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Maternal Plasma Concentration of the Pro-Inflammatory Adipokine Pre-B-Cell Enhancing Factor (PBEF)/ Visfatin Is Elevated In Pregnant Patients with Acute Pyelonephritis

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Abstract

Problem—Visfatin/pre-B-cell enhancing factor (PBEF) has been implicated in the regulation of the innate immune system, as well as in glucose metabolism. Specifically, visfatin plays a requisite role in delayed neutrophil apoptosis in patients with sepsis. The aim of this study was to determine whether pyelonephritis during pregnancy is associated with changes in maternal plasma visfatin concentration in normal weight and overweight/obese patients.

Methods of Study—This cross-sectional study included the following groups: 1) normal pregnant women (n=200); and 2) pregnant women with pyelonephritis (n=40). Maternal plasma visfatin concentrations were determined by ELISA. Non-parametric statistics were used for analyses.

Results—1) The median maternal plasma visfatin concentration was significantly higher in patients with pyelonephritis than in those with a normal pregnancy; 2) among overweight/obese pregnant women, those with pyelonephritis had a significantly higher median plasma visfatin concentration than women with a normal pregnancy; and 3) pyelonephritis was independently associated with higher maternal plasma visfatin concentrations after adjustment for maternal age, pre-gestational BMI, smoking status, gestational age at sampling, and birthweight.

Conclusions—Acute pyelonephritis during pregnancy is associated with a high circulating maternal visfatin concentration. These findings suggest that visfatin/PBEF may play a role in the regulation of the complex and dynamic crosstalk between inflammation and metabolism during pregnancy.

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Keywords

acute bacterial infection; adipokines; BMI; cytokine; infection; inflammation; maternal obesity; overweight; pregnancy; urinary tract infection

Introduction

Pregnant women are more susceptible to infections,¹⁻⁴ including lower urinary tract infection⁵ and pyelonephritis,⁶ than non-pregnant women. Indeed, pyelonephritis complicates 1–2% of pregnancies⁷ and is a common indication for hospitalization during pregnancy.⁸ The prevalence of pyelonephritis during the first trimester is relatively low (approximately 4%) and most cases occur during the second and third trimesters (about 67%) or are diagnosed in the postpartum period (approximately 25% of cases).⁶ While the clinical course of most patients is favorable with adequate antimicrobial treatment, pregnant women with pyelonephritis are at increased risk of developing acute respiratory distress syndrome (ARDS),^{9;10} sepsis,^{11;12} and septic shock.^{11;12}

Inflammation is strongly associated with metabolic derangements such as obesity and insulin resistance.^{13;14} A compelling body of evidence suggests that the interaction between metabolism and the immune system involves a complex network of soluble mediators secreted by adipose tissue, collectively termed *adipokines*. Consistent with this view, adipokines such as leptin^{15;16} and adiponectin¹⁷⁻¹⁹ have been implicated in the regulation of both the innate and adaptive limbs of the immune response, while others, such as resistin,^{20;21} are mediators of only the innate immune system. Furthermore, alterations in expression and concentration of adipokines are associated with inflammatory disorders including asthma,²² ulcerative colitis,²³ Crohn's disease,²⁴ rheumatoid arthritis,²⁵ multiple sclerosis,²⁶ recurrent pregnancy loss,²⁷⁻³¹ and obesity.³²⁻⁴⁰ These data have led to the notion of adipose tissue as an immune organ and to the hypothesis that an alteration in adipokines expression and/or secretion is causally linked to inflammation-related disorders.^{13;41}

Visfatin, a 52 kDa molecule, was originally reported to be secreted by activated lymphocytes and to synergize with IL-7 and stem cell factor to stimulate early B-cells, and thus named pre-B-cell enhancing factor (PBEF).⁴² Subsequently, visfatin was reported to be produced by adipose tissue,^{43;44} preferentially by visceral fat, and was recognized as an adipokine. In addition to its role in the regulation of glucose homeostasis, visfatin/PBEF has been implicated in the regulation of the innate immune system.^{13;45} Moreover, visfatin is widely induced by inflammatory stimuli in cells involved in innate immunity such as neutrophils,⁴⁶ monocytes⁴⁷ and macrophages⁴⁸ and plays a requisite role in the delayed neutrophil apoptosis in patients with sepsis.⁴⁶

Only a few studies have assessed the role of visfatin concentration in the presence of infection,^{46;49;50} and there are no studies regarding visfatin concentration in pregnant women with pyelonephritis. Thus, the aim of this study was to determine whether pyelonephritis during pregnancy is associated with changes in maternal plasma visfatin concentration in normal weight and overweight/obese patients.

