Published in final edited form as:
*J Matern Fetal Neonatal Med*. 2008 November ; 21(11): 796–815. doi:10.1080/14767050802266881.

# Adiponectin Multimers in Normal Pregnancy

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## Abstract

**Objective—**Adiponectin is an anti-diabetic, anti-atherogenic, anti-inflammatory and angiogenic adipokine that circulates in oligomeric complexes including: low-molecular-weight (LMW) trimers, medium-molecular-weight (MMW) hexamers and high-molecular-weight (HMW) isoforms. The aim of this study was to determine whether there are changes in adiponectin multimers in pregnancy and as a function of maternal weight.

**Study design—**In this cross-sectional study, serum concentrations of total, HMW, MMW and LMW adiponectin were determined in women included in three groups: 1) normal pregnant women of normal body mass index (BMI) (n=466); 2) overweight/obese pregnant women (BMI ≥25; n=257); and 3) non-pregnant women of normal weight (n=40). Blood samples were collected once from each pregnant woman between 11 and 42 weeks of gestation. Serum adiponectin multimers concentrations were determined by ELISA. Non-parametric statistics were used for analysis.

**Results—**1) The median HMW adiponectin concentration and the median HMW/Total adiponectin ratio were significantly higher and the median LMW adiponectin concentration was significantly lower in pregnant than in non-pregnant women; 2) among pregnant women, the median serum concentration of total, HMW and MMW adiponectin was significantly higher in normal weight women than in overweight/obese patients; 3) HMW adiponectin was the most prevalent multimer in maternal serum regardless of gestational age or BMI status; 4) there were no significant differences in the median concentration of total, MMW, LMW adiponectin, and their relative distribution with advancing gestation.

**Conclusion—**Human pregnancy is characterized by quantitative and qualitative changes in adiponectin multimers, especially of the most active isoform, HMW adiponectin.

### Keywords

Adiponectin; Adipokines; Pregnancy; High molecular weight (HMW) adiponectin; Medium molecular weigh (MMW) adiponectin; Low molecular weight (LMW) adiponectin; BMI

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## Introduction

Insulin resistance is one of the hallmarks of human pregnancy [1–14]. Teleologically, an increased maternal resistance to insulin and the amplified production of glucose are aimed to ensure adequate glucose transport to the developing fetus [15–17]. The ephemeral nature of this metabolic alteration during pregnancy, as well as empirical findings [18–24], led to the conventional view that this physiologic adaptation stems from the "diabetogenic" effect of the placental hormones.

Adipose tissue has emerged as a powerful endocrine organ [25–37] that can exert autocrine, paracrine and endocrine effects by the production and secretion of a variety of adipokines including: adiponectin [38–46], leptin [6,47–51], tumor necrosis factor (TNF) – α [46,52–55], and resistin [56–60]. These highly active peptides and proteins [30,31,61,62] have been implicated in the pathophysiology of the most common metabolic complications such as insulin resistance [25,63–70], obesity [71–75], and the metabolic syndrome [43,70,76–81]. An abundance of evidence demonstrates that adipokines play an important role in the metabolic homeostasis during normal gestation [82–89], as well as in complications of pregnancy such as gestational diabetes mellitus [63,90–100] and preeclampsia [101–112].

Adiponectin, identified independently by four groups [40,42,44,45], is the most abundant gene *(AMP1)* product of adipose tissue; it circulates at relatively high concentrations [38,40,71,74, 113,114] and accounts for 0.01% of the total serum proteins. The serum concentrations of adiponectin are paradoxically lower in obese than in non-obese individuals [38,40]. In addition, weight reduction is associated with an increase in serum adiponectin concentration [72,74], suggesting that adipose tissue exerts a negative feedback on adiponectin production or secretion. Adiponectin has an important role in the pathophysiology of insulin resistance and diabetes [115–122], atherosclerosis [77–79,123,124], hypertension [80,125,126], dyslipidemia [127–129] and angiogenesis [130,131]. Moreover, adiponectin has been suggested to play a regulatory role in the metabolic adaptation during human pregnancy [25,65,83,84], as well as in the pathophysiology of both gestational diabetes mellitus (GDM) [90,92–94,96] and preeclampsia [101–109].

Adiponectin circulates in human serum in distinct forms: 1) low-molecular-weight (LMW) trimers; 2) medium-molecular-weight (MMW) hexamers; and 3) high-molecular-weight (HMW) oligomers (12 to 18 subunits) [38,45,132–138]. These adiponectin multimers can exert distinct biological effects [133–140], activate different single transduction pathways [133, 138] and may have different affinities to the adiponectin receptors [141]. In particular, the adiponectin sensitivity index ($S_A$) [137], which is the ratio of HMW to total adiponectin, has been reported to be a more sensitive marker of the biological activity of adiponectin [134, 135,137,139,140,142–161]. Indeed, $S_A$ has a better correlation with insulin resistance [134, 135,137,140,142–146], obesity [147–150], cardiovascular diseases [134,139,151,152] and other impaired metabolic states [153–161] than total adiponectin.

Only a handful of studies have addressed the changes in maternal adiponectin multimers concentrations and their relative concentration during human pregnancy [25,162–165]. Moreover, data regarding the concentrations of the HMW, MMW and LMW adiponectin isoforms in each trimester as well as the association between maternal weight and the relative distribution of adiponectin multimers has not been reported. Thus, the aim of this study was to determine whether there are changes in adiponectin multimers in pregnancy and as a function of maternal body mass index (BMI).

## Materials and methods

### Study design and population

A cross-sectional study was conducted using samples and data retrieved from the bank of biological samples and clinical database of the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The following groups of subjects were included: 1) normal pregnant women of normal BMI (n=466); 2) overweight/obese pregnant women with normal pregnancy (n=257); and 3) non-pregnant women of normal weight (n=40) with no prior or current medical or metabolic conditions and who were not using oral contraceptives.

The inclusion criteria for normal pregnant women were: singleton gestation, no prior diabetes mellitus, no maternal or fetal complications during pregnancy, normal serum glucose concentrations in the first trimester, normal oral glucose challenge test, and delivery at term of a healthy neonate with a birthweight above the 10th percentile for gestational age. Maternal blood samples were collected once from each woman in the following gestational ages: 11–14 weeks (n=84), 15–18 weeks (n=93), 19–22 weeks (n=93), 23–26 weeks (n=94), 27–30 weeks (n=95), 31–34 weeks (n=86) and term (≥37 weeks) in labor (n=98) and not in labor (n=80). The BMI was calculated according to the formula: weight (kg)/height ($m^2$). Normal weight women were defined as those with a BMI of 18.5–25 kg/$m^2$ according to the definitions of the World Health Organization (WHO) [166]. Pregnant women were classified according to their first trimester BMI into two groups: normal weight and overweight/obese (BMI ≥ 25 kg/$m^2$) and by the gestational age at sample collection.

Written informed consent was obtained from all participants after approval by the Institutional Review Board of both the Sotero del Rio Hospital (Chile) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (Bethesda, Maryland, USA).

### Sample collection

Maternal serum supplies were collected from each pregnant woman. Many of these samples were used previously to study the biology of inflammation, hemostasis, angiogenesis regulation and growth factors concentrations in non-pregnant and normal pregnant women.

**Quantitative determination of multimeric forms of adiponectin in maternal serum—**Sensitive enzyme-linked immunoassays were used to determine the concentrations of adiponectin multimeric forms in maternal serum. Immunoassays were purchased from ALPCO Diagnostics (Salem, NH, USA). The assays were run according to the manufacturer's recommendations. To detect HMW adiponectin, serum samples were pretreated with a specific protease that selectively digested MMW and LMW adiponectin. 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. Maternal serum samples were assayed directly to determine total adiponectin concentrations. Briefly, untreated and 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 untreated or 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

(SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA). The concentration of adiponectin in untreated and treated 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 multimers immunoassays in our laboratory were 2.2% and 4.2%. The sensitivity was calculated to be 0.04 ng/ml.

**Statistical analysis—**Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Serum multimeric adiponectin isoforms concentrations were not normally distributed; thus, non-parametric methods were used to perform the statistical analysis. Correlation between the various adiponectin multimers and gestational age, maternal age, BMI and birthweight was conducted with the Spearman's rank correlation.

Comparison of the median concentration of adiponectin multimers among the gestational age groups was performed by Kruskal-Wallis test with post-hoc analyses with Mann-Whitney *U*-test and Bonferroni correction for the calculated p-value in order to maintain the significance level below 0.05. The statistical package used was SPSS 14.0 (SPSS, Inc., Chicago, IL, USA).

