-analyzed.

### Literature Search

We searched Medline and Embase from January 1995, when adiponectin was first described, to September 2010 to identify studies reporting on the relationship between SGA neonates and adiponectin concentration in the plasma or serum of the mother, neonate or child.

### Statistical Analysis

The distribution of serum adiponectin was made gaussian by square root (sqrt) transformation and normality was confirmed using Kolmogorov-Smirnov test ( $D = 0.03$ ,  $p = 0.20$ ). In the group of 300 non-SGA controls, multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation provided a significant contribution in predicting sqrt adiponectin [14]. Each value in the SGA and non-SGA group was then converted into a multiple of the non-SGA median (MoM) after adjustment for those characteristics found to be significant in the multiple regression analysis. Similarly, the distribution of PAPP-A was made gaussian after logarithmic transformation and each value in the SGA and non-SGA group was then converted in a MoM after adjustment for gestation, maternal age, racial origin, maternal weight, smoking, parity, and method of conception as previously described [15]. Mann-Whitney U test was used to compare median MoM values of adiponectin and PAPP-A between the outcome groups. Regression analysis was used to determine the significance of association between maternal serum adiponectin and PAPP-A in the SGA and non-SGA groups.

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

## Results

The maternal characteristics of the SGA and non-SGA groups are compared in table 1. In the SGA group the median maternal weight was lower, more women delivered SGA neonates in their previous pregnancies and more required assisted conception techniques.

Multiple regression analysis in the non-SGA 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 CRL ( $p = 0.459$ ), method of conception ( $p = 0.637$ ) or parity ( $p = 0.219$ ):  $\text{sqrt adiponectin expected} = 130.19 + 0.74 \times \text{maternal age in years} + (-18.24 \text{ if the racial origin was African, } -31.89 \text{ if South Asian, } 0 \text{ if Caucasian, East Asian or Mixed}) - 0.53 \times \text{maternal weight in kg} - 10.38 \text{ if cigarette smoker}$ ;  $R^2 = 0.223$ ,  $p < 0.0001$ .

In the SGA group, compared to the non-SGA controls, median maternal serum PAPP-A MoM was decreased but adiponectin MoM was not significantly different (table 2; fig. 1). There was no significant association of sqrt adiponectin MoM with birth weight percentile in either the

**Table 1.** Maternal and pregnancy characteristics in the outcome groups

Maternal characteristics	Unaffected controls (n = 300)	Small for gestation (n = 50)
Median maternal age, years (IQR)	32.2 (26.9–35.6)	30.5 (26.5–35.9)
Median maternal weight, kg (IQR)	63.3 (57.0–70.0)	59.3 (52.0–68.3)*
Median crown-rump length, mm (IQR)	64.0 (58.7–69.6)	62.1 (55.3–66.5)
Median gestation at sampling, weeks (IQR)	12.4 (12.1–12.9)	12.4 (12.1–12.6)
Racial origin, n (%)		
Caucasian	189 (63.0)	24 (48.0)
African	86 (28.7)	17 (34.0)
South Asian	10 (3.3)	4 (8.0)
East Asian	6 (2.0)	3 (6.0)
Mixed	9 (3.0)	2 (4.0)
Parity, n (%)		
Nulliparous	148 (49.3)	28 (56.0)
Parous – no previous SGA	140 (46.7)	12 (24.0)*
Parous – SGA	12 (4.0)	10 (20.0)*
Cigarette smoker, n (%)	28 (9.3)	9 (18.0)
Conception, n (%)		
Spontaneous	296 (98.7)	46 (92.0)
Assisted	4 (1.3)	4 (8.0)*
Median birth weight percentile (IQR)	50.5 (32.6–68.7)	1.3 (0.4–2.0)*
Median gestation at delivery, weeks (IQR)	40.1 (39.2–41.0)	39.0 (38.1–40.0)*

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

**Table 2.** MoM (IQR) for maternal serum adiponectin and PAPP-A in the outcome groups

Variable	Unaffected controls (n = 300)	Small for gestation (n = 50)
Adiponectin		
ng/ml	12,035 (8,595–17,085)	11,373 (8,193–14,938)
MoM	1.02 (0.70–1.29)	0.89 (0.65–1.31)
PAPP-A		
mIU/ml	3.07 (2.03–4.76)	2.21 (1.50–4.08)
MoM	1.00 (0.71–1.39)	0.79 (0.54–1.06)*

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

SGA group ( $p = 0.335$ ) or the non-SGA group ( $p = 0.558$ ). Similarly, there was no significant association of sqrt adiponectin MoM with gestation at delivery in the SGA group ( $p = 0.070$ ). There was a significant association of sqrt adiponectin MoM with  $\log_{10}$  PAPP-A MoM in the SGA group ( $r = 0.344$ ,  $p = 0.014$ ) but not in the non-SGA group ( $p = 0.094$ ).

