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Maternal visfatin concentration in normal pregnancy

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Abstract

Objective: Adipose tissue has now emerged as a powerful endocrine organ via the production of adipokines. Visfatin, a novel adipokine with diabetogenic and immunomodulatory properties has been implicated in the pathophysiology of insulin resistance in patients with obesity and Type-2 diabetes mellitus. The aim of this study was to determine whether there are changes in the maternal plasma concentration of visfatin with advancing gestation and as a function of maternal weight.

Study design: In this cross-sectional study, maternal plasma concentrations of visfatin were determined in normal weight and overweight/obese pregnant women in the following gestational age groups: 1) 11–14 weeks (n=52); 2) 19–26 weeks (n=68); 3) 27–34 weeks (n=93); and 4) >37 weeks (n=60). Visfatin concentrations were determined by ELISA. Non parametric statistics were used for analysis.

Results: 1) The median maternal plasma visfatin concentration was higher in pregnant women between 19–26 weeks of gestation than that of those between 11–14 weeks of gestation ($P<0.01$) and those between 27–34 weeks of gestation ($P<0.01$); 2) among normal

weight pregnant women, the median plasma visfatin concentrations of women between 19–26 weeks of gestation was higher than that of those between 11–14 weeks ($P<0.01$) and those between 27–34 weeks ($P<0.01$); and 3) among overweight/obese patients, the median maternal visfatin concentration was similar between the different gestational age groups.

Conclusion: The median maternal plasma concentration of visfatin peaks between 19–26 and has a nadir between 27–34 weeks of gestation. Normal and overweight/obese pregnant women differed in the pattern of changes in circulating visfatin concentrations as a function of gestational age.

Keywords: Adipokines; obesity; overweight; pregnancy; visfatin.

Introduction

Adipose tissue, originally considered to be a passive depot for energy storage, has recently emerged as a powerful endocrine organ via the production of adipokines [61, 62, 154, 185–187]. The adipokine family includes structurally and functionally diverse and highly active peptides and proteins. Indeed, the adipokines encompass cytokines [e.g., tumor necrosis factor (TNF)- α [76, 77, 96, 128, 190] and interleukin (IL)-6 [39, 59, 127, 151, 191, 192], chemokines (e.g., monocyte chemoattractant protein-1) [122, 168], mediators of vascular hemostasis (e.g., plasminogen activator inhibitor-1) [5, 47, 174], blood pressure (e.g., angiotensinogen) [84, 93], and angiogenesis (e.g., vascular endothelial growth factor) [37, 50], as well as hormones regulating glucose homeostasis (adiponectin [8, 15, 78, 85, 86, 115, 121, 130, 169], resistin [12, 75, 97, 105, 178], and leptin [51, 60, 63, 69, 110, 114, 203]). Much attention has been focused on the endocrine actions of the adipokines, particularly to their suggested roles in regulating metabolic processes. Adipokines have been implicated in the pathophysiology of insulin resistance [25, 99, 112, 124, 158, 175, 179], obesity [49, 100, 199], hyperlipidemia [52, 189], and atherosclerosis [143–145], thus providing a putative mechanistic linkage between obesity and abnormal metabolic conditions.

Recently, the important role of adipokines has been corroborated in normal human gestation and common complications of pregnancy: 1) increased circulating maternal concentrations of leptin [10, 94, 99, 124], C-reactive protein (CRP) [124], TNF- α [7, 10, 98, 99, 124,

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195], resistin [35] and visfatin [102, 107] were reported in patients with gestational diabetes mellitus (GDM). Consistent with these findings, patients with GDM had lower concentrations of adiponectin than normal pregnant women [10, 40, 98, 156, 158, 184, 188, 197]; 2) overweight pregnant women have a lower plasma concentration of adiponectin [73, 134] and a higher concentration of leptin [73] than non-obese pregnant women; and 3) preeclampsia is associated with increased concentrations of leptin [4, 33, 73, 87, 113, 123, 136, 137, 147, 183], visfatin [54], and TNF- α [38, 101, 172], as well as decreased concentrations of resistin [34, 40] and altered maternal circulating adiponectin [40, 71, 73, 90, 113, 131, 135, 155, 180].