## Results

Table I displays the maternal demographic and clinical characteristics of all pregnant women according to BMI. Overweight/obese pregnant women were older compared to normal weight pregnant women. There were no significant differences in parity, gestational age at sampling or gestational age at delivery between normal weight and overweight/obese women. Table II displays the maternal demographic and clinical characteristics of normal and overweight/obese according to the different gestational age groups. There were no significant differences in maternal age, parity, BMI or gestational age at delivery between the various gestational age groups.

When all pregnant women were pooled together, total adiponectin concentrations were negatively correlated with gestational age at sampling ($r=-0.11$, $p<0.01$). HMW adiponectin concentrations were negatively correlated with BMI at sampling only in overweight/obese patients ($r=-0.15$, $p=0.01$). HMW/Total adiponectin ratio was negatively correlated with BMI at sampling in both normal weight ($r=-0.10$, $p=0.03$) and overweight/obese ($r=-0.12$, $p=0.04$) pregnant women.

Reference tables of the normal serum adiponectin concentrations for each gestational age, including the 10th, 25th, 50th, 75th and 90th percentiles, in normal weight and overweight/obese pregnant women, are presented in tables III and IV, respectively.

### Adiponectin multimers concentrations and relative distribution in non-pregnant vs. pregnant women

When all pregnant women were pooled together (except those in labor), the median maternal concentration of HMW adiponectin was significantly higher in pregnant women than in non-pregnant women (median: 3554 ng/mL, range: 52–17548 ng/mL vs. median: 2812 ng/mL, range: 801–8937 ng/mL; $p=0.01$). Similarly, pregnant women had a higher median HMW/Total adiponectin ratio than non-pregnant women (median: 56.3%, range: 2–88% vs. median: 46.0%, range: 25–81%, respectively; $p<0.01$). In contrast, the median maternal serum concentration of LMW adiponectin was lower in pregnant than non-pregnant women (median: 1235 ng/mL, range: 56–6112 ng/mL vs. median: 1883 ng/mL, range: 766–3976 ng/mL;

p<0.01). The median maternal serum concentrations of total and MMW adiponectin did not differ between the two groups.

The median total adiponectin concentration was comparable between the different gestational age groups. Similarly, the median ratio of HMW, MMW and LMW to total adiponectin did not change significantly with advancing gestation. The median HMW adiponectin concentration was significantly higher than the median concentrations of MMW (p<0.01) and LMW (p<0.01) adiponectin at any gestational age. The median concentrations of MMW and LMW adiponectin did not differ with advancing gestation.

Among non-pregnant women, the median HMW adiponectin concentration was significantly higher than the median concentrations of MMW and LMW adiponectin (p<0.01, for both comparisons), while the median concentration of LMW was significantly higher than the median serum MMW adiponectin concentration (p<0.01) (Figure 1).

### Changes in adiponectin multimers serum concentrations of non-pregnant and pregnant women according to BMI

Compared to non-pregnant women, normal weight pregnant women had a higher median concentration of HMW adiponectin (3949 ng/mL, 945–17548 ng/mL vs. 2812 ng/mL, range: 801–8937 ng/mL; p<0.01) and a lower median concentration of LMW adiponectin (1217 ng/mL, range: 56–6112 ng/mL vs. median: 1883 ng/mL, range: 766–3976 ng/mL; p<0.01). In contrast, overweight/obese patients had a median concentration of LMW adiponectin lower only than non-pregnant women (1260 ng/mL, range: 85–4009 ng/mL vs. median: 1883 ng/mL, range: 766–3976 ng/mL; p<0.01).

Compared to overweight/obese pregnant women, those with normal weight had higher median serum concentrations of total adiponectin (median: 6792 ng/mL, range: 2442–21956 ng/mL vs. median: 5577 ng/mL, range: 2180–16301 ng/mL; p<0.01, Figure 1), HMW adiponectin (median: 3949 ng/mL, range: 945–17548 ng/mL vs. median: 2934 ng/mL, range: 52–11954 ng/mL; p<0.01) and MMW adiponectin (median: 1452 ng/mL, range: 220–5158 ng/mL vs. median: 1280 ng/mL, range: 174–11272 ng/mL; p<0.01, Figure 1). The median concentrations of LMW adiponectin were comparable between normal weight and overweight/obese pregnant women (1217 ng/mL, range: 56–6112 ng/mL vs. 1260 ng/mL, range: 85–4009 ng/mL, respectively; p=0.7).

### The ratio between of adiponectin multimers in non-pregnant women and pregnant women

The median HMW/Total adiponectin ratio was higher in normal weight than in overweight/obese pregnant women (median: 0.57, range: 0.33–0.86 vs. median: 0.53, 0.02–0.88; p<0.01). This ratio was also higher in overweight/obese patients compared to non-pregnant women (median: 0.53, range: 0.02–0.88 vs. median: 0.46, range: 0.25–0.81; p<0.01) (Figure 2). In contrast, the LMW to total adiponectin ratio was higher in non-pregnant women than in overweight/obese pregnant women (median: 0.33, range 0.10–0.53 vs. median: 0.21, 0.01–0.9; p<0.01) and as well as in the latter group compared to normal weight pregnant (median: 0.21, range 0.01–0.9 vs. median: 0.19, range 0.01–0.83; p<0.01) (Figure 2).

### Adiponectin multimers concentrations and their relative distribution with advancing gestation in normal and overweight/obese pregnant women

The median maternal serum concentration of total adiponectin was higher in normal weight than overweight/obese women between 11–14 weeks of gestation (median: 6578 ng/mL, range: 3293–18887 ng/mL vs. median: 5831 ng/mL, range: 2180–12554 ng/mL; p=0.02, Figure 3a), 19–22 weeks of gestation (median: 6697 ng/mL, range: 3446–21954 ng/mL vs. median: 5868 ng/mL, range: 2909–14988 ng/mL; p=0.01, Figure 3a) and between 31–34 weeks of gestation

(median: 7304 ng/mL, range: 3415–16504 ng/mL vs. median: 5056 ng/mL, range: 3060–11260 ng/mL; p=0.01, Figure 3a)

The median maternal serum concentration of HMW adiponectin was higher in normal weight than in overweight/obese women between 11–14 weeks of gestation (median: 3961 ng/mL, range: 1281–13384 ng/mL vs. median: 2723 ng/mL, range: 412–6584 ng/mL; p<0.01, Figure 3b), 19–22 weeks of gestation (median: 3674 ng/mL, range: 1462–17548 ng/mL vs. median: 2795 ng/mL, range: 52–11954 ng/mL; p<0.01, Figure 3b), 31–34 weeks of gestation (median: 4084 ng/mL, range: 1553–14196 ng/mL vs. median: 2672 ng/mL, range: 372–7592 ng/mL; p=0.01, Figure 3b) and at term (median: 3916 ng/mL, range: 945–7928 ng/mL vs. median: 2946 ng/mL, range: 1423–8589 ng/mL; p=0.01, Figure 3b)

The median maternal serum concentration of MMW adiponectin was higher in normal weight than overweight/obese women between 19–22 weeks of gestation (median: 1467 ng/mL, range: 268–4644 ng/mL vs. median: 1171 ng/mL, range: 263–2559 ng/mL; p<0.01, Figure 3c) and between 31–34 weeks of gestation MMW adiponectin (1551 ng/mL, range: 552–4227 ng/mL vs. 1204 ng/mL, range: 322–2129 ng/mL; p<0.01, Figure 3c). Serum LMW adiponectin did not differ between normal and overweight/obese pregnant women (Figure 3d).

The median maternal HMW/Total adiponectin ratio was higher in normal weight than overweight/obese women between 11–14 weeks of gestation (median: 0.58, range: 0.33–0.76 vs. median: 0.51, range: 0.18–0.81, respectively; p<0.01, Figure 4a) and between 19–22 weeks of gestation (median: 0.57, range: 0.4–0.82 vs. 0.52, range: 0.02–0.82, respectively; p=0.03, Figure 4b).

### The effect of labor on adiponectin multimers concentrations

Women at term in labor had a higher median concentration of HMW adiponectin than women at term not in labor (median: 4051 ng/mL, range: 182–9204 ng/mL vs. median: 3392 ng/mL, range: 945–8589 ng/mL; p=0.02, Figure 5). In addition, labor was associated with an increased median HMW/Total adiponectin ratio (58.6%, range: 6–82% vs. 53.9%, range: 34–75%; p=0.01) and a decreased LMW to total adiponectin ratio (17.7%, range: 3–83% vs. 20.0%, range: 2–39%, respectively; p=0.03).