Materials and methods

Study design and population

A cross-sectional study was conducted by searching our clinical database and bank of biological samples, and included women in the following groups: (1) normal pregnancy (n=200), and (2) pregnant women with pyelonephritis (n=40). Women were considered to

have a normal pregnancy if they met the following criteria: (1) no medical, obstetrical, or surgical complications, (2) absence of labor at the time of venipuncture, and (3) delivery at term (≥ 37 weeks) of a normal healthy infant whose birth weight was between the 10th and 90th percentile for gestational age.⁵¹ Pyelonephritis was diagnosed in the presence of fever (temperature ≥ 38°C), clinical signs of an upper urinary tract infection (e.g., flank pain, costovertebral angle tenderness), and a positive urine culture for microorganisms. None of the patients with pyelonephritis had signs or symptoms of respiratory distress. Women with multiple pregnancies and fetal anomalies were excluded.

The body mass index (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).⁵² The study population was further classified by the pre-gestational BMI into two groups: normal weight and overweight/obese (BMI ≥ 25 kg/m²).

All participating women provided written informed consent prior to enrollment and the collection of blood samples. The collection and use of blood samples for research purposes was approved by the Institutional Review Boards of both the Sotero del Rio Hospital (Santiago, Chile) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (Bethesda, Maryland, USA). Many of these samples have previously been used to study the biology of inflammation, homeostasis, and growth factor concentrations in normal pregnant women and those with pregnancy complications.

Sample collection and Human Visfatin C-terminal immunoassay—Samples of peripheral blood from pregnant women were obtained by venipuncture. Blood was centrifuged at 1300 g for 10 minutes at 4°C. The plasma obtained was stored at -80°C until analysis. Concentrations of visfatin in maternal plasma were determined using specific and sensitive enzyme immunoassays (Phoenix Pharmaceuticals, Inc. Belmont, CA, USA). A validation was performed in our laboratory prior to the conduction of this study. A detailed description of the assay has previously been published.^{39;40;53;54} The calculated inter- and intra-assay coefficients of variation for visfatin C-terminal immunoassays in our laboratory were 5.3% and 2.4%, respectively. The sensitivity of the assay was calculated to be 0.04 ng/ml.

Statistical analysis

Normality of the data was tested using the Kolmogorov-Smirnov test. Since plasma visfatin concentrations were not normally distributed, non-parametric tests were used for analyses. Comparisons between the two groups were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Multiple linear regression analysis was used to determine which factors were significantly and independently associated with maternal plasma visfatin concentration (after log transformation). The following parameters were included in the model: maternal age (years), smoking status, gestational age at blood sampling (weeks), birthweight (grams), pre-gestational BMI (as a categorical variable: <25 kg/m² vs. ≥ 25 kg/m²) and the presence of pyelonephritis. A *p* value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 14 (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of women with a normal pregnancy and those with pyelonephritis are displayed in Table I. Patients with pyelonephritis were younger than those with a normal pregnancy. The median birthweight was significantly lower in patients with pyelonephritis than in those with a normal pregnancy. Table II displays the demographic and

clinical characteristics of the study population according to pre-pregnancy BMI categories (normal weight vs. overweight/obese). There were no significant differences in the rate of nulliparity, smoking status, gestational age at blood sampling, or gestational age at delivery between normal pregnant women and those with pyelonephritis either in the normal weight or the overweight/obese group. The median birthweight was significantly lower in patients with pyelonephritis regardless of the BMI category.

