Maternal serum adiponectin multimers in patients with a small-for-gestational-age newborn

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Abstract

Objective: Several mechanisms of disease have been implicated in the pathophysiology of small-for-gestational-age (SGA) including an anti-angiogenic state, and an exaggerated intravascular pro-inflammatory response. Adiponectin plays a role in a wide range of biological activities including those that have been implicated in the pathophysiology SGA. Thus, the aim of this study was to determine if third trimester adiponectin concentrations differed between women with normal weight infants and those with an SGA neonate.
Study design: This cross-sectional study included women with: 1) a normal pregnancy (n=234); and 2) an SGA neonate (n=78). SGA was defined as a birth weight below the 10th percentile for gestational age at birth. The study population was further stratified by first trimester body mass index (BMI) (normal weight <25 kg/m^2 vs. overweight/obese ≥25 kg/m^2). Maternal serum adiponectin multimers [total, high-molecular-weight (HMW), medium-molecular-weight (MMW) and low-molecular-weight (LMW)] concentrations were determined by ELISA. Non-parametric statistics were used for analyses.
Results: 1) The median maternal serum concentrations of total, HMW and MMW adiponectin were significantly lower in patients with an SGA neonate than in those with normal pregnancies; 2) patients with an SGA neonate had a significantly lower median HMW/total adiponectin ratio and higher median MMW/total adiponectin and LMW/total adiponectin ratios than those with a normal pregnancy; 3) among patients with an SGA neonate, neither maternal serum concentrations of adiponectin multimers, nor their relative distribution differ between normal weight and overweight/obese patients.
Conclusion: 1) Pregnancies complicated by an SGA neonate are characterized by a alterations in the maternal serum adiponectin multimers concentrations and their relative abundance; 2) the findings reported herein suggest that maternal adipose tissue may play a role, in the pathogenesis of SGA.

Keywords: Adipokines; adipose tissue; body mass index (BMI); fetal growth; high-molecular-weight (HMW) adiponectin; low-molecular-weight (LMW) adiponectin; medium-molecular-weight (MMW) adiponectin; obesity; overweight; pregnancy; small-for-gestational-age (SGA).

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Introduction

Small-for-gestational-age (SGA) neonate, one of the "great obstetrical syndromes" [109, 110], is usually defined as a birth weight below the 10th percentile for gestational age at birth according to the birth weight distribution of a particular population [124]. In accordance with its syndromic nature, several mechanisms of disease have been implicated in the pathophysiology of this complication including: endothelial cell dysfunction [17], an anti-angiogenic state [21, 22, 34, 42, 111, 118, 139], failure of physiologic transformation of the spiral arteries [18, 39], and an increased maternal intravascular pro-inflammatory response [52, 66, 120, 125, 132]. Interestingly, maternal overweight/obesity, has a protective effect for the development of SGA fetuses [7, 19, 27, 33, 123, 145].

Adipose tissue, once considered a passive depot for energy storage, is now recognized as a potent endocrine organ [134]. Adipocytes, and other cellular components of adipose tissue, have a high capacity to produce and

secrete adipokines. Recently, adipokines have been implicated in the metabolic adaptation of normal gestation [20, 36, 73, 75, 77, 78, 80, 82, 84, 90, 92, 117, 130], as well as in complications of pregnancy such as preeclampsia [29, 31, 46, 47, 54, 70, 85, 88, 91, 107, 120, 140], gestational diabetes mellitus (GDM) [10, 23, 43, 56, 59, 60, 63, 68, 76, 108, 133, 149, 150], intra-amniotic infection/inflammation [65, 83, 141], and abnormal fetal growth [24, 35, 50, 53, 62, 67, 69, 79, 81, 95, 105, 136, 143].

Much attention has been focused on the biological actions of adiponectin, the adipokine [48, 71, 86, 119] that circulates at highest concentrations in humans [5]. Unlike other adipokines, circulating concentrations of this adiponectin are lower in obese than in non-obese subjects [8, 48], suggesting a negative feedback on its production or secretion by the adipose tissue. In addition to its insulin sensitizing [12, 28, 72, 151], anti-atherogenic [26, 38, 64, 94, 98], anti-inflammatory [25, 122, 127], and angiogenic [16, 100, 126] properties, adiponectin has been consistently shown to have protective effects on vasculature [74, 93, 96–98, 101]. Of note, several of the abovementioned conditions in which adiponectin has been implicated (e.g., angiogenesis, hypertension, atherosclerosis and inflammation) are known risk factors for the development of an SGA neonate.

Adiponectin circulates in human plasma in distinct forms: 1) low-molecular-weight (LMW) trimers; 2) medium-molecular-weight (MMW) hexamers; and 3) high-molecular-weight (HMW) oligomers (12–18 subunits) [9, 103, 104, 137, 138, 144]. A growing body of evidence suggests that the physiological activity of adiponectin is determined not only by the absolute concentrations of its multimeric complexes but, to a large extent, by the relative distribution of these isoforms [61, 103, 104, 135, 138, 144]. Thus, a comprehensive evaluation of its isoforms is essential to elucidate its role.

