

# Low circulating maternal adiponectin in patients with pyelonephritis: adiponectin at the crossroads of pregnancy and infection

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## Abstract

**Objective:** An emerging theme in modern biology is that adipose tissue can respond to metabolic stress, and to inflammatory stimuli, by regulating the secretion of a complex network of soluble mediators, termed adipokines. Adiponectin, the most prevalent circulating adipokine in human, has profound insulin-sensitizing and anti-inflammatory properties. Indeed, the notion that adiponectin plays an important role in the interactions between the metabolic and the immune systems has been strongly suggested. Thus, the aim of this study was to determine if pyelonephritis during pregnancy is associated with changes in maternal serum adiponectin concentrations.

**Study design:** This cross-sectional study included women in the following groups: 1) normal pregnant women (n = 200); and 2) pregnant women with pyelonephritis (n = 50). Maternal plasma adiponectin concentrations were determined by ELISA. Non-parametric statistics were used for analyses.

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**Results:** 1) The median maternal plasma adiponectin concentration was lower in patients with pyelonephritis than in those with a normal pregnancy ( $P < 0.001$ ); 2) among pregnant women with a normal weight, patients with pyelonephritis had a lower median plasma adiponectin concentration than those with a normal pregnancy ( $P < 0.001$ ); 3) similarly, among overweight/obese patients, those with pyelonephritis had a lower median plasma adiponectin concentration than those with a normal pregnancy ( $P < 0.001$ ); and 4) the presence of pyelonephritis was independently associated with maternal plasma adiponectin concentrations after adjustment for maternal age, smoking, gestational age at sampling, and pregestational body mass index (BMI).

**Conclusion:** 1) The findings that acute pyelonephritis in pregnancy is characterized by low maternal plasma concentrations of adiponectin in both lean and overweight/obese patients are novel and concur with the antiinflammatory properties of adiponectin; and 2) the results of this study support the notion that adiponectin may play a role in the intricate interface between inflammation and metabolism during pregnancy.

**Keywords:** Acute bacterial infection; adipokines; adiponectin; infection; inflammation; pregnancy; pyelonephritis.

## Introduction

Adipose tissue has emerged as an active endocrine organ [41, 110] that can orchestrate not only a metabolic response to insults, but also an inflammatory response. The mechanisms by which adipose tissue exerts its effects on the immune system have not been completely elucidated. A growing body of evidence suggests that adipocytes modulate resident immune cell functions directly or indirectly, in a paracrine and/or endocrine fashion via the secretion of adipokines [19, 90]. The latter is a group of active molecules which are adipocytesspecific or enriched proteins, and includes adiponectin [5, 40, 99], leptin [126], resistin [35, 45, 97, 108], visfatin [38, 101], and others [105, 110]. Adipokines have been implicated in a vast array of physiological processes, as well as in inflammation-related pathological conditions such as asthma [31, 32], inflammatory bowel disease [112], rheumatoid arthritis [9, 98], multiple sclerosis [7] and obesity [5, 22, 24, 46, 58, 68, 70, 77–79, 88, 120]. The metabolic and inflammatory effects of adipokines have been recently corroborated by reports concerning pregnant women, suggesting that adipokines play a role in metabolic adaptations to normal gestation [11, 62, 64, 66, 68, 70, 78, 79, 106], as well

as in inflammation-related [49, 59, 60, 67, 68, 71, 77, 113] and other complications of pregnancy [61, 63, 65, 69].

Adiponectin, identified independently by four groups [37, 55, 76, 99], is the adipokine that circulates in the highest concentrations in humans. The range of adiponectin's biological actions includes insulin-sensitizing [8, 119], anti-atherogenesis [25, 84], and angiogenesis [86, 103]. In addition to its well-established role in glucose metabolism and vasculature protection, adiponectin has anti-inflammatory properties [13, 104]. Furthermore, adiponectin is involved in the modulation of both the innate and adaptive limbs of the immune system [82, 83, 96, 117, 118, 123, 124].