Visfatin concentration in pyelonephritis vs. normal pregnancy

The median maternal plasma visfatin concentration was higher in patients with pyelonephritis than in those with a normal pregnancy (15.7 ng/mL, interquartile range [IQR] 12.9-17.4 vs. 14.4 ng/mL, IQR 11.5-16.5; $p=0.015$, Figure 1).

Visfatin concentration in normal weight pregnant women: pyelonephritis vs. normal pregnancy

Among pregnant women with a normal weight, the median maternal plasma visfatin concentration did not differ significantly between individuals with a normal pregnancy and those with pyelonephritis (14.3 ng/mL, IQR 11.5-16.6 vs. 14.3 ng/mL, IQR 12.6-17.2; $p=0.2$, Figure 2).

Visfatin concentrations in overweight/obese pregnant women: pyelonephritis vs. normal pregnancy

Among overweight/obese pregnant women, those with pyelonephritis had a higher median plasma visfatin concentration than women with a normal pregnancy (15.9 ng/mL, IQR 15.5-17.2 vs. 14.4 ng/mL, IQR 11.4-16.1; $p=0.03$, Figure 3).

Multiple linear regression analysis was employed to examine the relationship between the plasma concentrations of visfatin and pyelonephritis, while adjusting for maternal age, smoking, gestational age at blood sampling, birthweight, and pre-gestational BMI (as a categorical variable: $<25 \text{ kg/m}^2$ vs. $\geq 25 \text{ kg/m}^2$ and the interaction between overweight/obesity and pyelonephritis). The final regression model suggested that the presence of pyelonephritis was independently associated with high maternal plasma visfatin concentrations ($p=0.005$).

Discussion

Principal findings of the study

1) The median maternal plasma visfatin concentration was higher in patients with pyelonephritis than in those with a normal pregnancy; 2) among overweight/obese pregnant women, those with pyelonephritis had a higher median plasma visfatin concentration than normal pregnant women; and 3) among normal weight pregnant women, the median maternal plasma visfatin concentration did not differ significantly between those with a normal pregnancy and patients with pyelonephritis.

Visfatin/PBEF, an adipokine with important immunoregulatory properties

In addition to its well-described role in energy homeostasis,⁵⁵ compelling evidence suggests a pro-inflammatory role for visfatin. The observations that support this view include: 1) visfatin promotes the growth of B-cell precursors;⁴² 2) *in vitro*, visfatin up-regulates the production of pro- and anti-inflammatory cytokines such as IL-6, TNF- α , IL-1 β and IL-10 by human monocyte, in a dose dependent manner;⁵⁶ 3) the expression of visfatin is increased following exposure to TNF- α (monocytes,⁴⁷ macrophages⁴⁸ and neutrophils⁴⁶), IL-6 (synovial⁵⁷ and amniotic epithelial⁵⁸ cells), IL-8 (neutrophils⁴⁶) and granulocyte/

macrophage colony stimulating factor (neutrophils⁴⁶); 4) visfatin is a potent chemotactic factor, particularly for CD14⁺ monocytes and CD19⁺ B-cells; 5) increased visfatin expression has been documented in cells retrieved by bronchoalveolar lavage from patients with acute lung injury,⁵⁰ in the lung tissue of animals with acute lung injury,⁵⁹ as well as by neutrophils of septic patients;⁴⁶ and 6) a polymorphism in the visfatin gene (*1001G* allele) is associated with a greater risk of developing ARDS than wild-type homozygotes; in contrast, the *-1543T* allele is associated with a decreased risk of septic shock patients developing ARDS in.⁶⁰

Maternal circulating visfatin/PBEF concentration in normal gestation and in inflammatory-related complications of pregnancy

Similar to other cytokines⁶¹⁻⁶³ and adipokines,^{21;35-38;53;54;64-77} visfatin has been implicated in the regulation of metabolic adaptations to gestation, as well as in complications of pregnancy. Normal pregnancy is characterized by alterations in maternal circulating visfatin concentrations.^{40;78-82} Metabolic complications of pregnancy such as gestational diabetes mellitus,^{39;83-86} as well as inflammation-related complications of pregnancy such as preeclampsia^{82;87-89} and fetal growth restriction^{90;91} have been linked to changes in circulating maternal visfatin concentrations when compared to normal pregnant women.