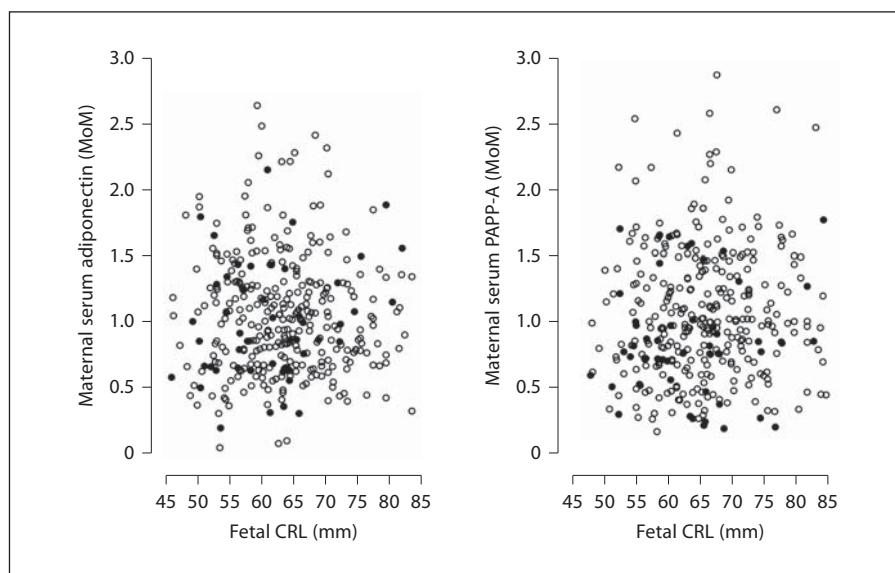
### Literature Search

The literature search identified 15 studies reporting on the association between serum or plasma adiponectin concentration and SGA neonates in pregnancy, the neonatal period and early childhood. In some of the studies, adiponectin was measured by radioimmunoassay (RIA) but in most studies an ELISA technique was used. The birth weight cut-off for definition of SGA was the 10th, 5th or the 3rd centile. The levels of adiponectin in the SGA group were lower than in the non-SGA group in about half of the studies and there were no significant differences in the other half (table 3).

### Discussion

The findings of this study confirm that in pregnancies delivering SGA neonates there is evidence of impaired placentation reflected in reduced maternal serum concentration of PAPP-A at 11–13 weeks' gestation. In contrast, the maternal serum adiponectin levels in pregnancies that subsequently deliver SGA neonates are not significantly different from pregnancies with normal fetal growth.

**Fig. 1.** Maternal serum adiponectin and PAPP-A, expressed as multiple of the normal median (MoM), at 11–13 weeks' gestation plotted against fetal CRL in pregnancies delivering SGA neonates (●) and non-SGA neonates (○).



**Table 3.** Studies reporting on the association between SGA and serum or plasma adiponectin concentration (mean or median) in the mother, neonate or child