Activation of the innate immune response and suppression of the adaptive immune response are hallmarks of normal human pregnancy [95]. Teleologically, these immunologic alterations aim to promote tolerance to the fetus and protect the mother against infection [74, 95]. Nevertheless, pregnant women are more susceptible to infections [15, 50, 91–93] including those of the lower urinary tract [20, 51] and pyelonephritis [27]. Furthermore, pregnant women with an episode of acute pyelonephritis are at risk of developing sepsis and adult respiratory distress syndrome (ARDS) [17, 89], though both complications are rare in young non-pregnant individuals. Recently, our group suggested that intraamniotic adipokines may play a role in the innate immune response against intra-amniotic infection/inflammation (IAI) [49, 67, 113]. However, despite the compelling evidence supporting the metabolic and inflammatory effects of adiponectin, no data exist about the association between circulating maternal adiponectin and acute systemic bacterial infections. Moreover, the serum/plasma adiponectin concentration in patients with pyelonephritis has not been reported either in pregnant or non-pregnant subjects. Thus, the aim of our study was to determine whether pyelonephritis during pregnancy is associated with changes in maternal plasma adiponectin 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 patients in the following groups: (1) normal pregnancy ( $n=200$ ), and (2) pregnant women with pyelonephritis ( $n=50$ ). 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 ( $\geq 37$  weeks) of a normal healthy infant whose birth weight was between the 10th and 90th percentile for gestational age [29]. 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.

The body mass index (BMI) was calculated according to the formula: weight (kg)/height ( $\text{m}^2$ ). Normal weight women were defined as those with a BMI of 18.5–24.9  $\text{kg}/\text{m}^2$ , according to the definition of the World Health Organization (WHO) [1]. The study population was further classified by the pre-gestational BMI into two groups: normal weight and overweight/obese (BMI  $\geq 25$   $\text{kg}/\text{m}^2$ ).

All participating women provided written informed consent prior to enrolment and the collection of blood samples. The collection and use of blood for research purposes was approved by the Institutional Review Boards 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). Many of these samples have previously been used to study the biology of inflammation, hemostasis, and growth factor concentrations in normal pregnant women and those with pregnancy complications.

### Maternal sample collection and determination of adiponectin concentrations

Maternal blood was collected in vials containing ethylenediamine-tetra-acetic acid, and centrifuged at 2500 RPM for 10 min at  $4^\circ\text{C}$ . The plasma obtained was stored at  $-80^\circ\text{C}$  until analysis. Plasma adiponectin concentrations were determined with the Human Adiponectin ELISA (LINCO Research Inc, St Charles, MO, USA) according to the manufacturer's instructions. The sensitivity of the assay was 0.91 ng/mL, and the intra- and inter-assay coefficients of variation were 4.6% and 6.6%, respectively.

### Statistical analysis

Normality of the data was tested using the Kolmogorov-Smirnov tests. Since plasma adiponectin concentrations were not normally distributed, non-parametric test were used for analysis. Comparisons between the two groups were performed using the Mann-Whitney *U*-test for continuous variables and the  $\chi^2$ -test for categorical variables. Multiple linear regression analysis was used to determine which factors were significantly and independently associated with maternal plasma adiponectin concentration. The following parameters were included in the model: maternal age, smoking, gestational age at sampling, pregestational BMI and the presence of pyelonephritis. A  $P < 0.05$  was considered statistically significant. Analysis was performed with SPSS, version 14 (SPSS Inc., Chicago, IL, USA).

## Results

The demographic and clinical characteristics of women with a normal pregnancy and those with pyelonephritis are displayed in Table 1. The median birthweight was significantly lower in patients with pyelonephritis than in those with a normal pregnancy. Table 2 displays the maternal demographic and clinical characteristics of all pregnant women according to BMI category (normal weight vs. overweight/obese). There were no significant differences in age, nulliparity, smoking status, gestational age at sampling, gestational age at delivery or birthweight between normal weight and overweight/obese women either in the normal pregnancy or pyelonephritis groups.

### Adiponectin concentrations in pyelonephritis vs. normal pregnancy

The median maternal plasma adiponectin concentration was lower in patients with pyelonephritis than in those with a normal pregnancy (median: 7223 ng/mL, interquartile range [IQR] 5852–8962 vs. 10,430 ng/mL, IQR 9262–12,112;  $P < 0.001$ , Figure 1).