Among pregnant women at term, in labor and not in labor, the median serum concentration of HMW adiponectin was higher than the median concentrations of LMW (p < 0.01) and MMW (p<0.01) adiponectin. The latter was higher than the median LMW adiponectin concentrations (p<0.01) (Figure 5).

Normal weight women at term, not in labor, had a higher median concentration of HMW adiponectin than overweight/obese patients. Among women in labor, those with normal weight had a higher median concentration of total adiponectin (median: 7080 ng/mL, range: 2844–13701 ng/mL vs. median: 5983 ng/mL, range: 2395–11367 ng/mL; p<0.01), HMW adiponectin (median: 4405 ng/mL, range: 182–9204 ng/mL vs. median: 3358 ng/mL, range: 1046–8130 ng/mL; p=0.01) and MMW adiponectin (median: 1657 ng/mL, range: 288–2772 ng/mL vs. median: 1331 ng/mL, range: 388–2796 ng/mL; p=0.03) than overweight/obese women.

## Discussion

### Principal findings of the study

1) HMW was the most prevalent adiponectin isoform, regardless of gestational age or BMI status; 2) the median HMW adiponectin concentration and HMW/Total adiponectin ratio were significantly higher, and the median LMW adiponectin concentration was lower, in pregnant than in non-pregnant women; 3) among pregnant women, the median concentration of total,

HMW and MMW adiponectin were significantly higher in normal weight compared to overweight/obese women; and 4) the median concentrations of total, MMW and LMW adiponectin as well as their relative distribution were comparable for each gestational age group.

## What is the rationale in assessing maternal circulating adiponectin?

Adiponectin is a member of a growing group of peptides and proteins secreted by adipose tissue, termed adipokines. In contrast to the other adipokines whose concentrations increase with the accumulation of fat mass, adiponectin concentrations are lower in overweight/obese and obese patients than in normal weight subjects [38,40,84,167,168]. The insulin sensitizing [115,116,121,169–174], anti-atherogenic [78–80,124,175–178] and the anti-inflammatory [126,179–183] properties of adiponectin have provided a mechanistic basis for the association between adiposity and metabolic complication. Indeed, low adiponectin concentrations were reported in type-2 diabetes mellitus and insulin resistance [115–122,182,184–189], cardiovascular disease [118,190,191] dyslipidemia [70,81,192–198] and atherosclerosis [43, 78,79,123,124,139,175,176,199,200]. Thus, the concept of the protective role of adiponectin has evolved [41,46,201–204].

Several factors prompted the investigation of adiponectin in human pregnancy: 1) the unique combination of its biological properties, including insulin sensitizing [115,116,121,169–174], anti-atherogenic [78–80,124,175–178], anti-inflammatory [126,179–183] and anti-angiogenic [130,131,205–207] effects; 2) physiologic adaptation to pregnancy is characterized by insulin resistance [1–12,14] and a remarkable fat depot [208–213]; and 3) the association between insulin resistance and increased adipose depots as well as angiogenesis in common pregnancy complications such as gestational diabetes [29,210,214–217] and preeclampsia [217–224].

## The role of adiponectin in human pregnancy

A solid body of evidence supports the role of adiponectin in normal gestation and pregnancy complications: 1) circulating maternal adiponectin concentrations correlate with insulin resistance indices during pregnancy [25,64–66]; 2) patients with GDM have a lower concentrations of adiponectin compared to those without GDM [90,92–94,96]; 3) women with adiponectin concentrations less than 6.4 μg/ml in first or early second trimester experienced a 4.6-fold increased risk of GDM, compared to those with higher concentrations [95]; 4) overweight/obese pregnant patients have lower adiponectin concentrations than normal weight pregnant women [84]; 5) preeclampsia is associated with altered maternal adiponectin concentrations. Both higher [101,104–109] and lower [102,225,226] adiponectin concentrations in patients with preeclampsia compared to normal pregnant women were reported. Collectively, these findings suggest that adiponectin plays a regulatory role in metabolic and vascular complications of pregnancy.

## Multimerization as a method of regulation: adiponectin isoforms regulate its pleiotropic effects

The structural diversity of adiponectin multimers has been proposed to be associated with its pleiotropic effects. Structurally, adiponectin belongs to the complement 1q family, which is known to form characteristic multimers [227–229]. This adipokine undergoes post-translational modification [230–231] within adipocytes into multimeric forms, including: LMW trimers, MMW hexamers, and HMW oligomers (12–18 monomers) [44,45,132,133, 136,138,232]. The multimeric forms do not interchange with each other after secretion, neither *in-vivo*, nor *in vitro* [136]. It has been suggested that the various adiponectin isoforms have distinct biological activities: 1) *in vitro*, HMW and MMW adiponectin have pro-inflammatory properties such as induction of IL-6 from human monocytes and activation of nuclear factor (NF)-κB [138,233–235], whereas LMW adiponectin inhibits the release of IL-6 [160,236], a

pro-inflammatory cytokine and increase the secretion of IL-10 [236], an anti-inflammatory cytokine. In addition, only HMW adiponectin has been shown to suppress apoptosis of endothelial cells [139]; 2) MMW and HMW can activate NF-κB, while LMW adiponectin activates AMP-activated protein kinase (AMPK) in skeletal muscle [138]. These findings represent a novel paradigm where multimerization state of a hormone can regulate a specific signal; 3) administration of HMW, but not LMW, adiponectin multimers to adiponectin knockout mice, results in a dose-depended reduction in serum glucose concentrations [137]; 4) mutations in the collagen domain are associated with type-2 diabetes mellitus and extremely low concentrations of HMW adiponectin [117,133,237]; 5) the serum HMW/Total adiponectin ratio has a better correlation with insulin resistance indices (e.g. HOMA-IR) compared to total adiponectin concentrations and the HMW/Total adiponectin ratio was lower in patients with diabetes compared to non-diabetic subjects [137,139,142,144,146,157]; 6) absolute concentrations of HMW adiponectin have a better correlation with metabolic indices (e.g. HDL cholesterol, total cholesterol concentrations), and endothelial dysfunction than total adiponectin [135,155,165,238,239]. Thus, HMW adiponectin concentrations may be the superior biomarker for insulin resistance and the metabolic syndrome; and 7) weight reduction and treatment with insulin sensitizing drugs (e.g thiazolidineone) preferentially elevates the HMW adiponectin concentrations compared to the other two isoforms [137,139,140] or to total adiponectin concentration [149,150,152]. In addition, re-feeding of patients with anorexia nervosa was associated with a decrease in HMW adiponectin concentrations [158,240].

Collectively, these data suggest that multimerization of adiponectin plays an important role in its metabolic and anti-inflammatory functions. In addition, those reports highlight the importance of the relative distribution of adiponectin multimers as more precise determinant governing adiponectin's protective properties against metabolic, inflammatory, and atherogenic disorders.

## Determination of circulating adiponectin multimers - The pros and cons of the available methods

Several methods have been developed to identify and measure the various adiponectin isoforms such as gel filtration chromatography [38,132,136] and SDS-PAGE [133,137,138]. Recently, an ELISA assay specific to adiponectin multimers has been developed [241–243]. ELISA has several advantages over the previously used methods: 1) formerly, determination of circulating adiponectin multimers were only semi-quantitative and required size fraction by velocity sedimentation followed by SDS-PAGE and Western blotting [135,137,139,155,244]; 2) although reproducible, those methods are time consuming and laborious and thus essentially precludes clinical implantation of their use. The use of ELISA, on the other hand, is accurate and negates the need for arduous laboratory work [241–243]. The current literature indicates that adiponectin isoforms differ in their biological activity. Therefore, to better understand the effects of this hormone, not only the absolute amount but also the distribution of its isoforms has to be considered. Applications of the measurements of the different adiponectin isoforms in maternal circulation have been limited, mostly due to the lack of high-throughput assays. However, the new ELISA assays provide a potential solution to this limitation.