Visfatin, a newly discovered 52 kDa adipokine, had already been identified more than a decade ago as a growth factor for early B cell, termed pre-B cell colony-enhancing factor (PBEF) [81, 119, 140, 166, 200]. The re-discovery of visfatin as an adipose tissue derived hormone has facilitated the investigation of its metabolic effects. This adipokine is preferentially produced by visceral adipose tissue [79, 171, 182], and exerts insulin-mimicking effects [171, 198] through the activation of an insulin receptor. *In vitro* exposure of adipocytes to glucose results in increased secretion of visfatin [67], and visfatin deficient mice have an impaired glucose tolerance [159]. Studies in humans have demonstrated that administration of glucose results in an increase in circulating visfatin concentration [67]. In addition there is a higher circulating concentration of this hormone in patients with Type-2 diabetes mellitus (Type-2 DM) when compared to non-diabetic subjects [36, 55, 111, 167].

Only few studies have addressed the concentration of visfatin in pregnant women [31, 53, 54, 65, 102, 107, 116, 117, 120]. Most of these reports are confined to complications of pregnancy such as preeclampsia [53, 54], fetal growth restriction [53, 116] and GDM [31, 65, 102, 107]. Only a single study reported maternal visfatin concentrations along gestation [120] and there is no information available regarding the comparison between circulating visfatin in normal and overweight pregnant women. Thus, the aims of this study were to determine whether there are changes in maternal plasma concentration of visfatin associated with advancing gestation and as a function of maternal weight.

Materials and methods

A cross-sectional study was conducted by searching our clinical database and bank of biological samples. Two-hundred and seventy-three pregnant women with a normal singleton pregnancy were included in the study. The inclusion criteria were: 1) no medical, obstetrical or surgical complications; 2) intact membranes; 3) delivery of a term neonate (>37 weeks), and 4) birth weight above the 10th percentile [6]. Women with multiple preg-

nancies, GDM and fetal congenital malformations were excluded.

Maternal blood samples were obtained once from each pregnant woman at the following gestational ages: 1) 11–14 weeks (n=52); 2) 19–26 weeks (n=68); 3) 27–34 weeks (n=93); and 4) >37 weeks (n=60). Blood was centrifuged at 1300 \times g for 10 min at 4°C. The plasma obtained was stored at -80°C until the assay was performed.

The body mass index (BMI) in the first trimester was calculated according to the following formula: weight (kg)/height (m)². According to the definitions of the World Health Organization (WHO) [1], normal BMI was defined as 18.5–24.9 kg/m² and overweight/obese as BMI \geq 25 kg/m².

All women provided written informed consent prior to the collection of maternal blood samples. The utilization of samples for research purposes was approved by the institutional review boards of Wayne State University, Sotero del Rio Hospital (Chile) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD/NIH/DHHS). Many of these samples have been previously employed to study the biology of inflammation, hemostasis, angiogenesis, and growth factors concentrations in normal pregnant women and those with pregnancy complications.