### Adiponectin concentrations in pyelonephritis: normal weight vs. overweight/obesity

Among patients with pyelonephritis, the median maternal plasma adiponectin concentration was lower in overweight/obese patients than in those with a normal weight (5164 ng/mL, IQR 4805–7997 vs. 7467 ng/mL, IQR 6649–9213;  $P=0.02$ ).

### Adiponectin concentrations in normal weight pregnant women: pyelonephritis vs. normal pregnancy

Among pregnant women with a normal weight, those with pyelonephritis had a lower median plasma adiponectin concentration than women with a normal pregnancy (7467 ng/mL, IQR 6649–9213 vs. 10,610 ng/mL, IQR 9351–12,255;  $P<0.001$ , Figure 2).

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

Among overweight/obese pregnant women, those with pyelonephritis had a lower median plasma adiponectin concen-

tration than women with a normal pregnancy (5164 ng/mL, IQR 4805–7997 vs. 9981 ng/mL, IQR 8801–11,850;  $P<0.001$ , Figure 3).

Multiple linear regression analysis was employed to examine the relationship between the plasma concentrations of adiponectin and pyelonephritis, while adjusting for maternal age, smoking status, and gestational age at blood sampling. The final regression model suggested that the presence of pyelonephritis and pre-gestational BMI were independently associated with low maternal plasma adiponectin concentrations ( $P<0.001$  and  $P=0.03$ , respectively).

## Discussion

### Principal findings of the study

1) The median maternal plasma adiponectin concentration was significantly lower in patients with pyelonephritis than in those with a normal pregnancy; 2) among pregnant women with a normal weight, those with pyelonephritis had a significantly lower median plasma adiponectin concentration than women with a normal pregnancy; 3) similarly, among pregnant women with overweight/obesity, those with pyelo-

**Table 1** Clinical and demographic characteristics of the study population.

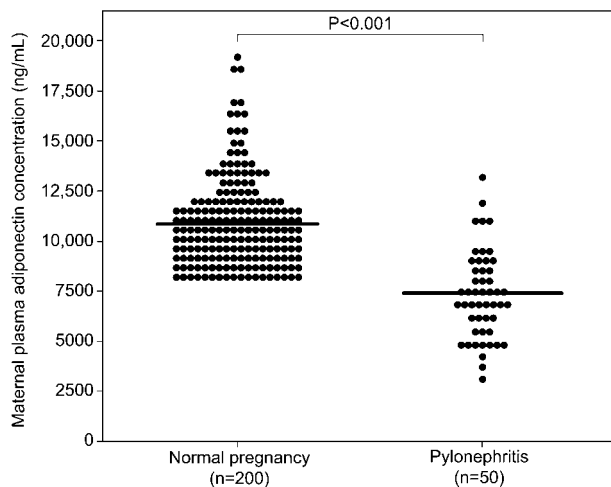
	Normal pregnancy (n=200)	Pyelonephritis (n=50)	P-value
Maternal age (years)	26 (21–31)	27 (21–30)	0.9
Nulliparity	78 (36%)	23 (46%)	0.4
Smoking	14 (7%)	7 (14%)	0.1
Pre-gestational BMI (kg/m <sup>2</sup> )	23.1 (21.1–24.9)	22.7 (20.2–25.6)	0.5
BMI at blood sampling (kg/m <sup>2</sup> )	26.9 (24.8–29.6)	25.4 (23.7–27.9)	0.09
GA at blood sampling (weeks)	31.0 (25.3–38.2)	28.9 (21.6–33.2)	0.2
GA at delivery (weeks)	39.8 (38.6–40.3)	39.2 (38.2–40.1)	0.09
Birth weight (g)	3400 (3172–3670)	3140 (2990–3505)	<0.01

Values are expressed as median (interquartile range) or numbers (%); GA = gestational age, BMI = body mass index.

