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Hyperresistinemia – a Novel Feature in Systemic Infection During Human Pregnancy

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Abstract

Problem—Resistin, originally described as an adipokine, has emerged as a potent pro-inflammatory protein associated with both acute and chronic inflammation. Moreover, resistin has been proposed as a powerful marker of sepsis severity, as well as a predictor of survival of critically ill non-pregnant patients. The aim of this study was to determine whether pyelonephritis during pregnancy is associated with changes in maternal plasma resistin concentrations.

Methods of Study—This cross-sectional study included the following groups: 1) normal pregnant women (n=85); and 2) pregnant women with pyelonephritis (n=40). Maternal plasma resistin concentrations were determined by ELISA. Non-parametric statistics were used for analyses.

Results—1) The median maternal plasma resistin concentration was higher in patients with pyelonephritis than in those with a normal pregnancy ($p<0.001$); 2) among patients with pyelonephritis, the median maternal resistin concentration did not differ significantly between those with and without a positive blood culture ($p=0.3$); 3) among patients with pyelonephritis who were diagnosed with systemic inflammatory response syndrome (SIRS), those who fulfilled 3 criteria for SIRS had a significantly higher median maternal plasma resistin concentration than those who met only 2 criteria; and 4) maternal WBC count positively correlated with circulating resistin concentration ($r=0.47$, $p=0.02$).

Conclusions—Hyperresistinemia is a feature of acute pyelonephritis during pregnancy. The results of this study support the role of resistin as an acute-phase protein in the presence of bacterial infection during pregnancy.

Keywords

acute bacterial infection; resistin; adipokines; pyelonephritis; BMI; cytokine; SIRS; urinary tract infection

Introduction

Resistin, a novel adipokine with a molecular weight of 12.5 kDa, belongs to the FIZZ (found in inflammatory zone) family, also known as RELM (resistin-like-molecules).^{1–6} In mice, resistin is mainly secreted by adipocytes while in humans, it is not a tissue-specific protein and expression and/or secretion of this protein has been determined in muscle,⁷ pancreatic islets,⁸ mononuclear cells,⁹ macrophages,¹⁰ neutrophils¹⁰ and placenta.^{7;11;12} Consistent with the aforementioned reports, resistin has been implicated in the regulation of glucose metabolism and insulin resistance in rodents^{13;14} whereas its role as a metabolic mediator in humans has been a subject of controversy.^{15–20}

Recently, resistin has emerged as a potent pro-inflammatory protein associated with both acute and chronic inflammation.^{21–25} Specifically, a compelling body of evidence supports a role for resistin in the regulation of the innate immune system and inflammation.^{21;22;24} The following observations support this view: 1) resistin mRNA expression by human peripheral blood mononuclear cells (PBMC) increases after exposure to interleukin (IL)-1 beta, IL-6, tumor necrosis factor (TNF)- α and lipopolysaccharide (LPS);⁹ 2) stimulation of human macrophages with LPS results in an increase in resistin mRNA expression;²⁶ 3) resistin upregulates the expression of TNF- α , and IL-6 by human PBMC;²¹ 4) administration of LPS to human subjects results in a significant increase in circulating resistin concentrations;²⁶ 5) chronic inflammatory conditions such as alcoholic liver disease, hepatitis C virus-induced chronic hepatitis,²⁷ rheumatoid arthritis, osteoarthritis, and chronic kidney disease^{21;28–30} are associated with high expression and/or secretion of resistin.

Acute pyelonephritis complicates 1–2% of pregnancies³¹ and it is a common indication for hospitalization during pregnancy.³² The clinical course of most patients is favorable with adequate antimicrobial treatment; nevertheless, pregnant women with pyelonephritis are at an increased risk of developing acute respiratory distress syndrome (ARDS),^{33;34} sepsis,^{35;36} and septic shock.^{35;36} Studies in non-pregnant patients have demonstrated that resistin expression and secretion by macrophages and neutrophils are elevated in the presence of acute bacterial infection. Moreover, circulating concentrations of this protein have been proposed as a powerful marker of the severity of sepsis in non-pregnant individuals.^{10;37} There are no studies regarding maternal circulating resistin concentration in pregnant women with acute bacterial infection. Thus, the aim of this study was to determine whether acute pyelonephritis during pregnancy is associated with changes in maternal plasma resistin concentrations.