Pyelonephritis is characterized by increased maternal circulating visfatin

The present study is the first to determine visfatin concentration in either pregnant or non-pregnant patients with pyelonephritis. Our data demonstrate that pyelonephritis during pregnancy is characterized by a higher median maternal plasma visfatin than normal pregnant women. This novel finding concurs with the observations by Ye et al⁵⁰ and Garcia⁴⁹ which demonstrated that patients with sepsis and acute lung injury had a higher serum visfatin/PBEF levels (as determined by Western blot) than healthy controls. Our findings are also consistent with the report by Jia et al.⁴⁶ in which mRNA expression of visfatin was elevated in cells of the innate immune system (neutrophils and macrophages) obtained from critically ill patients with sepsis. The findings of the present study extend the aforementioned observation by demonstrating an association between elevated plasma visfatin concentration and an infectious disease during pregnancy. Moreover, our findings indicate that elevated circulating visfatin characterized relatively young, hemodynamically stable pregnant women and is not limited to critically ill patients.

Our findings suggest that the difference in circulating visfatin concentrations between normal pregnant women and those with pyelonephritis is due to differences in the circulating concentration of this adipokine between overweight/obese patients with and without pyelonephritis. Indeed, among normal weight individuals the median maternal visfatin concentration was not statistically higher in patients with pyelonephritis than controls. We cannot ascertain from the current study whether the high maternal visfatin concentration is causally related to pyelonephritis and obesity. Nevertheless, it can be postulated that since this adipocytokine is preferentially produced by visceral fat, the findings of the present report may reflect the obvious quantitative differences in fat accrual or altered adipocyte function between normal weight and overweight/obese pregnant women in the presence of pyelonephritis. Importantly, multiple regression analysis has revealed an independent and significant association between circulating maternal visfatin and pyelonephritis. Thus, the disparity in visfatin concentrations between women with and without pyelonephritis in the normal weight and overweight/obese populations should not be attributed only to adiposity.

Visfatin/PBEF concentrations in pregnant patients with pyelonephritis – an evidence for the link between immunity and metabolism?

We recognize that the cross-sectional design of our study does not allow us to demonstrate either a temporal or a causal relationship between high maternal circulating visfatin concentrations and pyelonephritis. Nevertheless, several mechanisms can be invoked to explain our findings. Visfatin/PBEF, a pro-inflammatory adipocytokine, is a mediator of the innate immune system. In addition, the expression of visfatin by neutrophil and monocytes increases in response to inflammatory stimuli. Thus, it is tempting to postulate that the increased maternal visfatin concentration in patients with pyelonephritis is the result of enhanced production and/or secretion of visfatin by innate immune cells. This hypothesis is supported by the observation that pyelonephritis in pregnant women is accompanied by bacteremia and leukocytosis.⁹²⁻⁹⁶ Importantly, Jia et al.⁴⁶ have demonstrated that visfatin plays a requisite role in the delayed neutrophil apoptosis in patients with sepsis. Thus it is conceivable that similar to sepsis, increased maternal visfatin is a mechanism aimed at regulating neutrophil apoptosis.

An additional explanation for our findings relates to the metabolic properties of visfatin. Acute infection is associated with increased energy expenditure, and insulin resistance.⁹⁷⁻⁹⁹ The presence of infectious diseases necessitates prompt metabolic adaptations. The increase in energy demands during infection imposes a serious metabolic challenge on the gravid woman. Visfatin has an insulin-mimetic effect that can ameliorate insulin resistance. Thus, it is possible that the high concentration of circulating visfatin is part of the counter-reaction in response to the metabolic insult aimed at ensuring the glucose flux to maternal tissues. Consistent with these hypotheses, we have recently reported increased amniotic fluid visfatin concentrations in patients with intraamniotic infection/inflammation,⁵⁴ as well as high maternal circulating concentrations of this adipokine in patients with preterm labor.⁵³ Of note, in the latter report, the highest maternal visfatin concentrations were documented in patients with infection/inflammation.