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

	Normal pregnancy		P-value	Pyelonephritis		P-value
	Normal weight (n = 149)	Overweight/obese (n = 51)		Normal weight (n = 35)	Overweight/obese (n = 15)	
Maternal age (years)	25 (20–31)	27 (22–31)	0.2	24 (21–31)	28 (21–29)	0.7
Nulliparity	62 (42%)	16 (31%)	0.2	17 (48%)	6 (40%)	0.8
Smoking	12 (8%)	2 (4%)	0.4	5 (14%)	2 (13%)	0.9
Pre-gestational BMI (kg/m <sup>2</sup> )	22.3 (20.8–23.4)	26.9 (26.0–30.0)	<0.001	21.6 (19.9–23.1)	27.4 (26.0–28.4)	0.02
BMI at blood sampling (kg/m <sup>2</sup> )	25.8 (24.0–27.7)	31.5 (29.3–34.0)	<0.001	24.7 (22.3–25.6)	28.0 (27.4–31.0)	0.02
GA at blood sampling (weeks)	29.1 (24.7–33.7)	29.2 (25.8–38.4)	0.4	28.8 (21.4–34.4)	28.2 (21.5–32.1)	0.3
GA at delivery (weeks)	40.0 (38.6–40.0)	39.7 (39.0–40.4)	0.8	39.1 (38.3–39.1)	40.0 (37.3–40.3)	0.9
Birth weight (g)	3410 (3210–3780)	3440 (3155–3670)	0.5	3140 (3020–3430)	3160 (2640–3780)	0.3

Values are expressed as median (interquartile range) or numbers (%); GA = gestational age, BMI = body mass index.



**Figure 1** Comparison of the median maternal plasma adiponectin concentration between women with normal pregnancies and patients with pyelonephritis.

The median maternal plasma adiponectin concentration was lower in patients with pyelonephritis than in those with a normal pregnancy (7223 ng/mL, IQR 5852–8962 vs. 10,430 ng/mL, IQR 9262–12,112;  $P < 0.001$ ).

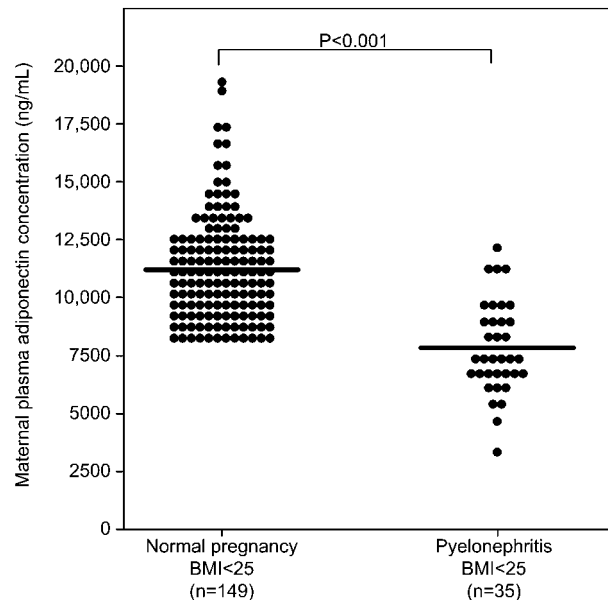
nephritis had a significantly lower median plasma adiponectin concentration than women with a normal pregnancy; and 4) the presence of pyelonephritis was independently associated with maternal plasma adiponectin concentrations after adjustment for maternal age, smoking, gestational age at sampling, and pre-gestational BMI.

### Pregnancy and pyelonephritis – an ominous combination

Pyelonephritis complicates 1–2% of pregnancies [34, 72], and it is one of the most common indications for antepartum hospitalization [6, 23]. Pyelonephritis occurs ~70% of the time during the second and third trimesters, 25% in the postpartum period and only 4% of cases present during the first trimester [27, 72]. The clinical course of most patients is favorable and resolution of the fever is expected in 95% of the cases within 72 h of adequate antimicrobial treatment [72]. Nonetheless, pregnant women with pyelonephritis are at risk of developing sepsis [10, 53, 102] and ARDS [3, 12, 14, 16, 21, 33, 34, 52, 89]. Moreover, pyelonephritis is the most common cause of septic shock during pregnancy [53, 102] and the most frequent indication for admission to obstetric intensive care units [125].