To date, no study has evaluated maternal circulating concentrations of adiponectin multimers in patients with an SGA neonate. Thus, the aim of this study was to determine if third trimester adiponectin concentrations differed between women with normal weight infants and those with SGA neonate.

Materials and methods

Study groups and inclusion criteria

A cross-sectional study was conducted including patients in the following groups: 1) women with a normal pregnancy (n = 234); and 2) patients with an SGA neonate (n = 78). The study population was further stratified by first trimester body mass index (BMI: normal weight 18.5–24.9 kg/m² vs. overweight/obese ≥ 25 kg/m²).

Samples and data were retrieved from our bank of biological samples and clinical databases. Many of these samples have previously been employed to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concen-

trations in normal pregnant women and those with pregnancy complications.

Written informed consent was obtained from all participants after approval by the Institutional Review Boards of the Sotero del Rio Hospital (Chile), Wayne State University (Detroit, MI, USA) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; Bethesda, MD, USA).

Clinical definitions

The inclusion criteria for women with a normal pregnancy were: singleton gestation, no prior diabetes mellitus, no maternal or fetal complications during pregnancy, normal plasma glucose concentrations in the first trimester, normal oral glucose challenge test [1], and delivery at term of a healthy neonate with a birth weight above the 10th percentile for gestational age [6, 41]. The diagnosis of SGA was based on ultrasonographic estimated fetal weight and confirmed by a birth weight below the 10th percentile for gestational age [6, 41].

The BMI was calculated according to the formula: weight (kg)/ height (m²). Normal weight women were defined as those with a BMI of 18.5–24.9 kg/m² according to the definition of the World Health Organization (WHO) [2]. Pregnant women were classified by their first trimester BMI into two groups: normal weight and overweight/obese (BMI ≥ 25 kg/m²).

Sample collection and quantitative determination of maternal serum adiponectin multimers

Maternal blood samples were collected with a vacutainer into tubes. Samples were centrifuged and the sera were stored at –80°C until analysis. Sensitive enzyme-linked immunoassays were used to determine the concentrations of adiponectin multimeric forms in maternal serum. Immunoassays kits were purchased from ALPCO Diagnostics (47-ADPHU-E01, Salem, NH, USA). The assays were run according to the manufacturer's recommendations. Maternal serum plasma samples that treated with SDS-containing acid buffer to convert multimeric adiponectin to a dimmer form were assayed to determine total adiponectin concentrations. To detect HMW adiponectin, serum samples were pretreated with a specific protease that selectively digested MMW and LMW adiponectin and then treated with the SDS-buffer that also stopped the digestion reaction. We were also able to determine the combined HMW and MMW adiponectin concentrations by pretreating the samples with a protease that specifically digested LMW adiponectin. Briefly, recombinant adiponectin (standards) and SDS-buffer-treated or protease-pretreated maternal serum samples were incubated in duplicate wells of the micro titer plates, which had been pre-coated with a monoclonal antibody specific for adiponectin. During this incubation any adiponectin present in the standards and SDS-buffer-treated or protease-pretreated maternal serum samples was bound by the immobilized antibodies. After repeated washing and aspiration to remove all unbound substances, an enzyme-linked polyclonal antibody specific for adiponectin was added to the wells. Unbound materials were removed with repeated washing and a substrate solution was added to the wells and color developed in proportion to the amount of adiponectin bound in the initial step. The color development was stopped with the addition of an acid solution and the intensity of color was read using a programmable spectrophotometer

(Spectra-Max M2, Molecular Devices, Sunnyvale, CA, USA). The concentration of adiponectin in SDS-buffer-treated or protease-pretreated maternal serum samples was determined by interpolation from individual standard curves composed of human adiponectin. Total, HMW, and HMW-MMW adiponectin concentrations were derived directly from the assay plates. MMW adiponectin concentrations were obtained by subtracting HMW adiponectin value from the combined HMW-MMW value. Finally, the LMW adiponectin value was computed by subtracting HMW and MMW adiponectin values from the total adiponectin values. The calculated inter- and intra-assay coefficients of variation for adiponectin multimer immunoassays in our laboratory were 2.2% and 4.2%, respectively. The sensitivity was calculated to be 0.04 ng/mL.

Statistical analysis

Normality of the data was tested using the Kolmogorov-Smirnov test. Since serum multimeric adiponectin isoforms concentrations were not normally distributed, Mann-Whitney U-tests were used for comparisons of continuous variables. Kruskal-Wallis test was used for the comparison between normal weight and overweight/obese pregnant women with and without SGA. Comparison of proportions was performed with χ^2-tests. Multiple linear regression analysis was performed to determine which factors were significantly and independently associated with maternal serum adiponectin isoforms concentrations as well as their relative distribution. Due to skewed distribution of the data, logarithmic (log) transformation was employed in the latter analysis. The following parameters were included in the model: maternal age, maternal first trimester BMI (as a continuous variable), gestational age at blood sampling, gestational age at delivery, ethnic origin and the presence of SGA. A $P < 0.05$ was considered statistically significant. Analysis was performed with SPSS, version 14 (SPSS Inc., Chicago, IL, USA).