Human visfatin C-terminal immunoassay

The concentrations of visfatin in maternal plasma were determined using specific and sensitive enzyme immunoassays purchased from Phoenix Pharmaceuticals, Inc (Belmont, CA, USA). Visfatin C-terminal assays were validated in our laboratory for human plasma prior to the conduction of this study. Validation included spike and recovery experiments, which produced parallel curves indicating that maternal plasma matrix constituents did not interfere with antigen- antibody binding in this assay system. Visfatin enzyme immunoassays are based on the principle of competitive binding and were conducted according to the manufacturer's recommendations. Briefly, assay plates are pre-coated with a secondary antibody and the non-specific binding sites have been blocked. Standards and samples were incubated in the assay plates along with primary antiserum and biotinylated peptide. The secondary antibody in the assay plates bound to the Fc fragment of the primary antibody whose Fab fragment competitively bound with both the biotinylated peptide and peptide standard or targeted peptide in the samples. Following incubation, the assay plates were repeatedly washed to remove unbound materials and incubated with a streptavidin-horseradish peroxidase (SA-HRP) solution. Following incubation, unbound enzyme conjugate was removed by repeated washing and a substrate solution was added to the wells of the assay plates and color developed in proportion to the amount of biotinylated peptide-SA-HRP complex but inversely proportional to the amount of peptide in the standard solutions or the samples. 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). Maternal plasma concentrations of visfatin C were determined by interpolation from individual standard curves composed of human visfatin peptide. The calculated inter- and intra-assay coefficients of variation (CVs) for visfatin C-terminal immunoassays in our laboratory were 5.3% and 2.4%, respectively. The sensitivity was calculated to be 0.04 ng/mL.

Statistical analysis

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normal distribution of the data. Data were presented as median and interquartile range (IQR) or median and range. Non-parametric methods were used for parameters which were not normally distributed such as maternal visfatin concentrations and comparisons among groups were performed using the Kruskal-Wallis test with post hoc test (Mann-Whitney *U*). For those parameters which were normally distributed, parametric tests were used for analysis and the comparisons among groups were performed using one-way ANOVA with Bonferroni adjustment for the calculated P-value in order to maintain the significance level at 0.05.

Correlation between visfatin and gestational age at sampling, maternal age, maternal BMI, birth weight and storage time was conducted with the Spearman's rank test. The statistical package employed was SPSS 14 (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 was considered statistically significant.

Results

The clinical and obstetrical characteristics of the study groups are presented in Table 1. There were no significant differences in maternal age, first trimester BMI, gestational age at delivery and birth weight among the four gestational age groups.

Maternal plasma concentrations of visfatin in normal pregnancy

Visfatin was detected in the plasma of all subjects. Pregnant women between 19–26 weeks of gestation had a higher median concentration of visfatin than those between 11–14 weeks of gestation (median: 17.5 ng/mL range: 5.6–31.0 vs. 15.0 ng/mL, 9.3–27.8, respectively; $P < 0.01$). Similarly, pregnant women between 19–26 weeks of gestation had a higher median concentration of visfatin than those between 27–34 weeks of gestation (median: 17.5 ng/mL range: 5.6–31.0 ng/mL vs. 14.8 ng/mL, 5.6–37.0, respectively; $P < 0.01$) (Figure 1). There was no significant difference in the median maternal plasma visfatin concentration among the other groups (Figure 1).

Comparison between maternal visfatin in normal and overweight/obese women

Among normal weight pregnant women, the median plasma visfatin concentrations between 19–26 weeks of gestation were higher than that of those between 11–14 weeks (median: 18.1 ng/mL, range: 5.6–31.0 vs. 14.7 ng/mL, 9.4–27.8, respectively; $P < 0.01$) and those between 27–34 weeks (median: 18.1 ng/mL, range: 5.6–31.0 vs. 13.9 ng/mL, 5.6–36.4, respectively; $P < 0.01$) (Figure 2). In contrast, among overweight/obese patients, the median maternal plasma visfatin concentration did not significantly differ among the various gestational age groups.

The median maternal plasma visfatin concentration was compared between normal and overweight/obese patients regardless of gestational age group (Figure 2). There was no correlation between the maternal plasma visfatin concentration and maternal age, gestational age at blood collection or birthweight irrespective of BMI category or gestational age group.

Discussion

Principal findings of the study

1) Pregnant women between 19–26 weeks of gestation had a significantly higher median plasma concentration of visfatin than those between 11–14 weeks and 27–34 weeks of gestation; 2) among normal weight women, the median plasma visfatin concentration at 19–26 weeks of gestation was higher than those between 11–14 weeks and those between 27–34 weeks; 3) among overweight patients, the median maternal visfatin concentration was similar between the different gestational age groups.