## Human pregnancy is characterized by quantitative and qualitative alterations in adiponectin concentration

Only a handful of studies have addressed the maternal adiponectin multimers concentrations and their relative distribution [25,162–165]. Catalano et al. [25] conducted a longitudinal study in which total, HMW and LMW adiponectin were measured in 10 normal lean women, before pregnancy, in both early (12–14 weeks) and in late gestation (34–36 weeks). The authors reported that maternal circulating HMW adiponectin and HMW/Total adiponectin ratio were lower in late gestation than in non-pregnant state, and that there were no significant differences

in circulating adiponectin multimers between early and late gestation. Ong et al.[162] found a negative correlation between third trimester HMW/Total adiponectin ratio and birthweight in 58 patients. In addition, changes in maternal adiponectin multimers concentrations were reported in complications of pregnancy. Retnakaran et al.[165] reported a lower HMW adiponectin concentration in patients with GDM (n=41) compared to third trimester normal pregnant women (n=80). In study conducted by the same group [163] the HMW/Total adiponectin ration, measured between 28 to 31 weeks of gestation, was decreased in pregnant women of Indo-Asian descent (n=30) as compared to Caucasian women (n=65). Takemura et al. [164] described a higher maternal concentration of HMW adiponectin and an elevated HMW/Total adiponectin ratio in patients with preeclampsia (n=14) than in normal pregnant women (n=14). Of note, ELISA assay was used only the latter study.

The findings reported herein are in accordance with previous studies [65,84,102,245] in which total adiponectin concentration did not differ between pregnant and non-pregnant women. However, our results indicate that pregnancy is associated with a higher median HMW adiponectin concentration and HMW/Total adiponectin ratio, as well as a lower median LMW adiponectin concentration as compared to the non-pregnant state. The discrepancy in the findings reported herein and those previously reported [25] may result from differences in the study design, the definition of adiponectin multimers, and the methods to determine serum adiponectin isoforms. In particular, our study was cross-sectional, included a large number of women at a wide range of gestational ages, both lean and overweight/obese, determined the adiponectin total concentrations and its isoforms by ELISA assay and distinguished in the analysis between MMW and LMW adiponectin isoforms.

## Human pregnancy is characterized by a shift from LMW adiponectin to HMW adiponectin species

The increase in the median HMW adiponectin concentration and the median HMW/Total adiponectin ratio and the parallel decrease in the median LMW adiponectin concentration in pregnant than in non-pregnant women are novel. There can be several explanations for these findings:

**1. Compensatory reaction to metabolic alterations of pregnancy—**The shift from LMW adiponectin to HMW adiponectin and the consequently higher HMW/Total adiponectin ratio in pregnant than in non-pregnant state may represent a compensatory response. Human pregnancy can be viewed as a *forme frusta* of the metabolic syndrome, as the maternal physiological adaptation to normal pregnancy includes core components of this conditions including: weight gain and increase in fat deposition [25,208–213], hyperlipidemia [246–249] and insulin resistance [1–14]. The current literature indicates that HMW adiponectin has a prominent protective role, particularly against metabolic complications such as insulin resistance [137,142,144,146,155,157,239] and hyperlipidemia [135,152,238]. Total adiponectin concentrations are comparable between non-pregnant and pregnant women. However, gestation is characterized by a shift from a less active (LMW) to a more active isoform (HMW) of adiponectin suggesting that the higher HMW adiponectin concentrations may be a counter-regulatory response to the metabolic changes (e.g. insulin resistance, hyperlipidemia) associated with a normal pregnancy.

**2. Adipogenesis during pregnancy favors production and secretion of HMW adiponectin—**An alternative explanation for the elevated HMW adiponectin observed in women with normal pregnancy can be the significant weight gain and increased fat depot that accompanies normal gestation [25,208–213]. Previously, the mechanism for increased fat mass in normal and obese individuals was attributed exclusively to adipocyte hypertrophy; however, adipose tissue accretion during pregnancy is now known to be associated also with adipocyte

hyperplasia [250–255]. This finding is supported by reports demonstrating the effect of peroxisome proliferator-activated receptor (PPAR)-γ agonist on adipose tissue. Treatment with PPAR-γ agonist (e.g. Thiazolidinediones), results in distinct increase in the number of newly differentiated small adipocytes [256], as well as body weight gain, and increase serum adiponectin concentrations [232,257–263]. Treatment with PPAR-γ agonist (in mice and human) has resulted in a decreased insulin resistance and a dramatic increase in circulating adiponectin concentration, mostly due to the elevation in HMW adiponectin [137,140] In conclusion, adipogenesis can contribute to the shift towards HMW adiponectin in pregnant women. It is important to note in this context that the major role of the HMW multimers has been highlighted in the context of the effect of PPAR-γ.

### Adiponectin multimers concentrations and advancing gestation

When normal weight and overweight/obese patients were pooled together, the median total adiponectin concentration, the median concentration of adiponectin multimers and their relative distribution did not change with advancing gestational age. HMW adiponectin was the most prevalent adiponectin species regardless of gestational age or BMI. These finding are in agreement with the report by Catalano et al.[25] in which maternal HMW and LMW adiponectin concentrations did not differ between 12–14 and 34–36 weeks of gestation. This present study extends the available data by showing comparable concentrations of adiponectin concentrations with advancing gestation. Moreover, the nomogram (Tables III and IV) presented herein should be beneficial to those investigating the intriguing relationships between adiponectin multimers and human pregnancy.

### The perils of portliness - maternal overweight/obese is associated with decreased HMW adiponectin

The contribution of excess body weight to the concentration of adiponectin multimers and their relative distribution by comparing the concentrations of adiponectin species in normal weight and overweight/obese pregnant women is reported herein. Consistent with the non pregnant state [38,40,84,167,168], normal weight pregnant women had a higher median total, HMW and MMW adiponectin concentrations than overweight/obese patients. In contrast to normal weight pregnant women who had a higher HMW adiponectin than non-pregnant subjects, median concentration of HMW adiponectin was comparable between overweight/obese pregnant patients and non-pregnant women. The median HMW/Total adiponectin ratio was significantly higher in normal weight than in overweight/obese pregnant women. In addition, overweight/obese pregnant women had a distinct median concentration and relative distribution of adiponectin multimers with advancing gestation between 11–14, 19–22 and 31–34 weeks of gestation and at term. Specifically, a higher median concentration of HMW and MMW adiponectin was detected in normal weight than in overweight/obese pregnant women.

Lower concentrations of total adiponectin in overweight/obese pregnant women have been recently reported by our group [84]. The results of the current study are also in agreement with previous reports regarding decreased total adiponectin concentrations in overweight/obese and obese non-pregnant patients [38,40]. Contrary to other adipokines (e.g. leptin, TNF-α, and resistin), mRNA expression and serum concentrations of adiponectin are paradoxically lower in overweight/obese and obese than in normal weight individuals [38,40,120]; moreover, weight reduction is associated with an increase in circulating total [72,74,2264–267] and HMW adiponectin concentrations [135,149,264]. In addition to obesity, the inverse relationship between this hormone and body weight is upheld in extremely lean subjects with anorexia nervosa [158,26–270]. Taken together, these findings suggest that excess adipose tissue exerts a negative feedback on adiponectin production and/or secretion and regulates the relative distribution of its multimers. The current study extends the heretofore studies by analyzing both the absolute and the relative distribution of HMW, MMW and LMW adiponectin

concentrations in the setting of normal weight and overweight/obese pregnant women with advancing gestation and in labor.

In conclusion, the current report provides a comprehensive assessment of the ratio between the different adiponectin multimers concentrations in the maternal circulation during normal human pregnancy. Comparison of adiponectin species between non-pregnant and pregnant women, normal weight and overweight/obese patients revealed quantitative and qualitative changes suggesting that adiponectin multimers, especially its most active isoform, HMW adiponectin, play a role in the metabolic changes associated with pregnancy. Moreover, these findings, along with the nomograms presented herein, lay the groundwork for further studies addressing the complex and intriguing relationships between body weight, adiponectin and metabolic pathways in human pregnancy.