Results

The demographic and clinical characteristics of women with a normal pregnancy and those with an SGA neonate are displayed in Table 1. Women with a normal pregnancy had a higher median maternal age. There were no significant differences in parity, gestational age at blood sampling, gestational age at delivery and first trimester BMI between patients with a normal pregnancy and those with an SGA neonate (Table 1). Table 2 displays the demographic and clinical characteristics of the study

Table 1   Clinical and demographic characteristics of the study population.

	Normal pregnancy (n = 234)	SGA (n = 78)	P-value
Maternal age (years)	28.0 (22.0–32.0)	24.0 (19.0–31.8)	0.004
Parity	1 (0–2)	2 (1–3)	0.3
Ethnic origin			
Hispanic	203 (87%)	62 (79%)	0.1
African American	20 (9)	10 (13%)	0.3
Caucasian	6 (3%)	4 (5%)	0.3
Others	5 (2%)	2 (3%)	0.8
Smoking	12 (5%)	8 (10%)	0.1
First trimester BMI (kg/m²)	24.9 (22.8–27.3)	25.9 (22.6–30.9)	0.1
Gestational age at blood sampling (weeks)	32.7 (28.7–39.3)	34.5 (27.8–38.5)	0.3
Gestational age at delivery (weeks)	39.9 (39.0–40.4)	38.5 (37.2–39.5)	0.08
Birth weight (g)	3470 (3220–3700)	2452 (2140–2651)	<0.001

Values are expressed as median (interquartile range) or numbers (percents).
SGA = small for gestational age, BMI = body mass index.

Table 2   Clinical and demographic characteristics of the study population according to body mass index.

	Normal pregnancy		P-value	SGA		P-value
	Normal weight (n = 118)	Overweight/obese (n = 116)		Normal weight (n = 35)	Overweight/obese (n = 43)	
Maternal age (years)	26.5 (21.0–31.0)	29.0 (24.0–34.0)	<0.01	21.0 (18.2–29.7)	24.0 (20.0–32.0)	NS
Parity	1 (0–2)	1 (1–2)	0.7	2 (1–3)	2 (1–3)	0.6
First trimester BMI (kg/m²)	22.7 (21.4–23.8)	27.3 (25.9–30.3)	<0.01	22.1 (20.2–23.5)	30.6 (28.6–32.2)	<0.01
Gestational age at blood sampling (weeks)	33.7 (31.2–40.0)	31.5 (27.3–33.8)	0.2	33.8 (28.0–37.5)	35.0 (27.0–38.6)	0.8
Gestational age at delivery (weeks)	40.0 (39.1–40.2)	39.8 (38.8–40.5)	0.9	36.0 (32.7–39.0)	38.6 (37.3–40.0)	0.3
Birth weight (g)	3420 (3205–3690)	3505 (3245–3735)	0.3	2422 (1813–2643)	2455 (2245–2650)	0.4

Values are expressed as median (interquartile range).
SGA = small for gestational age, BMI = body mass index.

population according to BMI. Among women with a normal pregnancy, those with normal weight were younger than overweight/obese patients. There were no significant differences in parity, gestational age at blood sampling, gestational age at delivery and neonatal birth weight between normal weight and overweight/obese women in both groups (Table 2).

Adiponectin multimers concentrations and their relative distribution in SGA vs. normal pregnancy

The median maternal serum concentration of total adiponectin was lower in patients with an SGA neonate than that of women with a normal pregnancy [median: 3961 ng/mL, interquartile range (IQR) 3075–4958 vs. 6070 ng/mL, IQR 4640–8240; $P < 0.001$, Figure 1]. Similarly, patients with an SGA neonate had lower median serum concentrations of HMW (1575 ng/mL, IQR 973–2600 vs. 3312 ng/mL, IQR 2236–4773; $P < 0.001$, Figure 1) and MMW adiponectin (1062 ng/mL, IQR 775–1361 vs. 1355 ng/mL, IQR 913–1804; $P < 0.001$, Figure 1) than women with a normal pregnancy. The median maternal serum concentration of LMW adiponectin did not differ significantly between patients with an SGA neonate and women with a normal pregnancy (1120 ng/mL, IQR 811–1493 vs. 1272 ng/mL, IQR 870–1722 respectively; $P = 0.06$, Figure 1).