Adipokines – a new culprit in insulin resistance during pregnancy

Pregnancy is a unique physiologic state characterized by profound and transitory insulin resistance [17, 21–23, 26–28, 42, 58, 64, 103, 104, 106, 109, 149, 157, 164,

Table 1 Clinical and demographic characteristics of the study population.

	11–14 weeks (n=52)	19–26 weeks (n=68)	27–34 weeks (n=93)	≥37 weeks (n=60)	P*
Maternal age (years)	25.0 (22.0–31.0)	27.0 (22.0–33.0)	25.0 (21.0–31.0)	27.0 (22.0–30.0)	0.81
Parity	1 (0–2)	1 (0–2)	1 (0–1)	1 (0–2)	0.74
BMI (kg/m ²)	(23.2–27.0)	22.8 (21.0–25.2)	23.4 (21.6–26.3)	23.5 (22.0–25.6)	0.45
Gestational age at sampling (weeks)	13.0 (12.2–13.5)	20.7 (20.0–21.5)	31.7 (27.8–33.0)	39.5 (38.6–40.4)	<0.01
Gestational age at delivery (weeks)	39.4 (38.7–40.4)	39.7 (38.7–40.4)	40.0 (39.0–40.4)	39.5 (38.6–40.1)	0.33
Birth weight (g)	3420 (3205–3660)	3380 (3120–3740)	3470 (3235–3702)	3415 (3157–3717)	0.67

Values are expressed as median and interquartile range (IQR); BMI = body mass index.

*Kruskal-Wallis test.

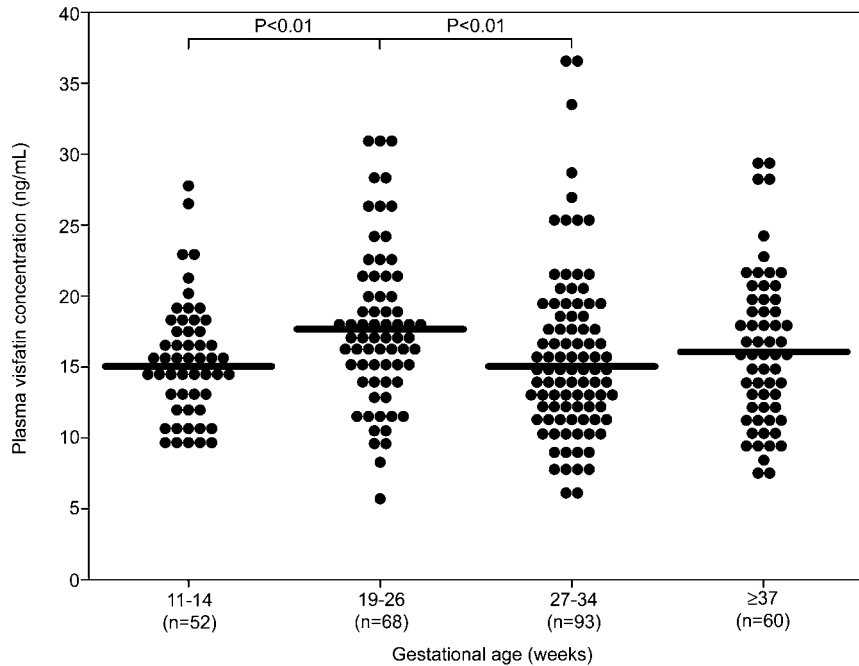


Figure 1 Comparison of median maternal plasma concentrations of visfatin between 11–14, 19–26, 27–34, and ≥ 37 weeks of gestation. Pregnant women between 19–26 weeks of gestation had a higher median concentration of visfatin than women between 11–14 weeks of gestation (median: 17.5 ng/mL range: 5.6–31.0 vs. 15.0 ng/mL, 9.3–27.8, respectively; $P < 0.01$). Similarly, pregnant women between 19–26 weeks of gestation had a higher median concentration of visfatin than women between 27–34 weeks of gestation (median: 17.5 ng/mL range: 5.6–31.0 vs. 14.8 ng/mL, 5.6–37.0, respectively; $P < 0.01$). There was no difference in the median maternal plasma visfatin concentration between the other groups.