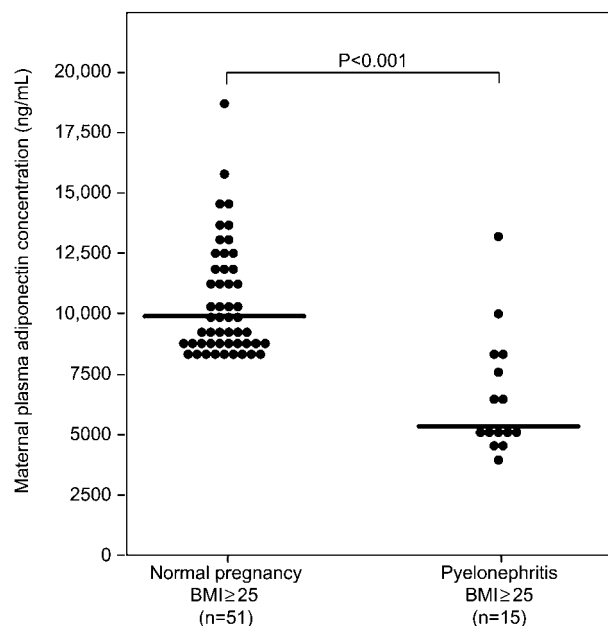
### Adiponectin and immunity: bridging the gap between inflammation and metabolism?

Adiponectin, the most abundant gene (*AMP1*) product of adipose tissue [37, 55, 76, 99], has a wide range of biological activities. Adiponectin has been implicated in the pathophysiology of insulin resistance [8, 36, 73, 115, 119], atherosclerosis [81, 83, 85], hypertension [39, 42], and dyslipidemia [18, 57]. In addition to its wellcharacterized



**Figure 2** Comparison of the median maternal plasma adiponectin concentration in normal weight pregnant women with normal pregnancy and patients with pyelonephritis.

Among pregnant women with a normal weight, those with pyelonephritis had a lower median plasma adiponectin concentration than women with a normal pregnancy (7467 ng/mL, IQR 6649–9213 vs. 10,610 ng/mL, IQR 9351–12,255;  $P < 0.001$ ).



**Figure 3** Comparison of the median maternal plasma adiponectin concentration in overweight/obese pregnant women with normal pregnancy and patients with pyelonephritis.

Among overweight/obese pregnant women, those with pyelonephritis had a lower median plasma adiponectin concentration than women with a normal pregnancy (5164 ng/mL, IQR 4805–7997 vs. 9981 ng/mL, IQR 8801–11,850;  $P < 0.001$ ).



metabolic effects, several lines of evidence suggest that adiponectin is an important mediator of inflammatory responses: 1) adiponectin suppresses macrophage production of pro-inflammatory cytokines, such as TNF- $\alpha$  [124], (IFN- $\gamma$ ) [117] and IL-6 [100]; 2) exposure of macrophages to adiponectin results in inhibition of their phagocytic activity in response to stimulation with lipopolysaccharide (LPS) [124]; 3) adiponectin inhibits activation of the nuclear transcription factor NF- $\kappa$ B in endothelial cells [85]; and 4) in knockout mice, gene deletion of adiponectin results in higher TNF- $\alpha$  mRNA expression in adipose tissue, as well as higher circulating TNF- $\alpha$  concentrations than “adiponectin-sufficient” mice (wild type) [56]. Taken together, this unique combination of biological effects makes adiponectin a plausible candidate to orchestrate the functional interphase between metabolism and inflammation.

### **Pyelonephritis is characterized by low maternal circulating adiponectin**

The findings reported herein characterize pyelonephritis during pregnancy as a condition associated with low maternal circulating adiponectin concentrations. Moreover, lower maternal concentrations were detected in pyelonephritis in patients who were either of normal weight or overweight/obese. These findings are novel. Reports concerning circulating adiponectin concentrations in the presence of infectious disorders in nonpregnant patients are scarce and no data exist concerning maternal circulating concentrations of this adipokine in any infectious disease. Furthermore, no information regarding plasma/serum adiponectin concentrations in the presence of pyelonephritis either in non-pregnant or in pregnant patients is available.