In conclusion, the present study is the first to report an association between circulating visfatin concentration and acute infectious disease in pregnant women. Visfatin has been proposed to play a role in the complex and dynamic crosstalk between inflammation and metabolism. While the relevant mechanisms remain to be elucidated, it is conceivable that visfatin can orchestrate both pathways in the context of infectious disease during human pregnancy.

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Figure 1. Box and whisker plot of the comparison of the median maternal plasma visfatin concentration between women with a normal pregnancy and patients with pyelonephritis
The median maternal plasma visfatin concentration was higher in patients with pyelonephritis than in those with a normal pregnancy (15.7 ng/mL, interquartile range [IQR] 12.9-17.4 vs. 14.4 ng/mL, IQR 11.5-16.5; $p=0.015$).

Figure 2. Box and whisker plot of the comparison of median maternal plasma visfatin concentration in normal weight pregnant women with a normal pregnancy and patients with pyelonephritis

Among pregnant women with a normal weight, the median maternal plasma visfatin concentration did not differ significantly between women with a normal pregnancy and patients with pyelonephritis (14.3 ng/mL, IQR 11.5-16.6 vs. 14.3 ng/mL, IQR 12.6-17.2; p=0.2).

Figure 3. Box and whisker plot of the comparison of median maternal plasma visfatin concentration in overweight/obese pregnant women with a normal pregnancy and patients with pyelonephritis

Among overweight/obese pregnant women, those with pyelonephritis had a higher median plasma visfatin concentration than women with a normal pregnancy (15.9 ng/mL, IQR 15.5-17.2 vs. 14.4 ng/mL, IQR 11.4-16.1; $p=0.03$).

Table I

Demographic and clinical characteristics of the study population

	Normal Pregnancy (n=200)	Pyelonephritis (n=40)	p
Maternal age (years)	25 (22-31)	21 (19-27)	<0.01
Nulliparity	67 (33.5%)	18 (45%)	0.2
Smoking	15 (7.5%)	5 (12.5%)	0.3
Pre-gestational BMI (kg/m²)	23.4 (21.5-26.2)	22.7 (20.4-25.2)	0.2
GA at blood sampling (weeks)	31.0 (25.3-38.2)	28.9 (21.6-33.2)	0.2
GA at delivery (weeks)	39.7 (38.7-40.4)	39.2 (38.4-40.4)	0.2
Birthweight (g)	3430 (3200-3682)	3130 (2900-3380)	<0.01

Values are expressed as median (interquartile range) or numbers (%).

GA- Gestational age; BMI – Body Mass Index

Table II
Demographic and clinical characteristics of the study population according to the pre-pregnancy body mass index

	Normal Weight		Overweight/Obese	
	Normal Pregnancy (n=132)	Pyelonephritis (n=28)	Normal Pregnancy (n=68)	Pyelonephritis (n=12)
Maternal age (years)	24 (21-30)	21 (18-27)	29 (24-32)	21 (19-26)
Nulliparity	51 (38.6%)	14 (50%)	19 (27.9%)	6 (50%)
Smoking	11 (8.3%)	2 (7.1%)	4 (5.8%)	2 (16.6%)
Pre-gestational BMI (kg/m²)	22.3 (20.5-23.4)	22.0 (20.1-23.2)	27.7 (26.2-29.2)	27.4 (26.0-28.3)
GA at blood sampling (weeks)	27.7 (19.7-33.3)	26.4 (20.9-33.5)	27.2 (18.4-33.3)	24.2 (22.6-35.1)
GA at delivery (weeks)	40.0 (38.7-40.4)	39.2 (38.7-40.4)	39.3 (38.8-40.1)	40.0 (38.1-40.3)
Birthweight (g)	3390 (3165-3610)	3160 (3055-3380)	3505 (3225-3742)	3080 (2640-3780)

Values are expressed as median (interquartile range) or numbers (%).

GA- Gestational age; BMI – Body Mass Index