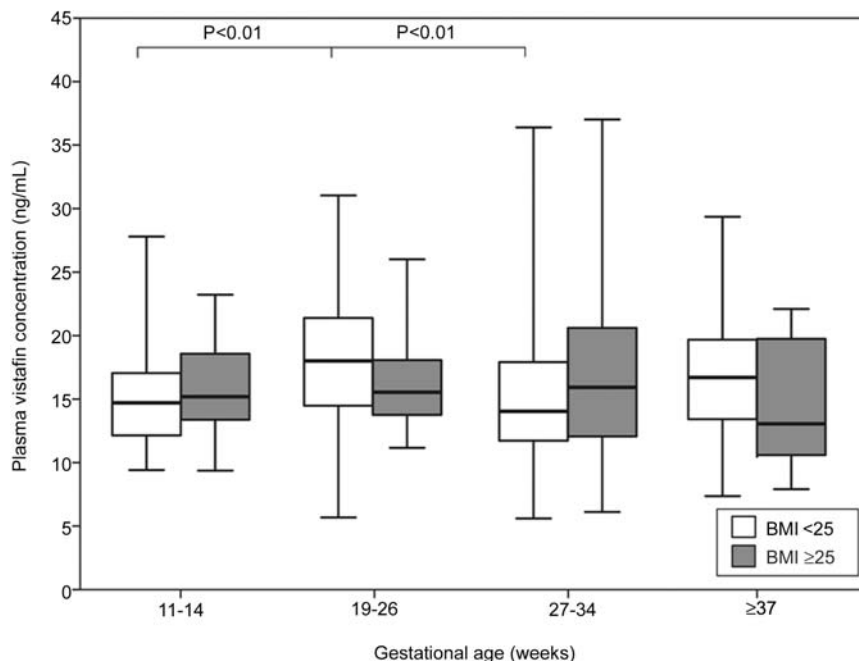


Figure 2 Median maternal plasma visfatin concentrations during pregnancy in women of normal weight (BMI < 25) and overweight/obese (BMI ≥ 25). Among normal weight pregnant women, the median plasma visfatin concentration of women between 19–26 weeks of gestation was higher than those between 11–14 weeks (median: 18.1 ng/mL range: 5.6–31.0 vs. 14.7 ng/mL, 9.4–27.8, respectively; $P < 0.01$) and those between 27–34 weeks (median: 18.1 ng/mL range: 5.6–31.0 vs. 13.9 ng/mL, 5.6–36.4, respectively; $P < 0.01$). Among overweight/obese patients, the median maternal visfatin concentration was comparable between the different gestational age groups.

177]. This important metabolic alteration is thought to be induced by placental hormones. Several lines of evidence support this view: 1) *in vitro*, exposure of adipocytes to progesterone, cortisol, prolactin, or human placental lactogen, induced post binding defect in insulin action [163]; 2) insulin resistance can be induced by administration of human placental lactogen (HPL) [92, 165], progesterone [14, 41, 91], estrogen [41, 150] and glucocorticosteroids [92] to non-pregnant subjects and mice [13]; and 3) insulin resistance during pregnancy rises in the third trimester [17, 21, 29, 164, 176, 193] with the increase in the placental hormone secretion.