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=85), and (2) pregnant women with acute pyelonephritis (n=40). Women with multiple pregnancies and fetal chromosomal or congenital anomalies were excluded. 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 neonate whose birth weight was between the 10th and 90th percentile for gestational age.³⁸

Pyelonephritis was diagnosed in the presence of fever (temperature $\geq 38^{\circ}\text{C}$), clinical signs of an upper urinary tract infection (e.g., flank pain, costovertebral angle tenderness), and a positive urine culture for microorganisms. Blood cultures were also obtained. Systemic

inflammatory response syndrome (SIRS) was diagnosed in the presence of two or more of the following signs: (1) temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$; (2) pulse ≥ 90 beats/min; (3) respiration ≥ 20 per minute or a $\text{PaCO}_2 < 32$ mmHg; and (4) white blood cell (WBC) count ≥ 12000 or ≤ 4000 , or $>10\%$ immature neutrophil.³⁹ Patients with SIRS were further classified to those who met only two SIRS criteria vs. those with 3 or more. A small-for-gestational age (SGA) neonate was defined as birth weight below the 10th percentile for the gestational age.³⁸

The body mass index (BMI) was calculated according to the formula: weight (kg)/height² (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).⁴⁰ 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 a written informed consent prior to enrollment and collection of blood samples. The collection and use of blood samples for research purposes was approved by the Institutional Review Boards of both Wayne State University (Detroit, Michigan, USA) 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.^{41–47}

Sample collection and human resistin immunoassay

Samples of peripheral blood from pregnant women were obtained by venipuncture. The samples were stored at -70°C until assay. Plasma resistin concentrations were determined with Human Resistin ELISA (LINCO Research Inc, St Charles, MO, USA), following the recommendations of the manufacturer. The sensitivity of the assay was 0.09 ng/mL and the inter- and intra-assay coefficients of variation were 5.9% and 5.8%, respectively.

Statistical analysis

Normality of the data was tested using the Kolmogorov-Smirnov test. Comparisons between the study groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Spearman rank correlation was utilized to assess correlations between resistin concentration and maternal WBC count. Multiple linear regression analysis was used to determine which factors were significantly associated with maternal plasma resistin concentration (after log transformation). The following parameters were included in the model: maternal age (years), smoking status, gestational age at blood sampling (weeks), pre-gestational BMI (as a continuous variable) 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. The median birthweight was significantly lower in patients with pyelonephritis than in those with a normal pregnancy. There were no significant differences in the other variables between the two study groups.

Resistin concentrations in pyelonephritis vs. normal pregnancy

The median maternal plasma resistin concentration was higher in patients with pyelonephritis than in those with a normal pregnancy (20.6 ng/mL, interquartile range [IQR] 11.7–31.9 vs. 10.7 ng/mL, IQR 8.4–15.5; $p < 0.001$, Figure 1).

Resistin concentrations in patients with pyelonephritis with and without a positive blood culture

The most common microorganism isolated from urine cultures was *Escherichia coli* [77.5% (31/40)]. Other microorganisms included *Klebsiella pneumoniae* (n=2), *Proteus mirabilis* (n=1), *Enterobacter aerogenes* (n=1), *Pseudomonas aeruginosa* (n=1), *Streptococcus viridans* (n=1), *Citrobacter koseri* (n=1), *Streptococcus agalactiae* (n=1), and mixed flora (n=2). One patient had more than one germ isolated from the urine culture. Blood cultures were performed in 87.5% (35/40) of patients with pyelonephritis and 45.7% (16/35) of them were positive for microorganisms. *Escherichia coli* was the most common microorganism isolated from blood cultures [68.8% (11/16)]. Other microorganisms isolated from maternal blood were Gram-positive cocci (n=1), *Klebsiella pneumoniae* (n=1), *Enterobacter aerogenes* (n=1), and coagulase-negative *Staphylococcus* (n=2).