Reference (first author)	Assay	Time point of evaluation	Small for gestational age		Appropriate for gestational age		p	SGA definition
			n	Adiponectin $\mu\text{g/ml}$	n	Adiponectin $\mu\text{g/ml}$		
<b>During pregnancy</b>								
Fasshauer, 2007 [17]	ELISA	33–41 WG	6	6.5	10	7.7	NS	<5th centile
Kyriakakou, 2008 [7]	RIA	36–40 WG	20	5.4	20	11.8	<0.05	<3rd centile
Savvidou, 2008 [18]	ELISA	23–25 WG	15	12.7	44	10.8	NS	<5th centile
Mazaki-Tovi, 2009 [19]	ELISA	28–39 WG	78	4.0	234	6.1	<0.001	<10th centile
Meral, 2010 [20]	ELISA	36–41 WG	20	0.81	20	1.51	<0.05	<10th centile
<b>Neonatal period</b>								
Kamoda, 2004 [8]	RIA	cord blood	28	23.2	34	33.2	0.02	<2.5th centile
Martínez-Cordero, 2006 [21]	RIA	cord blood	50	29.7	50	23.5	NS	<2,500 g
Takaya, 2007 [22]	ELISA	cord blood	20	11.4	45	17.1	<0.005	<5th centile
Ibáñez, 2008 [23]								
Girls	RIA	cord blood	24	31.6	24	35.5	NS	
Boys	RIA	cord blood	24	24.0	24	33.6	NS	<2.5th centile
Kyriakakou, 2008 [7]	RIA	cord blood	20	19.9	20	27.3	NS	<3rd centile
Meral, 2010 [20]	ELISA	1–4 days	20	2.6	20	6.7	<0.05	<10th centile
<b>Childhood</b>								
Cianfarani, 2004 [9]	RIA	5–14 years	51	35.2	24	77.5	<0.0001	<3rd centile
López-Bermejo, 2004 [24]	ELISA	3–9 years	32	18.7	37	14.5	<0.0001	<10th centile
Evangelidou, 2007 [25]	ELISA	6–8 years	20	14.3	35	10.8	<0.05	<10th centile
Sancakli, 2008 [26]	RIA	5–7 years	24	20.5	62	21.6	NS	<2.5th centile

WG = Weeks' gestation.

In normal pregnancy, maternal serum adiponectin concentration increases with maternal age, decreases with weight and is lower in women of African and South-Asian racial origin and in cigarette smokers. Within the narrow gestational range of 11–13 weeks there was no significant association between maternal serum adiponectin and fetal CRL. A previous longitudinal study of 11 normal pregnancies reported that maternal serum adiponectin levels were inversely related to body mass index and increased between 7 and 17 weeks, decreasing thereafter until term [16]. Consequently, in the comparison between the SGA and non-SGA groups, the appropriate adjustments were made for these maternal characteristics.

Previous studies examining adiponectin levels in the mothers, neonates and children from SGA pregnancies reported that the levels were lower or not significantly different from non-SGA pregnancies [7–9, 17–26]. Similarly, studies investigating the relation between adiponectin levels and birth weight in healthy pregnancies have found contradictory results with some reporting a positive correlation [27–31] and others no significant association [32, 33]. These conflicting results may be the consequence of methodological differences between studies, including assay techniques, definitions of SGA and differences in study populations, because most of these studies did not adjust the measured levels for maternal characteristics.

The reduced adiponectin levels in association with poor fetal growth, observed in some of the studies, may reflect the suggested role of this protein in the regulation of angiogenesis, the inflammatory response and insulin resistance. In previous studies, we reported that at 11–13 weeks the maternal serum adiponectin concentration is increased in pregnancies that subsequently develop preeclampsia and decreased in pregnancies that develop gestational diabetes mellitus [13, 14]. The possible association between reduced adiponectin levels and impaired

fetal growth is compatible with the findings that SGA neonates are more likely to develop the metabolic syndrome [34] and children born SGA exhibit altered body composition with increased visceral adiposity [35].

Impaired fetal growth is associated with increased risk of perinatal death and handicap. Early estimation of patient-specific risks for SGA could potentially improve pregnancy outcome by shifting antenatal care from a series of routine visits to a more individualised approach both in terms of the schedule and content of such visits [36]. These risks of perinatal death and handicap are substantially reduced in cases of SGA identified antenatally, compared to those detected after birth [37]. Additionally, there is evidence that the prophylactic use of low-dose aspirin started in early pregnancy can potentially halve the incidence of SGA [38]. We have previously reported that the use of an algorithm combining maternal characteristics and a series of biophysical and biochemical markers at 11–13 weeks could potentially identify, at a false positive rate of 10%, about 75% of pregnancies without preeclampsia delivering SGA neonates before 37 weeks and 45% of those delivering at term [39]. Our finding of no significant differences in maternal serum adiponectin levels at 11–13 weeks' gestation between the SGA and non-SGA groups implies that the altered maternal levels do not precede the onset of fetal growth deficiency and therefore, measurement of maternal serum adiponectin in the first trimester is unlikely to contribute in the early prediction of fetal growth restriction.

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