## Acknowledgments

This research was supported in part by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

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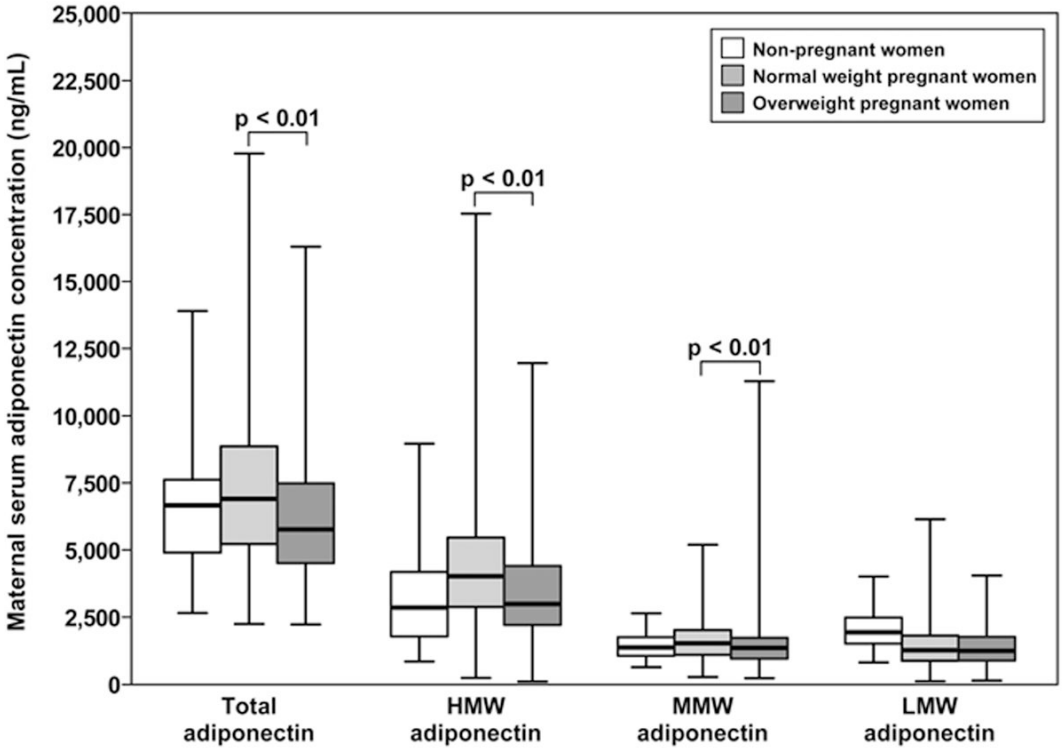



**Figure 1. Comparison of the median serum total, HMW, MMW and LMW adiponectin concentrations between non-pregnant, normal weight and overweight/obese pregnant women**

The median serum concentration of total, HMW and MMW adiponectin was significantly higher in normal weight than overweight/obese women. Among non-pregnant women, the median HMW adiponectin concentration was significantly higher than the median concentrations of MMW and LMW adiponectin. The median concentration of the latter was significantly higher than MMW adiponectin

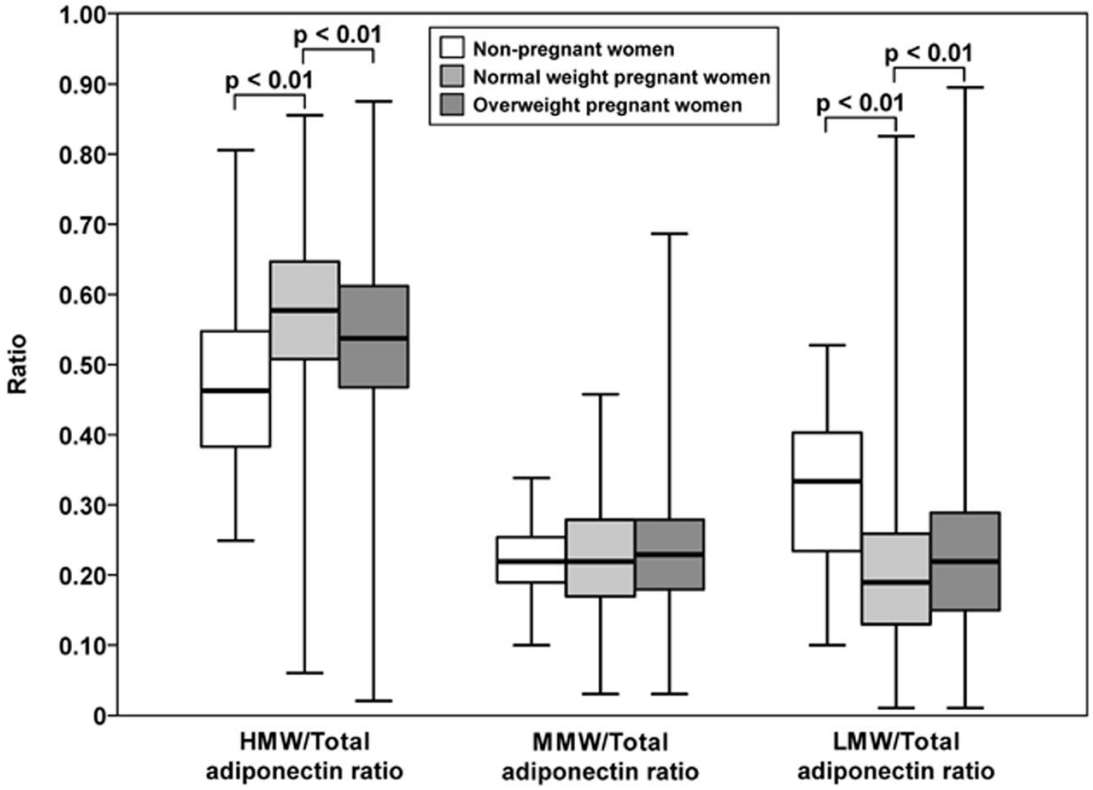
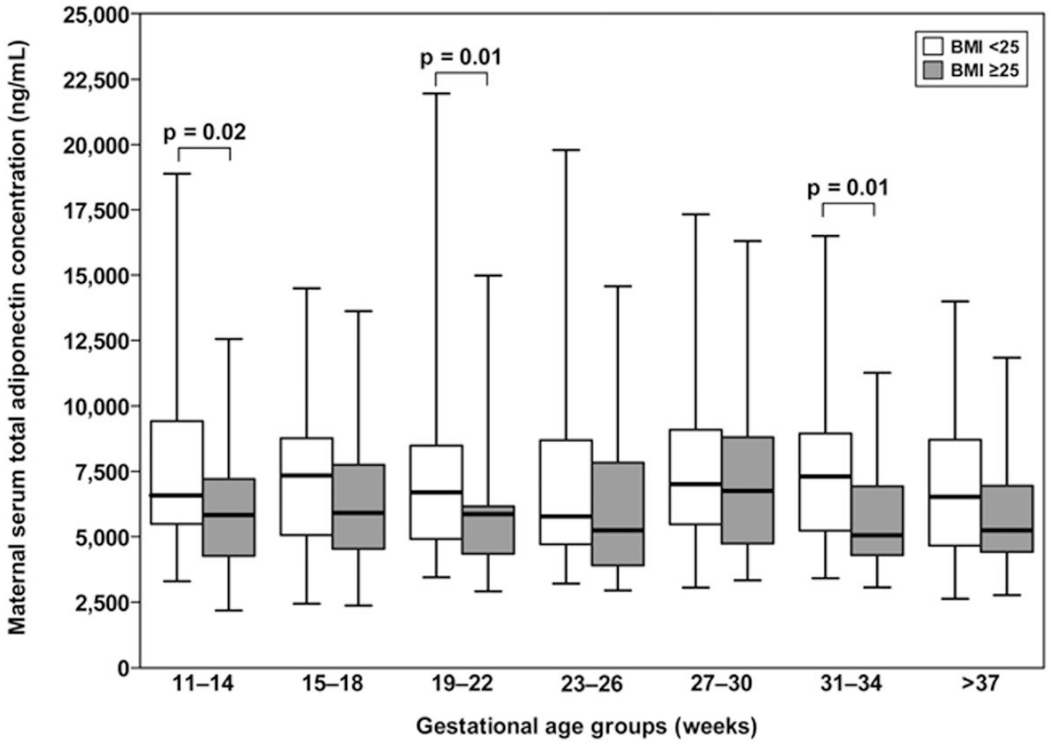
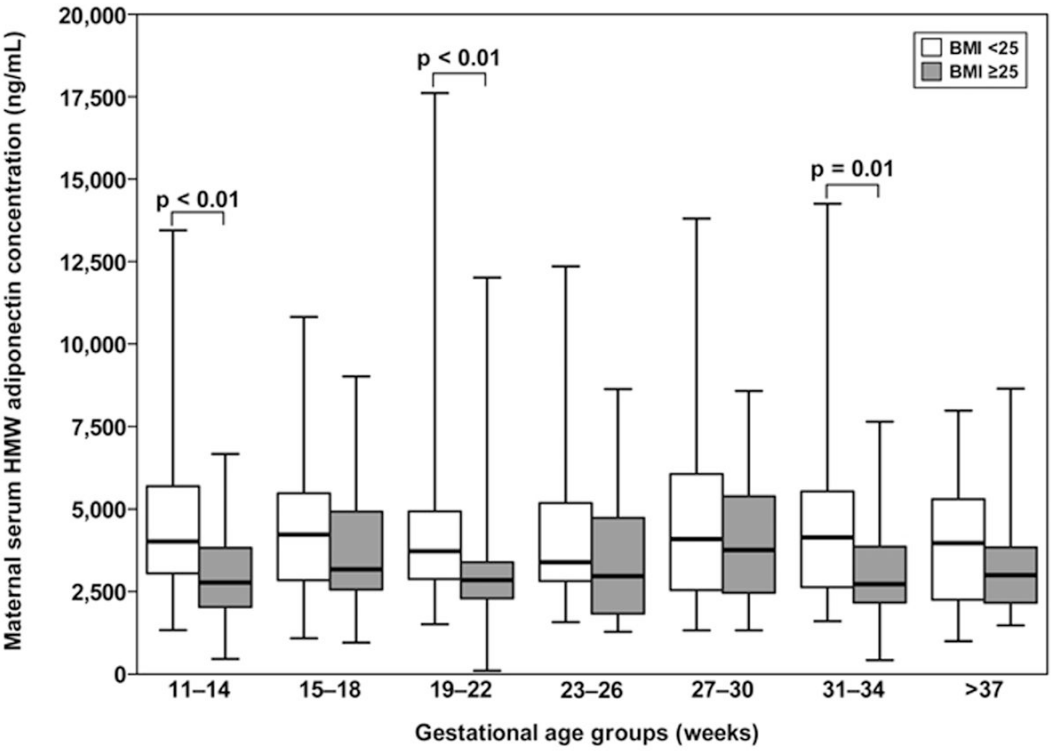