Among pregnant women with pyelonephritis, no significant differences were found in the median maternal plasma resistin concentration between patients with pyelonephritis who had a positive blood culture and those with a negative culture (25.8 ng/mL, IQR 11.8–38.4 vs. 20.7 ng/mL, IQR 12.1–29.4; $p=0.3$, Figure 2).

Resistin concentrations in patients with pyelonephritis and SIRS

Among all patients with pyelonephritis, 90% (36/40) fulfilled the criteria for SIRS. Of these patients, 21 patients met two, while 15 had 3 or more of the diagnostic criteria for SIRS. There were no patients with ARDS. Among patients with pyelonephritis and SIRS, those who met 3 criteria had a higher median resistin concentration than those who met only 2 of the criteria for SIRS. (24.2 ng/mL, IQR 20.7–37.9 vs. 14.0 ng/mL, IQR 11.3–30.8; $p=0.023$, Figure 3). In addition, there was a positive correlation between maternal WBC count and plasma resistin concentration ($r=0.47$, $p=0.02$).

Multiple linear regression analysis was employed to examine the relationship between maternal plasma concentration of resistin and the presence of pyelonephritis, while adjusting for maternal age, smoking status, gestational age at blood sampling, and pre-gestational BMI. The final regression model suggested that the only presence of pyelonephritis was associated with high maternal plasma resistin concentrations ($p<0.001$).

Discussion

Principal findings of the study

1) The median maternal plasma resistin concentration was significantly higher in patients with pyelonephritis than in those with a normal pregnancy; 2) among patients with pyelonephritis, the median maternal resistin concentrations did not differ significantly between those with and those without a positive blood culture; and 3) among patients with pyelonephritis who were diagnosed with SIRS, those who fulfilled 3 criteria had higher median maternal plasma resistin concentration than those who met only 2 criteria..

Maternal plasma resistin concentrations in normal gestation and complications of pregnancy

Resistin has been implicated in the metabolic adaptations to a normal gestation,^{48–50} as well as in complications of pregnancy such as preeclampsia,^{11;51} gestational diabetes mellitus,^{52–54} preterm labor^{55;56} and intraamniotic infection/inflammation.^{55;56} These observations are consistent with reports in which a role for other cytokines^{57–59} and adipocytokines,^{44;48;55;60–87} in physiological and pathological conditions in human pregnancy have been proposed. We have reported higher circulating resistin concentrations in normal pregnant women than in non-pregnant individuals⁴⁸ and found no significant

differences in maternal plasma resistin between normal weight and overweight/obese normal pregnant women.⁴⁸ Recently, using Isobaric Tag for Relative and Absolute Quantitation (iTRAQ™) method we were able to determine that resistin is differentially expressed in amniotic fluid of patients with intra-amniotic infection/inflammation (IAI). This observation has been confirmed in an independent cohort of samples using sensitive and specific ELISA kit in which amniotic fluid resistin concentrations were higher in patients with IAI than in controls.⁵⁵

Hyperresistinemia is a novel feature of pyelonephritis in pregnancy

Our data indicate that pyelonephritis during pregnancy is characterized by higher median maternal plasma resistin than normal pregnant women. Based on a nomogram for normal pregnant women, recently published by our group,⁴⁸ among patients with pyelonephritis, 24 out of the 40 (60%) patients with pyelonephritis had resistin concentration higher than the 75th percentile and 38% had a resistin concentration higher than the 90th percentile. Thus, the results of the present study suggest that the significant difference in the median maternal plasma resistin concentrations should be attributed to hyperresistinemia in patients with pyelonephritis.

This novel finding is consistent with previous reports by Sunden-Cullberg et al.³⁷ Johansson et al.¹⁰ and Koch et al.⁸⁸ in which septic patients had a higher circulating resistin concentration when compared to controls. Moreover, Lehrke et al.²⁶ have demonstrated increased resistin concentrations in experimental human endotoxemia. The results of the present study extend the aforementioned observation by reporting hyperresistinemia in pregnant women with acute bacterial infection. Moreover, our findings suggest that hyperresistinemia characterized not only critically ill patients but also young healthy individuals with acute infectious disease.