The median maternal HMW/total adiponectin ratio was lower in patients with an SGA neonate than in those with a normal pregnancy (0.42, IQR 0.33–0.54 vs. 0.55, IQR 0.47–0.62; $P < 0.001$, Figure 2). In contrast, patients with an SGA neonate had higher median MMW/total adiponectin (0.27, IQR 0.20–0.35 vs. 0.22, IQR 0.16–0.28;

$P < 0.001$, Figure 2) and LMW/total adiponectin ratios (0.28, IQR 0.21–0.37 vs. 0.21, IQR 0.15–0.28; $P < 0.001$, Figure 2) than women with a normal pregnancy.

Adiponectin multimers concentrations and their relative distribution in normal weight pregnant women: normal pregnancy vs. SGA

Among pregnant women with a normal weight, patients with an SGA neonate had lower median serum concentrations of total adiponectin (3993 ng/mL, IQR 2869–5515 vs. 6859 ng/mL, IQR 4982–8695; $P < 0.001$, Figure 3A), HMW adiponectin (1717 ng/mL, IQR 878–2609 vs. 3910 ng/mL, IQR 2467–5134; $P < 0.001$, Figure 3B) and MMW adiponectin (1025 ng/mL, IQR 775–1376 vs. 1411 ng/mL, IQR 961–1911; $P = 0.006$, Figure 3C) than women with a normal pregnancy. There was no significant difference in the median maternal serum concentrations of LMW adiponectin between patients with an SGA neonate and those with a normal pregnancy (1145 ng/mL, IQR 788–1490 vs. 1295 ng/mL, IQR 915–1731 respectively; $P = 0.1$, Figure 3D).

Among normal weight women, patients with an SGA neonate had a lower median HMW/total adiponectin ratio than those with a normal pregnancy (0.45, IQR 0.33–0.55 vs. 0.56, IQR 0.49–0.63; $P < 0.001$, Figure 4A). In contrast, the median MMW/total adiponectin (0.26, IQR 0.22–0.33 vs. 0.23, IQR 0.15–0.29; $P = 0.007$, Figure 4B) and LMW/total adiponectin ratios (0.27, IQR 0.21–0.36 vs. 0.21, IQR 0.15–0.27; $P = 0.001$, Figure 4C) were higher in patients with an SGA neonate than in those with a normal pregnancy.
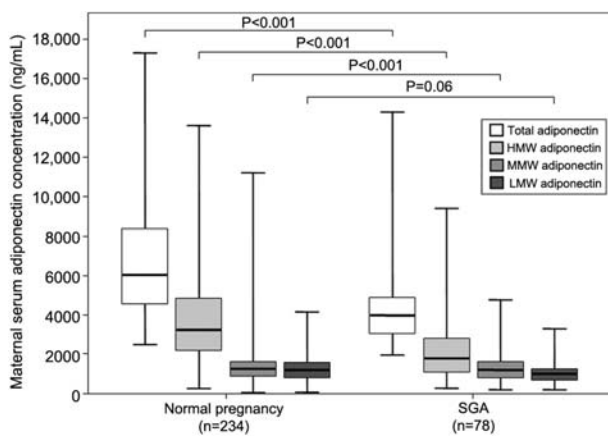

Figure 1 Comparison of the median serum total, HMW, MMW and LMW adiponectin concentrations between women with normal pregnancies and those with an SGA neonate.
The median maternal serum concentrations of total, HMW and MMW adiponectin were lower in patients with an SGA neonate than that of those with a normal pregnancy. The median maternal serum concentration of LMW adiponectin did not differ significantly between patients with SGA and those with a normal pregnancy.
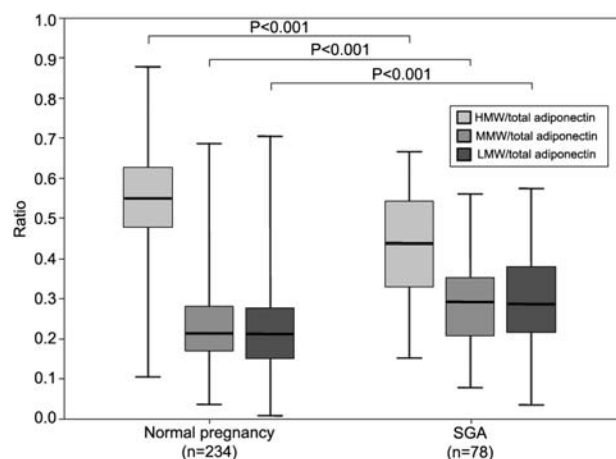