**Figure 2. Comparison of HMW/Total adiponectin MMW/Total adiponectin and LMW/Total adiponectin ratio between non-pregnant, normal weight and overweight/obese pregnant women**

The median HMW to total adiponectin ratio was significantly higher in normal weight than overweight/obese pregnant women and in overweight/obese patients compared to non pregnant women. The median LMW to total adiponectin ratio was significantly higher in non-pregnant women than the median LMW/Total adiponectin ration in normal weight and overweight/obese pregnant women. The median LMW to total adiponectin ratio was significantly higher in overweight/obese pregnant than in normal weight pregnant women.



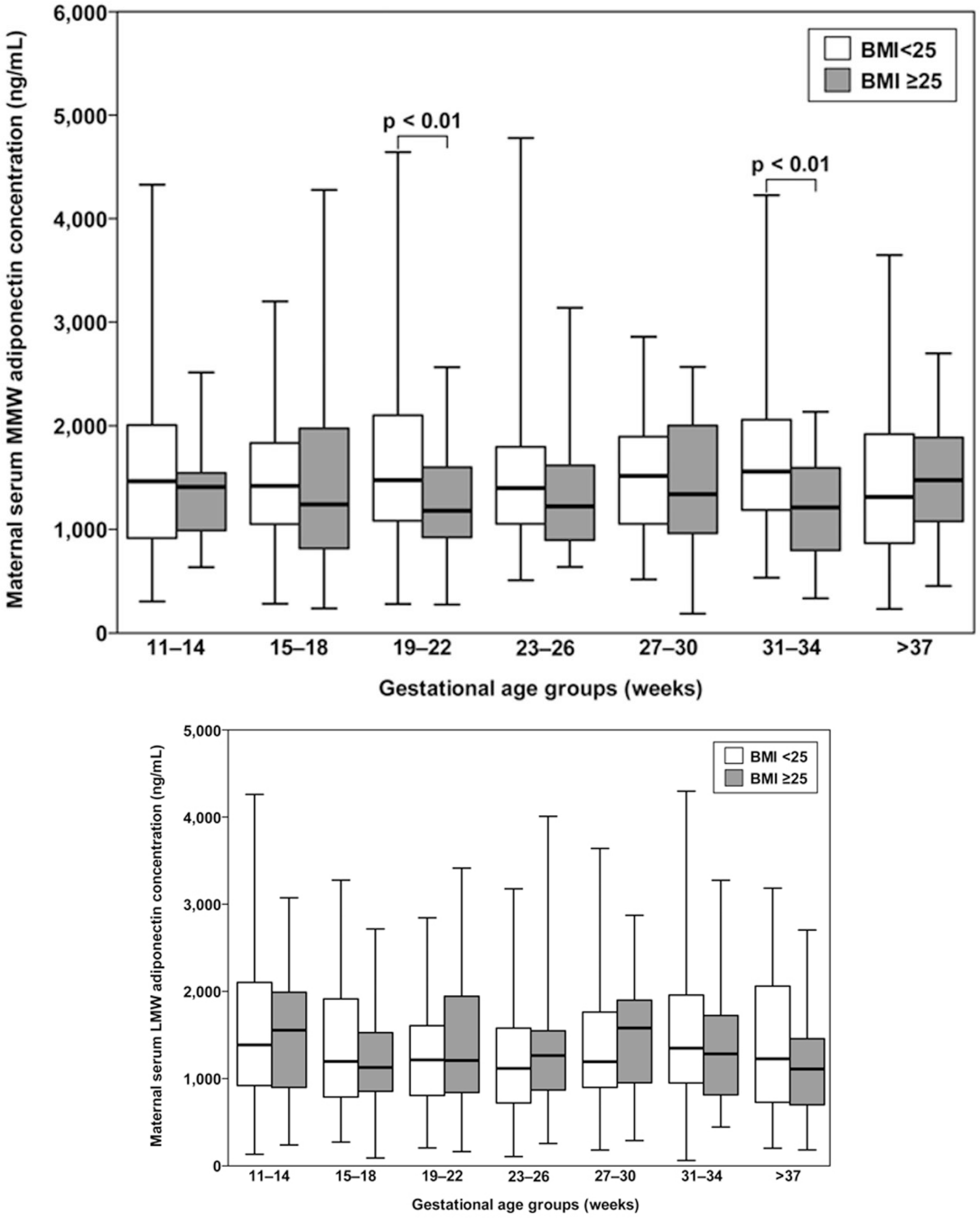



**Figure 3. Maternal serum total adiponectin (a), HMW adiponectin (b), MMW adiponectin (c) and LMW adiponectin (d) concentrations in normal weight and pregnant overweight/obese women according to gestational age groups**

Among women between 11–14 weeks of gestation, normal weight women had a higher median concentration of total (a) and HMW (b) adiponectin than overweight/obese patients. Among women between 19–22 weeks of gestation, normal weight women had a higher median concentration of total (a), HMW (b) and MMW (c) adiponectin than overweight/obese patients. Among women between 31–34 weeks of gestation, normal weight women had a higher median concentration of total (a), HMW (b) and MMW (c) adiponectin than overweight/obese patients.

Among women at term, normal weight women had a higher median concentration of HMW (b) adiponectin than overweight/obese patients.