The relationship between circulating maternal resistin and the severity of pyelonephritis

Among patients with pyelonephritis and SIRS, those who met 3 criteria for SIRS had a higher maternal resistin concentration than those who met only two, suggesting that circulating resistin concentrations may be associated with the severity of the disease. This finding is consistent with the previous reports in which circulating resistin concentrations have been proposed as a biomarker for the severity of septic shock and severe sepsis,³⁷ and for survival in non-septic, critically ill patients.⁸⁸ A possible explanation for the association between high maternal resistin concentration and a greater number of SIRS criteria may be the association between circulating resistin and WBC count. This view is supported by the observations that resistin is produced and secreted by neutrophils¹⁰ and macrophages.^{26;89} In addition, the results of the present study demonstrate a positive correlation between maternal WBC count and circulating resistin concentration. Of note, a similar relationship between circulating resistin concentration and WBC³⁷ and neutrophils¹⁰ count has been documented in non-pregnant, critically ill patients. Collectively, these data suggest that enhanced secretion by neutrophils and other immune cells may account for the association between maternal circulating resistin and the severity of pyelonephritis.

Why is acute pyelonephritis in pregnancy characterized by hyperresistinemia?

The cross-sectional nature of our study does not allow us to infer causal relationships between maternal hyperresistinemia and acute pyelonephritis. Similarly, we can not ascertain from the current study whether hyperresistinemia precedes or follows the development of pyelonephritis. Nevertheless, several explanations for our finding can be hypothesized.

Exposure of human primary neutrophils to *Escherichia coli* results in a significant increase in secretion of this protein.¹⁰ In addition, LPS robustly increases circulating resistin concentrations in human subjects.²⁶ Consistent with this finding, among critically ill patients admitted to the intensive care unit, those with sepsis had a higher circulating resistin concentration than those without sepsis.⁸⁸ In our study population, *Escherichia coli* was the most common microorganism isolated from either urine (78%) or blood cultures (69%). Thus, it is conceivable that exposure to *Escherichia coli* or its endotoxin can account for the hyperresistinemia in patients with pyelonephritis. It has been proposed that LPS induces increased production and/or secretion by neutrophils through the induction of TNF- α .²⁶ Indeed, LPS induction of TNF- α by human macrophages precedes the increase in resistin. Furthermore resistin gene expression is induced by TNF- α treatment of these cells. Of note, we have reported that pregnant patients with acute pyelonephritis had a higher circulating TNF- α concentration than that of normal pregnant woman.⁴¹ Collectively, these data suggest that similarly to the non-pregnant state, LPS can induce resistin through the induction of TNF- α .

The metabolic alterations associated with acute bacterial infection can represent an additional explanation for the increased concentrations of resistin in pregnant women with pyelonephritis. Studies in a murine model, in which resistin is produced exclusively by adipocytes,^{1;2;5} have provided a compelling evidence to suggest that resistin plays an important role in glucose homeostasis. *In vitro* neutralization of resistin results in enhanced insulin-stimulated glucose uptake by adipocytes.⁵ In addition, the treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action while administration of anti-resistin antibodies potentiates insulin stimulated glucose uptake.⁵ Studies in humans have yielded conflicting results: a lack of correlation between circulating resistin, insulin resistance and obesity has been reported,^{17;19} while other studies have documented increased resistin concentrations in subjects with insulin resistance.^{18;90} Importantly, polymorphisms in the promoter region of resistin gene are associated with insulin resistance in obese individuals.^{91;92} An acute infection is associated with enhanced energy expenditure, hyperglycemia and insulin resistance.^{93–96} Indeed, systemic infection can be challenging during gestation since pregnancy *per se* imposes an increase energy demand on the gravid woman. The changes in circulating maternal plasma resistin concentrations reported in the present study favor a state of insulin resistance, which enhances the availability of glucose to the fetus as well as to vital maternal organs. Thus, it is tempting to postulate that hyperresistinemia that accompanies pyelonephritis during pregnancy is an adaptive response aimed at ensuring fetal and maternal well being.