Figure 2 Comparison of HMW/total adiponectin MMW/total adiponectin and LMW/total adiponectin ratio between women with normal pregnancies and those with an SGA neonate.
The median maternal HMW/total adiponectin ratio was lower in patients with an SGA neonate than that of those with a normal pregnancy. In contrast, patients with an SGA neonate had higher median MMW/total adiponectin and LMW/total adiponectin ratios than that of those with a normal pregnancy.
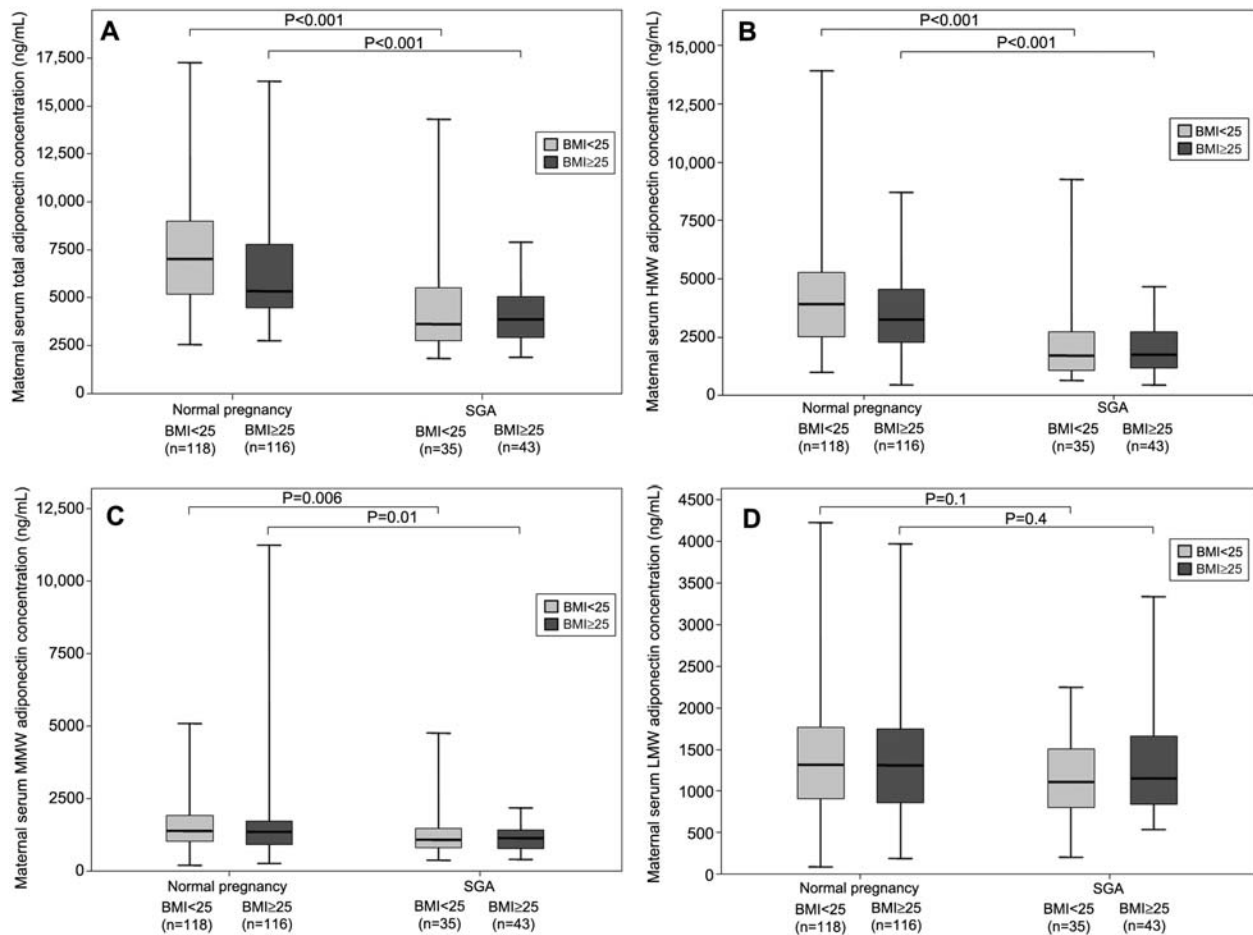
Figure 3 Maternal serum total adiponectin (A), HMW adiponectin (B), MMW adiponectin (C) and LMW adiponectin (D) concentrations in women with normal pregnancies and patients with an SGA neonate according to first trimester BMI (normal weight vs. overweight/obese).
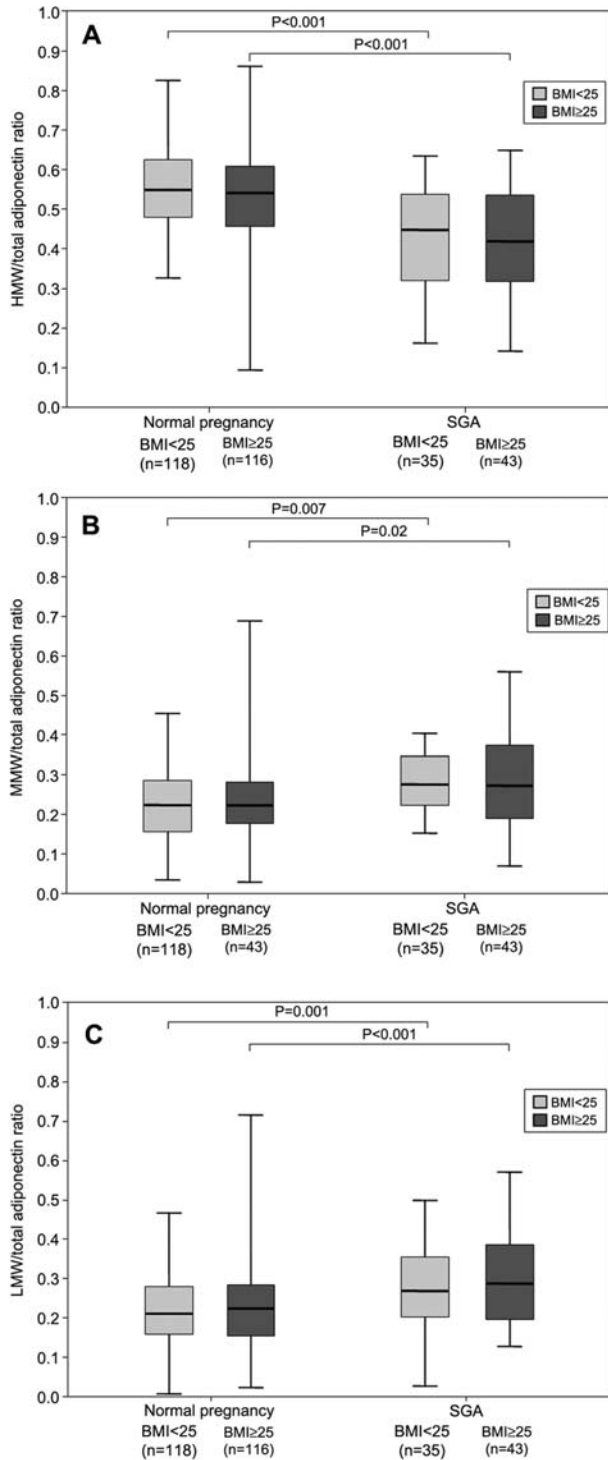
Among patients with an SGA neonate, normal weight pregnant women and those with overweight/obesity did not differ in the median serum concentrations of total, HMW, MMW, and LMW adiponectin. Among patients with a normal weight, the median serum concentrations of total (A), HMW (B), and MMW (C) adiponectin were higher in pregnant women with a normal pregnancy than that of those with an SGA neonate. Similar findings were found among patients with overweight/obesity. The median maternal serum concentration of LMW did not differ significantly between pregnant women with a normal pregnancy and those with an SGA neonate regardless of maternal first trimester BMI category (D).