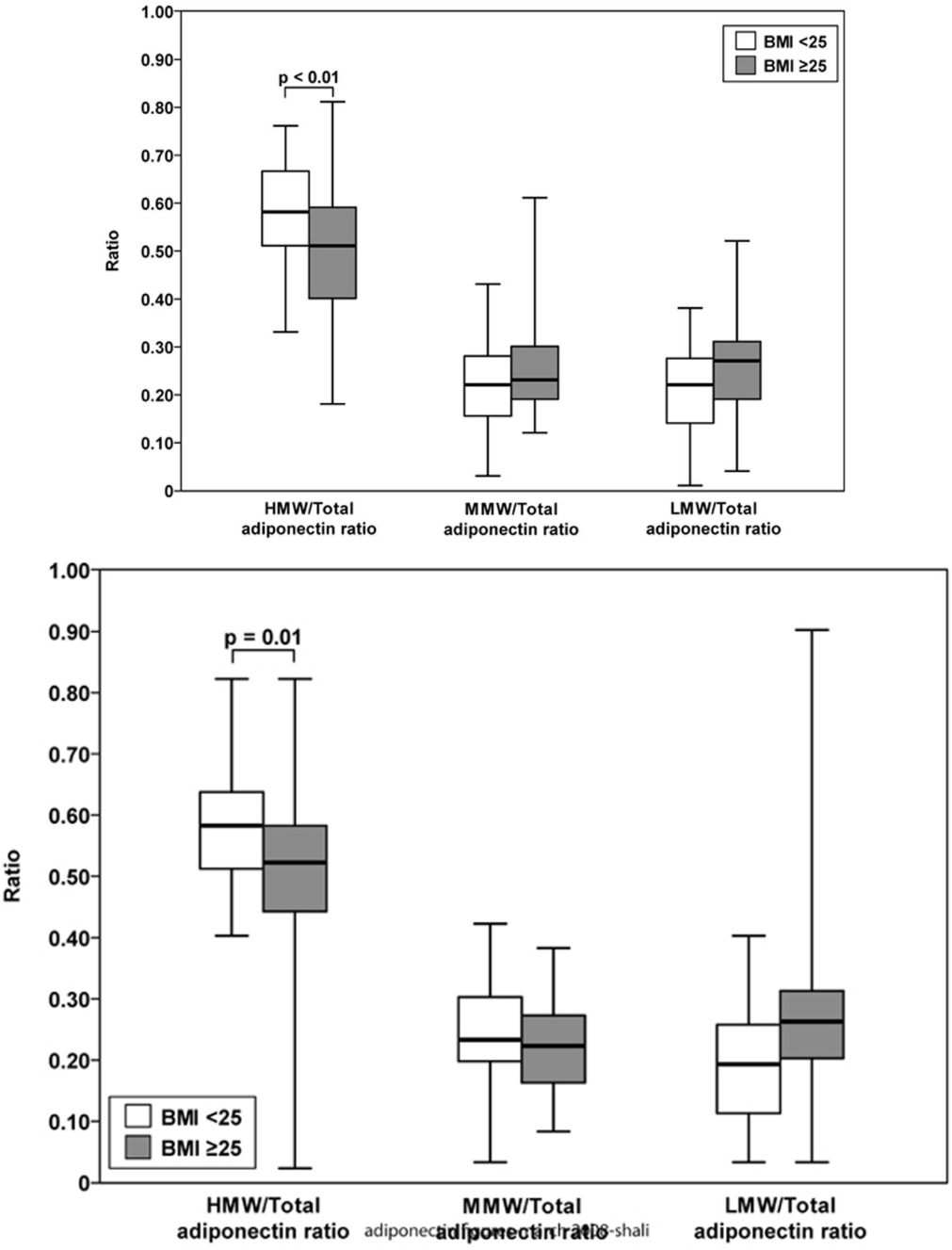



**Figure 4. Comparison of median HMW/Total adiponectin MMW/Total adiponectin and LMW/Total adiponectin ratio between normal weight and overweight/obese pregnant women in 11–14 weeks (a) and 19–22 weeks (b) of gestation**

The median HMW/Total adiponectin ratio was higher in normal weight than in overweight/obese pregnant women between 11–14 (a) and 19–22 (b) weeks of gestation.

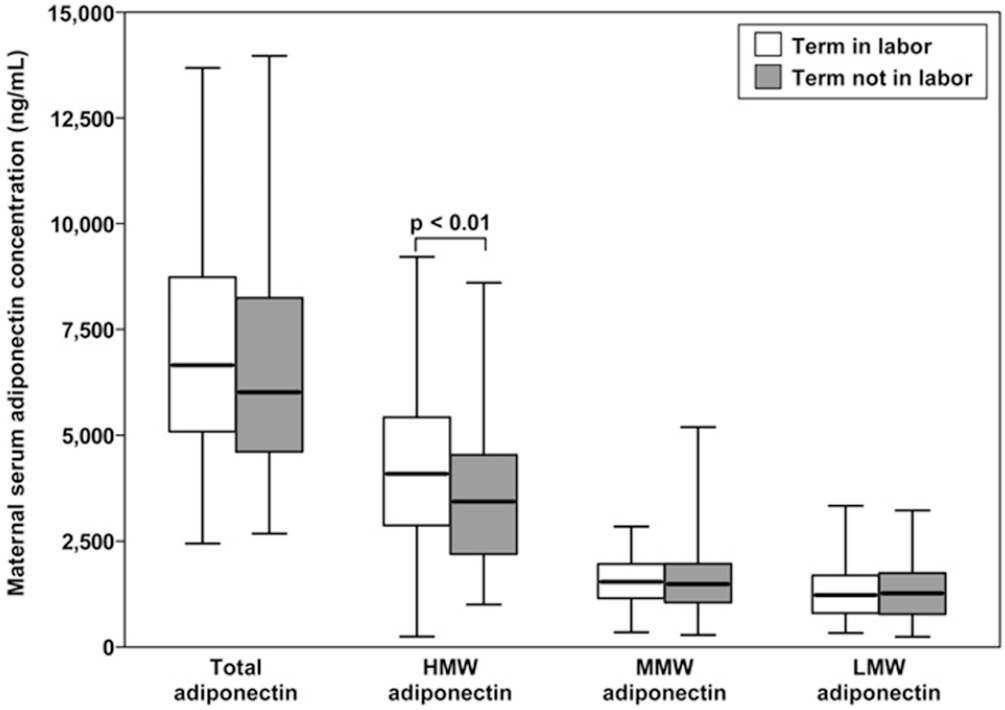



**Figure 5. Comparison of median serum total, HMW, MMW and LMW adiponectin concentrations between women at term in labor and not in labor**

Women at term in labor had a higher median concentration of HMW adiponectin compared to women at term not in labor. Among pregnant women in labor and not in labor at term, the median serum concentration of HMW adiponectin was higher than the median concentrations of LMW and MMW adiponectin. The latter was higher than the median LMW adiponectin concentrations.

**Table I**

Clinical characteristics normal weight and overweight/obese pregnant women.

| | Normal-weight (n=466) | Overweight (n=257) | p |
|---|---|---|---|
| **Maternal age (years)** | 25 (21–30) | 28 (23–33) | <0.01 |
| **Parity** | 1 (0–2) | 1 (0–2) | NS |
| **BMI at first trimester (kg/m$^2$)** | 22.2 (20.6–23.4) | 27.2 (25.8–29.5) | <0.01 |
| **BMI at delivery (kg/m$^2$)** | 28.0 (26.2–29.6) | 32.8 (30.7–24.9) | <0.01 |
| **Gestational age at sampling (weeks)** | 25.2 (18.7–33.4) | 27.4(19.0–37.9) | NS |
| **Gestational age at delivery (weeks)** | 39.8 (38.8–40.4) | 39.7 (39.0–40.5) | NS |

Values are expressed as median and interquartile range (IQR)

BMI-Body Mass Index; NS- not significant

**Table II**

Demographic and clinical characteristics of normal weight and overweight/obese pregnant women according to gestational age at sampling.

| | 11–14 weeks (n=53) | 15–18 weeks (n=62) | 19–22 weeks (n=62) | 23–26 weeks (n=65) | 27–30 weeks (n=61) | 31–34 weeks (n=54) | Term in labor (n=58) | Term not in labor (n=51) |
|---|---|---|---|---|---|---|---|---|
| **Normal weight** | | | | | | | | |
| **Maternal age (years)** | 24 (21–30) | 24 (21–29) | 25 (21–31) | 24 (20–30) | 25 (21–30) | 24 (21–31) | 25 (21–30) | 24 (20–29) |
| **BMI at first trimester (kg/m2)** | 22.5 (20.1–23.6) | 22.0 (20.5–23.6) | 21.9 (20.3–23.0) | 22.2 (20.9–23.4) | 22.1 (20.7–22.9) | 22.6 (20.8–23.7) | 22.3 (20.9–23.7) | 21.8 (20.4–23.2) |
| **BMI at delivery (kg/m2)** | 28.3 (26.6–30.0) | 28.4 (26.4–30.0) | 27.6 (25.9–29.2) | 27.8 (26.0–29.6) | 27.7 (26.2–28.7) | 28.5 (27.0–30.2) | 28.0 (25.7–29.4) | 28.0 (25.2–29.6) |
| **Gestational age at delivery (weeks)** | 40.0 (39.0–40.4) | 39.7 (38.5–40.2) | 39.8 (38.6–40.5) | 39.7 (38.6–40.4) | 39.8 (39.0–40.4) | 40.0 (39.3–40.2) | 39.7 (38.6–40.2) | 39.7 (38.8–40.1) |
| **Overweight/Obese** | | | | | | | | |
| | **11–14 weeks (n=31)** | **15–18 weeks (n=31)** | **19–22 weeks (n=31)** | **23–26 weeks (n=29)** | **27–30 weeks (n=34)** | **31–34 weeks (n=32)** | **Term in labor (n=40)** | **Term not in labor (n=29)** |
| **Maternal age (years)** | 26 (23–32) | 26 (21–32) | 27 (24–34) | 31 (26–36) | 30 (25–34) | 25 (22–30) | 27 (24–32) | 30 (23–34) |
| **BMI at first trimester (kg/m2)** | 27.9 (25.8–29.4) | 26.2 (25.4–28.4) | 27.9 (25.9–29.9) | 27.2 (25.8–30.2) | 27.4 (25.9–31.4) | 26.8 (25.7–28.8) | 27.0 (25.6–29.7) | 28.1 (26.2–31.2) |
| **BMI at delivery (kg/m2)** | 32.4 (31.4–35.5) | 32.4 (30.1–34.0) | 32.4 (31.5–35.0) | 32.0 (30.0–35.1) | 32.4 (30.1–35.6) | 33.1 (30.4–34.7) | 33.3 (30.9–34.5) | 33.9 (31.4–37.4) |
| **Gestational age at delivery (weeks)** | 39.2 (39.0–40.2) | 40.0 (39.0–40.8) | 39.7 (39.0–40.1) | 39.8 (38.9–40.7) | 40.0 (39.0–40.5) | 39.3 (38.8–40.5) | 39.4 (38.5–40.4) | 40.0 (38.7–40.7) |