Previously, placental hormones were thought to be the only culprits for insulin resistance in pregnancy. However, with the recognition of the adipose tissue as a powerful endocrine organ [45, 88, 89, 161], its role in the pathophysiology of insulin resistance via the production and secretion of adipokines [61, 62, 154, 185–187] has been established. The adipokine family includes highly active molecules such as: IL-6 [191, 192], TNF- α [77, 190], leptin [51, 60], adiponectin [8, 15, 85, 121], resistin [12, 75, 97, 105, 178], and others [16, 105, 146, 160, 161]. Accumulating evidence suggests that adipokines play a role in the regulation of insulin resistance during human pregnancy: 1) maternal serum concentrations of leptin [120, 124, 126], adiponectin [7, 25, 43, 112, 124, 158], TNF- α [7, 19, 99, 124–126], resistin [71] and visfatin [120] are correlated with insulin resistance indices such as homeostasis model of assessment of insulin resistance (HOMA-IR); 2) patients with gestational diabetes mellitus (GDM) have increased concentrations of leptin [10, 94, 99, 124], C-reactive protein (CRP) [124], TNF- α [7, 10, 98, 99, 124, 195], resistin [35] and visfatin [102, 107], and lower concentrations of adiponectin than normal pregnant women [10, 40, 98, 156, 158, 184, 188, 197]; and 3) high concentrations of CRP [152, 196] and leptin [153], as well as low concentrations of adiponectin [194] in first and early second trimester, are associated with increased risk for GDM, suggesting a role for these adipokines in the pathophysiology of this condition.

Visfatin is a novel adipokine with metabolic and immunoregulatory properties

Visfatin, a newly discovered 52 kDa adipokine, is preferentially produced by visceral adipose tissue [79, 171, 182]. However, this protein is not tissue specific, and it can be expressed in placenta, fetal membranes [95, 119, 132, 133, 139–142] and myometrium [48], as well as in bone marrow, liver, muscle [166], heart, lung, kidney [166], macrophages [44], and neutrophils [81, 166, 200]. The specific physiologic role of visfatin has eluded elucidation; nevertheless, increasing body of evidence suggests that this hormone has immunoregulatory and metabolic properties.

The role of visfatin in the regulation of the inflammatory response has been highlighted in several reports: 1) vis-

fatin promotes the growth of B cell precursors [166]; 2) *in vitro*, visfatin up-regulates the production of the pro- and anti-inflammatory cytokines (e.g., IL-6, TNF- α , IL-1 β and IL-10) by human monocytes, in a dose dependent manner [129]; 3) the expression of visfatin is increased following exposure to TNF- α (in monocytes [44], macrophages [80] and neutrophils [81]), IL-6 (synovial [138] and amniotic epithelial [139] cells), IL-8, as well as granulocyte/macrophage colony stimulating factor (in neutrophils [81]); 4) the expression of visfatin increased in cells retrieved by bronchoalveolar lavage from patients with acute lung injury [200] in neutrophils of septic patients, [81] and in lung tissue of animals with acute lung injury [201]; 5) patients with the -1001G allele in the visfatin gene have increased risk of developing ARDS than wild-type homozygotes, while the -1543T allele is associated with decreased risk of developing ARDS in septic shock patients [11]; and 6) patients with chronic inflammatory disorders (e.g., inflammatory bowel disease, rheumatoid arthritis) have an elevated serum visfatin concentration [81, 200, 201].

The evidence for the metabolic effect of this hormone includes: 1) visfatin has insulin mimetic properties [171, 198]; 2) *in vitro* exposure of adipocytes to glucose results in increased secretion of visfatin [67]; 3) serum concentration of visfatin in humans correlates with the amount of intra-visceral fat as determined by computerized tomography scan [167]; 4) administration of glucose to human subjects results in an increase in circulating visfatin concentration [67]; 5) patients with Type-2 diabetes mellitus or metabolic syndrome [56, 57] have higher circulating visfatin concentrations than non-diabetic subjects [36, 55, 111, 167]; and 6) visfatin serum concentrations are higher in patients with GDM [102, 107] than in normal pregnant women.

Changes in plasma visfatin concentration during normal pregnancy

Our findings that the median maternal plasma concentration of visfatin peaks between 19–26 weeks and has a nadir between 27–34 weeks of gestation only in normal weight women, are novel. There are only a few reports regarding circulating visfatin concentrations in pregnant women [31, 53, 65, 102, 107, 116, 117, 120]. Indeed, only a single study reported the results of comparison of maternal visfatin concentrations between the three trimesters of pregnancy [120], and none included a comparison of circulating maternal visfatin concentrations between normal and overweight pregnant women. Our results are in agreement with the findings reported by Mastorakos et al. [120] in which median concentration of visfatin were higher in the second (24–26 weeks) and third trimester (34–36 weeks) than those in the first trimester (10–12 weeks) in a longitudinal study of 80 normal lean women. Our findings extend the latter report by demonstrating that the increase in the median plasma

visfatin concentration is confined to normal weight pregnant women. In addition, we included pregnant women with a wide range of gestational ages; thus, we were able to report a nadir in maternal visfatin concentrations during the early third trimester.