Adiponectin multimers concentrations and their relative distribution in overweight/obese women: normal pregnancy vs. SGA

Among pregnant women with overweight/obesity, patients with an SGA neonate had lower median serum concentrations of total adiponectin (3950 ng/mL, IQR 3086–4939 vs. 5434 ng/mL, IQR 4481–7732; P < 0.001, Figure 3A), HMW adiponectin (1526 ng/mL, IQR 1112–2624 vs. 3019 ng/mL, IQR 2133–4405; P < 0.001, Figure 3B) and MMW adiponectin (1080 ng/mL, IQR 695–1387 vs. 1344 ng/mL, IQR 898–1722; P = 0.01, Figure 3C) than women with a normal pregnancy. There was no significant difference in the median maternal serum

concentrations of LMW adiponectin (1130 ng/mL, IQR 824–1622 vs. 1265 ng/mL, IQR 826–1719 respectively; P = 0.4, Figure 3D) between patients with an SGA neonate and those with a normal pregnancy.

Overweight/obese women with an SGA neonate had a lower HMW/total adiponectin ratio than those with a normal pregnancy (0.42, IQR 0.32–0.55 vs. 0.54, IQR 0.46–0.62; P < 0.001, Figure 4A). In contrast, MMW/total adiponectin (0.27, IQR 0.19–0.36 vs. 0.22, IQR 0.18–0.28; P = 0.02, Figure 4B) and LMW/total adiponectin (0.28, IQR 0.20–0.39 vs. 0.22, IQR 0.15–0.28; P < 0.001, Figure 4C) ratios were higher in overweight/obese pregnant women with an SGA neonate than in those with a normal pregnancy.

Figure 4 Comparison of HMW/total adiponectin (A), MMW/total adiponectin (B) and LMW/total adiponectin (C) ratios between women with a normal pregnancy and those with an SGA neonate according to first trimester BMI (normal weight vs. overweight/obese).

Among pregnant women with an SGA neonate, normal weight patients and those with overweight/obesity had comparable median HMW/total adiponectin, MMW/total adiponectin and LMW/total adiponectin ratios. Both normal weight and overweight/obese women with a normal pregnancy had a higher HMW/total adiponectin ratio than that of those with an SGA neonate (A). In contrast, MMW/total adiponectin (B) and LMW/total adiponectin ratios (C) were lower in pregnant women with a normal pregnancy than that of those with an SGA neonate, regardless of first trimester maternal BMI category.