An alternative explanation for the higher circulating maternal resistin concentration in patients with acute pyelonephritis than in normal pregnant women is the altered renal function associated with acute pyelonephritis and decreased excretion of resistin. The molecular weight of plasma resistin is relatively low (12.5 kDa).⁵ Proteins with similar molecular weight are thought to be freely filtered at the glomerulus.⁹⁷ Consistent with this view, resistin concentrations are elevated in patients with chronic kidney disease and are negatively correlated with glomerular filtration rate.^{30;98–100} Of note, more than 25% of patients with acute pyelonephritis have transient renal insufficiency with at least a 50% decrease in creatinine clearance.¹⁰¹ Thus, the association between hyperresistinemia and pyelonephritis is the result of renal dysfunction and decreased clearance by the kidneys of this protein.

Conclusion

the finding that women with pregnancies complicated by pyelonephritis have a higher maternal plasma concentration of resistin than those with a normal pregnancy is novel, and concurs with the observations that resistin is an acute phase protein. The mechanism(s)

whereby resistin is elevated in the course of an acute bacterial infection during pregnancy require further investigation. Nevertheless, it is conceivable that hyperresistinemia is secondary to increased secretion by neutrophils and macrophages and/or a decrease in renal excretion of this molecule. While the relevant mechanisms responsible for hyperresistinemia in systemic infection during pregnancy remain to be elucidated, the findings reported herein support the importance of resistin in the regulation of inflammatory and immune responses.

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Figure 1. Maternal plasma resistin concentration in pregnant women with pyelonephritis
 The median maternal plasma resistin concentration was higher in patients with pyelonephritis than in those with a normal pregnancy (20.6 ng/mL, interquartile range [IQR] 11.7–31.9 vs. 10.7 ng/mL, IQR 8.4–15.5; $p < 0.001$).

Figure 2. Maternal plasma resistin concentration in pregnant women with pyelonephritis with and without a positive blood culture

Among pregnant women with pyelonephritis, the median maternal plasma resistin concentration did not differ significantly between women with and without a positive blood culture (25.8 ng/mL, IQR 11.8–38.4 vs. 20.7 ng/mL, IQR 12.1–29.4; $p=0.3$).

Figure 3. Maternal plasma resistin concentration in pregnant women with pyelonephritis who were diagnosed with SIRS by 2 criteria vs. those who were diagnosed by ≥ 3 criteria
 Among patients with pyelonephritis and SIRS, those who met ≥ 3 criteria for SIRS had a higher median resistin concentration than those who met only 2 criteria for SIRS. (24.2 ng/mL, IQR 20.7–37.9 vs. 14.0 ng/mL, IQR 11.3–30.8; $p=0.023$).

Table I

Demographic and clinical characteristics of the study population

	Normal Pregnancy (n=85)	Pyelonephritis (n=40)	p
Maternal age (years)	23 (21–27)	22 (19–29)	0.3
Ethnic Origin			
African American	71 (83.5)	30 (75.0)	0.3
Caucasian	10 (11.7)	6 (15.0)	0.7
Hispanic	2 (2.3)	3 (7.5)	0.2
Other	2 (2.3)	1 (2.5)	0.9
Nulliparity	17 (20)	8 (20)	0.9
Smoking	17 (20)	5 (12.5)	0.3
Pre-gestational BMI (kg/m²)	30.3 (25.0–33.8)	27.1 (23.5–32.0)	0.07
GA at blood sampling (weeks)	31.1 (26.4–33.7)	30.4 (24.7–35.4)	0.1
GA at delivery (weeks)	39.5 (38.7–40.6)	39.0 (37.5–40.3)	0.8
Birthweight (grams)	3335 (3082–3602)	3135 (2750–3558)	0.02

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

BMI – Body Mass Index; GA- Gestational age