Values are expressed as median and interquartile range (IQR)

**Table III**

Total HMW, MMW and LMW adiponectin serum concentrations (ng/mL) in normal weight pregnant women

| | Gestational Age (weeks) | Percentiles | | | | |
|---|---|---|---|---|---|---|
| | | 10 | 25 | 50 | 75 | 90 |
| **Total Adiponectin ng/mL** | **11–14 (n=53)** | 4604 | 5490 | 6578 | 9416 | 10897 |
| | **15–18 (n=62)** | 3593 | 5087 | 7338 | 8716 | 9745 |
| | **19–22 (n=62)** | 4190 | 4953 | 6697 | 8364 | 10580 |
| | **23–26 (n=65)** | 4215 | 4712 | 5780. | 8689 | 10142 |
| | **27–30 (n=61)** | 4081 | 5473 | 7008 | 9085 | 10847 |
| | **31–34 (n=54)** | 4236 | 5249 | 7304 | 8927 | 10963 |
| | **Term in labor (n=58)** | 4649 | 6012 | 7080 | 8823 | 11554 |
| | **Term not in labor (n=51)** | 3379 | 4658 | 6528 | 8707 | 10133 |
| **HMW Adiponectin ng/mL** | **11–14 (n=53)** | 2040 | 2998 | 3961 | 5636 | 7317 |
| | **15–18 (n=62)** | 1744 | 2815 | 4172 | 5391 | 6724 |
| | **19–22 (n=62)** | 2048 | 2837 | 3674 | 4872 | 7115 |
| | **23–26 (n=65)** | 1824 | 2768 | 3338 | 5126 | 6981 |
| | **27–30 (n=61)** | 1866 | 2496 | 4036 | 6005 | 6831 |
| | **31–34 (n=54)** | 1940 | 2587 | 4084 | 5472 | 6470 |
| | **Term in labor (n=58)** | 2434 | 3277 | 4405 | 5585 | 7771 |
| | **Term not in labor (n=51)** | 1802 | 2203 | 3916 | 5240 | 6061 |
| **MMW Adiponectin ng/mL** | **11–14 (n=53)** | 619 | 915 | 1456 | 2008 | 2701 |
| | **15–18 (n=62)** | 794 | 1055 | 1412 | 1813 | 2215 |
| | **19–22 (n=62)** | 645 | 1077 | 1467 | 2075 | 2565 |
| | **23–26 (n=65)** | 859 | 1044 | 1391 | 1790 | 2979 |
| | **27–30 (n=61)** | 683 | 1044 | 1507 | 1889 | 2425 |
| | **31–34 (n=54)** | 778 | 1180 | 1551 | 2048 | 2451 |
| | **Term in labor (n=58)** | 751 | 1253 | 1657 | 2090 | 2541 |
| | **Term not in labor (n=51)** | 545 | 884 | 1312 | 1916 | 2441 |
| **LMW Adiponectin ng/mL** | **11–14 (n=53)** | 360 | 916 | 1381 | 2099 | 2592 |
| | **15–18 (n=62)** | 385 | 785 | 1193 | 1897 | 2238 |
| | **19–22 (n=62)** | 438 | 817 | 1211 | 1580 | 2118 |
| | **23–26 (n=65)** | 355 | 759 | 1114 | 1595 | 2009 |

| | Gestational Age (weeks) | Percentiles | | | | |
|---|---|---|---|---|---|---|
| | | **10** | **25** | **50** | **75** | **90** |
| | **27–30 (n=61)** | 536 | 894 | 1188 | 1757 | 2519 |
| | **31–34 (n=54)** | 341 | 959 | 1345 | 1944 | 2706 |
| | **Term in labor (n=58)** | 532 | 782 | 1227 | 1800 | 2132 |
| | **Term not in labor (n=51)** | 478 | 723 | 1223 | 2056 | 2786 |

HMW – high molecular weight; MMW – medium molecular weight; LMW - low molecular weight.

**Table IV**

Total HMW, MMW and LMW adiponectin serum concentrations (ng/mL) in overweight/obese pregnant women

| | Gestational Age (weeks) | Percentiles | | | | |
|---|---|---|---|---|---|---|
| | | 10 | 25 | 50 | 75 | 90 |
| **Total Adiponectin ng/mL** | **11–14 (n=31)** | 3445 | 4270 | 5831 | 7208 | 10264 |
| | **15–18 (n=31)** | 3813 | 4534 | 5912 | 7744 | 10781 |
| | **19–22 (n=31)** | 3142 | 4348 | 5868 | 6162 | 7768 |
| | **23–26 (n=29)** | 3384 | 3905 | 5241 | 7826 | 10567 |
| | **27–30 (n=34)** | 3818 | 4770 | 6745 | 8715 | 11467 |
| | **31–34 (n=32)** | 3625 | 4291 | 5056 | 7183 | 8836 |
| | **Term in labor (n=40)** | 3869 | 4675 | 5983 | 8019 | 9534 |
| | **Term not in labor (n=29)** | 3751 | 4418 | 5238 | 6945 | 9096 |
| **HMW Adiponectin ng/mL** | **11–14 (n=31)** | 1235 | 1980 | 2723 | 3770 | 6033 |
| | **15–18 (n=31)** | 1961 | 2509 | 3123 | 4869 | 6960 |
| | **19–22 (n=31)** | 1587 | 2246. | 2795 | 3334 | 4537 |
| | **23–26 (n=29)** | 1411 | 1782 | 2913 | 4678 | 6305 |
| | **27–30 (n=34)** | 1937 | 2535 | 3711 | 5277 | 6946 |
| | **31–34 (n=32)** | 1704 | 2115 | 2672 | 3847 | 5869 |
| | **Term in labor (n=40)** | 1739 | 2255 | 3358 | 4792 | 6602 |
| | **Term not in labor (n=29)** | 1583 | 2110 | 2946 | 3783 | 4775 |
| **MMW Adiponectin ng/mL** | **11–14 (n=31)** | 724 | 1049 | 1402 | 1733 | 2349 |
| | **15–18 (n=31)** | 712 | 808 | 1233 | 1968 | 2286 |
| | **19–22 (n=31)** | 495 | 915 | 1171 | 1590 | 1933 |
| | **23–26 (n=29)** | 711 | 886 | 1212 | 1609 | 2111 |
| | **27–30 (n=34)** | 619 | 955 | 1418 | 2015 | 2479 |
| | **31–34 (n=32)** | 539 | 786 | 1204 | 1608 | 1829 |
| | **Term in labor (n=40)** | 676 | 907. | 1331 | 1715 | 2531 |
| | **Term not in labor (n=29)** | 701 | 1068 | 1468 | 1879 | 2343 |
| **LMW Adiponectin ng/mL** | **11–14 (n=31)** | 387 | 894 | 1550 | 1986 | 2579 |
| | **15–18 (n=31)** | 640 | 851 | 1123 | 1523 | 2443 |
| | **19–22 (n=31)** | 503 | 835 | 1203 | 1941 | 2383 |
| | **23–26 (n=29)** | 676 | 864 | 1260 | 1545 | 2859 |

| | Gestational Age (weeks) | Percentiles | | | | |
|---|---|---|---|---|---|---|
| | | **10** | **25** | **50** | **75** | **90** |
| | **27–30 (n=34)** | 530 | 967 | 1576 | 1861 | 2451 |
| | **31–34 (n=32)** | 498 | 802 | 1280 | 1719 | 2456 |
| | **Term in labor (n=40)** | 373 | 731 | 1101 | 1623 | 1832 |
| | **Term not in labor (n=29)** | 578 | 695 | 1104 | 1453 | 2548 |

HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.