Adiponectin multimers concentrations and their relative distribution in women with an SGA neonate: normal weight vs. overweight/obesity

Among patients with an SGA neonate, normal weight pregnant women and those with overweight/obesity did not differ significantly in the median serum concentra-

tions of total adiponectin (P=0.98, Figure 3A), HMW adiponectin (P=0.7, Figure 3B), MMW adiponectin (P=0.9, Figure 3C) and LMW adiponectin (P=0.7, Figure 3D). Similarly, patients with an SGA neonate with normal weight and those with overweight/obesity had comparable median HMW/total adiponectin (P=0.4, Figure 4A), MMW/total adiponectin (P=0.8, Figure 4B), and LMW/total adiponectin (P=0.8, Figure 4C) ratios.

Linear regression analysis was used to examine the contribution of the presence of SGA on the serum concentration of adiponectin isoforms, while adjusting for maternal age, gestational age at blood sampling, and gestational age at delivery and ethnic origin. The final regression model suggested that the presence of SGA and first trimester BMI were independently associated with low maternal serum concentrations of total adiponectin (P<0.001 and P=0.01, respectively), and HMW adiponectin (P<0.001 and P=0.002, respectively). In addition, only the presence of SGA was independently associated with low maternal serum concentrations of MMW adiponectin (P=0.04), and HMW/total adiponectin ratio (P<0.001) as well as with high MMW/total adiponectin (P=0.001) and LMW/total adiponectin ratios (P<0.001).

Discussion

Principal findings of the study

1) The median maternal serum concentrations of total, HMW and MMW adiponectin were significantly lower in patients with an SGA neonate than that of those with normal pregnancies; 2) patients with an SGA neonate had a significantly lower median HMW/total adiponectin ratio and higher median MMW/total adiponectin and LMW/total adiponectin ratios than those with a normal pregnancy; 3) among patients with an SGA neonate, neither maternal serum concentrations of adiponectin multimers, nor their relative distribution differed between normal weight and overweight/obese patients; and 4) the presence of SGA was independently associated with a

low maternal serum total, HMW, and MMW adiponectin concentration, as well as with low HMW/total adiponectin ratio and high MMW/total adiponectin and LMW/total adiponectin ratios.

What is the rationale to assess maternal circulating adiponectin in patients with SGA fetuses?

The rationale to determine the association between maternal circulating adiponectin concentrations and fetal growth hinges on the following findings: 1) adiponectin is an important mediator of several biological processes that have been implicated in the pathophysiology of SGA. Adiponectin has insulin sensitizing [12, 28], anti-atherogenic [26, 38, 64, 94], anti-inflammatory [25, 51, 114], and angiogenic [14, 16, 100] properties, as well as vasculature protective effects [74, 93, 96–98, 101]. This unique and diverse combination of biological activities made adiponectin an attractive candidate to account for both physiologic adaptations and pathologic states. Indeed, SGA has been associated with an anti-angiogenic state [15, 21, 22, 30, 34, 40, 42, 111, 118, 139, 142, 146], an exaggerated intravascular pro-inflammatory response [40, 52, 66, 115, 120, 125, 132], and hypertension [128, 129]; and 2) a growing body of evidence supports a role for adiponectin in complications of pregnancy, including those closely associated with SGA, such as preeclampsia. Indeed, preeclampsia is associated with altered maternal adiponectin concentrations [29, 32, 46, 47, 54, 70, 88, 91, 107, 131] and low circulating maternal adiponectin concentrations have been reported in GDM [10, 59, 108, 133, 150]; and overweight pregnant patients [90].

Modifications of maternal serum adiponectin multimers – functional implications

A solid body of evidence suggests that the biological effects of adiponectin are determined not only by the absolute concentrations of adiponectin multimeric complexes, but, to a large extent, by the relative distribution of its isoforms [9, 13, 61, 103, 104, 135, 138, 144]. Moreover, each isoform has different biological effects. This view is supported by the following findings: 1) *in vitro*, HMW and MMW adiponectin have pro-inflammatory effects such as induction of IL-6 secretion by human monocytes and activation of nuclear factor (NF)-κB [4, 45, 112, 138]; 2) LMW adiponectin inhibits the release of IL-6 [89, 121], and increases the secretion of IL-10 [89], an anti-inflammatory cytokine; and 3) plasma HMW/total adiponectin ratio has a better correlation with insulin resistance indices than total adiponectin concentrations. Collectively, these data suggest a structure-function relationship of adiponectin multimers. Importantly, the post-translational modifications resulting in the various adiponectin isoforms, are performed exclusively by adipocytes [147, 148]. Indeed, none of the multimeric forms interchange with each other after their secretion [103].

Thus, the dysregulation of adiponectin multimers can be viewed as an index for adipose tissue dysfunction.