Why are there fluctuations in circulating visfatin with advancing gestation?

Given the diabetogenic effect of visfatin, it is tempting to suggest that the median visfatin concentration increases during pregnancy in association with insulin resistance and the increase in maternal weight. Indeed, several reports concerning non-pregnant subjects have argued in favor of this association [18, 36, 55, 66–68, 111, 167]. Our findings regarding the nadir in the median plasma concentration of visfatin in the early third trimester, does not support this hypothesis. Of note, recent reports have challenged the association between visfatin and insulin resistance [9, 20, 46, 70, 148], BMI or obesity [46, 148]. Hence, additional explanations must be thought in order to explain our results.

Prima facie, our findings indicate that there is no association between weight gain during pregnancy and the fluctuations in the median visfatin concentrations along gestation. However, previous studies have indicted that the highest maternal weight gain rate (expresses as the increase in body weight per week) occurs during the second trimester [3, 72, 74, 170]. Furthermore, the fetal weight gain is lower during the second trimester than in the third trimester; thus, second trimester maternal weight gain reflects mainly maternal tissue growth. In summary, the pattern of the alteration in maternal plasma visfatin concentration with advancing gestation in normal weight pregnant women may follow the changes in the rate of maternal weight gain rather than weight gain *per se*.

Pregnancy, maternal BMI and circulating visfatin concentration – is increased BMI associated with alteration in circulating visfatin?

The finding that normal and overweight/obese pregnant women had a comparable median visfatin concentration is novel. The association between circulating visfatin and obesity, BMI and visceral fat depot is still shrouded with uncertainty. Indeed, the lack of an association between circulating visfatin and BMI [36, 46, 53, 55, 83, 102, 118, 173, 181, 202], as well as a positive [18, 32, 108, 167] and negative [31] association between the two have been reported. Other investigators could not demonstrate an association between visceral fat mass and plasma visfatin concentrations [18]. Moreover, both higher [18, 32, 56, 57, 66, 83, 167, 202] and lower [82, 148] concentrations of visfatin in obese, than in normal subjects, were reported. Although one can explain some of the discrepancies by differences in the methods and the

characteristics of the various study groups, currently, it is unclear whether or not circulating visfatin concentrations are associated with body weight and adipose tissue. In summary, the comparable median maternal visfatin concentration between normal and overweight/obese women reported herein, supports the recent studies challenging the suggested association between visfatin and overweight and obesity.

We hypothesized that, in normal weight healthy pregnant women, the alteration in visfatin concentrations with advancing gestation corresponds with the rate of maternal weight gain. Interestingly, during pregnancy, overweight and obese patients gain less weight [2, 24, 30, 162] and at a slower rate [3] than normal weight women. Thus, it is tempting to suggest that the different pattern of maternal circulating visfatin concentrations with advancing gestation in overweight than in normal weight women reflects the decreased rate and the lower absolute weight gain in overweight pregnant patients.

Currently, clinical data concerning maternal circulating visfatin concentrations are scant. Indeed, this is the first description of a nadir in maternal visfatin concentrations in the early third trimester and a blunted change in maternal circulating visfatin with advancing gestational age in overweight pregnant women. A cause and effect relationship between BMI and maternal circulating visfatin concentrations cannot be discerned from the data of the present study; however, a plausible explanation for our result can be the differences in weight gain rate in the different trimesters and between normal and overweight pregnant women, suggesting a role for visfatin in physiologic metabolic alterations of human pregnancy.

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