Pregnancy complicated by an SGA neonate – a state of adipose tissue dysregulation?

The present report is the first study explicitly designed to compare maternal serum concentrations of adiponectin multimers between normal pregnant women and those who delivered an SGA neonate. The findings that the median maternal serum concentrations of total, HMW and MMW adiponectin are lower in patients with SGA neonates than in those with a normal pregnancy are novel. The lower total adiponectin concentrations in patients with SGA neonates is the consequence of a significant lowering in maternal serum HMW adiponectin concentrations, as evidenced by the low HMW/total adiponectin ratio, yet, high MMW/total and LMW/total adiponectin ratios. The shift from the HMW adiponectin isoform to MMW and LMW adiponectin multimers may have functional implications since the metabolic effects of adiponectin are primarily mediated by HMW adiponectin.

The finding reported herein concerning the lower total adiponectin in patients with SGA fetuses than in those with a normal pregnancy is in agreement with the results of Kyriakakou et al. [67] in which maternal serum concentrations of total adiponectin were lower in patients with an intrauterine growth restricted (IUGR) neonate (n = 20) than in controls (n = 20). Consistent with the latter report, Ong et al. [95] reported a negative correlation between neonatal birth weight and maternal total adiponectin, HMW adiponectin and HMW/total adiponectin ratio in 58 women with normal pregnancies and AGA neonates. The results of the present study extend the previous studies by demonstrating that the low maternal serum total adiponectin concentration is the result of a selective lowering in HMW adiponectin. Moreover, we were able to show that low maternal serum adiponectin concentrations are a feature of normal weight as well as overweight/obese patients. Our findings are in contrast with those of Verhaeghe et al. [143], Fasshauer et al. [35] and Savvidou et al. [118] who reported similar maternal circulating total adiponectin concentrations in patients with SGA neonates and those with a normal pregnancy. Differences in study design, definition of SGA, and clinical characteristics of the study population can explain the disparity among studies. In particular, our study included a large group of mothers with SGA fetuses, at a wider range of gestational ages and a relatively higher rate of overweight/obese patients.

Why do patients with SGA fetuses have low serum concentrations of total and HMW adiponectin concentrations?

The alteration in maternal serum adiponectin multimers reported herein favors insulin resistance. In such obser-

vational study, it is difficult to unravel a cause and effect relationship between circulating maternal adiponectin isoforms concentrations and the delivery of an SGA neonate. However, it is tempting to postulate that these changes are aimed at meeting the metabolic demands of the small fetus. Indeed, it has been proposed that the insulin-sensitizing properties of adiponectin are mediated specifically by the HMW isoforms [11, 37, 44, 55, 61, 87, 104].

An alternative explanation can be that the low adiponectin concentrations are not an adaptive metabolic response to a primary insult that resulted in an SGA fetus, but rather a consequence of this primary insult. Pregnancies complicated by an SGA neonate are associated with an anti-angiogenic state and an intravascular pro-inflammatory response. Since adiponectin has anti-inflammatory and angiogenic properties, it is conceivable that its low concentration is a reflection of these underlying mechanisms. Indeed, low circulating adiponectin concentrations have been reported in other conditions associated with pro-inflammatory state such as overweight/obesity [3, 8, 48, 58, 90] and systemic lupus erythematosus [113, 116], diseases characterized by impairment in vasculature integrity such as atherosclerosis [99, 106] and hypertension [51, 57, 101], and those with anti-angiogenic states such as preeclampsia [29, 31, 32, 49, 102].

Adiponectin multimers in normal and overweight/obese patients with SGA fetuses – evidence for altered regulation of adiponectin multimers

In contrast to normal pregnancy [8, 48, 75, 90], overweight/obese patients with SGA neonates did not have lower serum concentrations of total adiponectin or its multimers compared to normal weight patients with SGA. Similarly, overweight/obese and normal weight patients with SGA did not differ in the relative distribution of adiponectin isoforms. These findings suggest a genuine association between the presence of SGA and alterations in maternal circulating adiponectin, regardless of the presence of obesity. This is further supported by the fact that the presence of SGA was independently associated with a low maternal serum concentration of HMW adiponectin, as well as with a low HMW/total adiponectin ratio. Collectively, these findings suggest altered regulation of maternal serum adiponectin multimeric complexes in the presence of SGA.

In conclusion, the present study is the first to determine maternal serum adiponectin multimers concentrations in patients with SGA neonates. The findings reported herein suggest that maternal adipose tissue plays an important and hitherto unrecognized role in the pathogenesis of SGA. These observations lend support to the hypothesis that adipokines play an important role not only in the physiologic adaptation of human gestation but also in complications of pregnancy. The implicit

promise of adipokines research during normal and abnormal pregnancy is that lifestyle or pharmacologic interventions may be helpful in the prevention and/or treatment of pregnancy complications such as the delivery of an SGA neonate.

Acknowledgment

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