The findings reported herein contrast with two studies that examined the effect of experimental endotoxemia on human circulating adiponectin concentrations. Keller et al. [43] reported no change in adiponectin plasma concentrations in endotoxin-injected subjects ( $n=23$ ). Similarly, Anderson et al. [4] found no significant difference in plasma adiponectin before and after intra-venous endotoxin injection ( $n=20$ ). Differences in study design may contribute to explain the apparent inconsistency between the studies. Specifically, the studies of Keller et al. [43] and Anderson et al. [4] included only 4 and 10 women, respectively, and pregnancy was an exclusion criterion. In addition, the study population was younger than the one included in the present study, and almost all participants had a normal BMI. Finally, the effect on adiponectin concentrations was determined in both studies no more than 24 h after exposure to the endotoxin.

### **Why is pyelonephritis associated with low maternal adiponectin concentrations?**

Several possibilities can account for the low maternal circulating adiponectin concentrations and pyelonephritis:

1. Regulatory mechanism to increase insulin resistance – An episode of acute infection imposes metabolic challenges to the mother. Indeed, acute infection/inflammation is

associated with hypermetabolism, enhanced energy expenditure, and insulin resistance [26, 28, 109, 111]. The acute nature of pyelonephritis necessitates prompt metabolic adaptations to ensure constant flow of nutrients to both the fetus and the mother. The low maternal plasma adiponectin concentrations reported herein in patients with pyelonephritis favor a state of insulin resistance which enhances the availability of glucose to the fetus. Thus, it is conceivable that the low concentrations of circulating adiponectin are part of the metabolic adaptations aimed at ensuring the flux of glucose to the fetus.

2. Counter-inflammatory response – Low concentrations of circulating adiponectin have been associated with the presence of systemic inflammation. Indeed, patients with inflammatory bowel disease [114], atopic dermatitis and eczema [75], asthma and overweight/obesity [2, 5, 37, 44, 78, 88] have lower circulating adiponectin concentrations than normal controls. The results of the present study support the association between pro-inflammatory conditions and low adiponectin concentrations and extend these data by showing that low circulating concentrations of this adipokine characterize acute bacterial infection during pregnancy.
3. Binding to circulating lipopolysaccharide (LPS) – Bacteremia is a common finding in pregnant women with pyelonephritis since 15–45% of patients have a positive blood culture [30, 48, 54, 80, 107]. Furthermore, pyelonephritis-related sepsis is the most frequent indication for admission to obstetric intensive care units [125], as well as the most common cause of septic shock during pregnancy [53, 102]. Bacterial pathogens that are isolated from blood cultures rarely differ from those that are found in the corresponding urine culture and include predominantly Gram-negative bacteria that possess endotoxin (e.g., *E. coli* and *Klebsiella pneumoniae*). A recent report demonstrated that human adiponectin directly binds LPS derived from several different bacteria including *E. coli* [87]. It was proposed that adiponectin infiltrates into inflammation sites, and may act as a scavenging anti-inflammatory agent through its interaction with LPS [87]. It is tempting to suggest that the low circulating maternal adiponectin concentration is the consequence of adiponectin binding to the LPS and the infecting bacteria.
4. Increased urine secretion – While there are conflicting data as to whether chronic renal diseases are associated with higher [127] or lower [122] circulating adiponectin concentrations, than in normal subjects, several studies have demonstrated an increase in urine adiponectin in the presence of renal dysfunction [47, 94, 121]. Transient renal insufficiency with a decrease in creatinine clearance of at least 50% or more is reported in >25% of patients with pyelonephritis [72, 116]. Thus, a possible explanation for the lower maternal plasma adiponectin could be increased secretion of this adipokine in the urine. Further studies are needed in order to establish the relationship between maternal serum and urine adiponectin in pyelonephritis.

In conclusion, acute pyelonephritis in pregnancy is characterized by low maternal plasma concentrations of adiponectin. The present study represents the first work to describe an *in vivo* association between acute bacterial infection and altered circulating adiponectin concentrations. The unique combination of the biologic properties of adiponectin and its important role in energy homeostasis and inflammatory processes supports a role for this adipokine in the complex linkage between metabolism and infection. As pregnancy is characterized by physiologic adaptations involving metabolic processes and immunologic systems, the regulation of these two systems is particularly pertinent during normal gestation and complications of pregnancy. Taken together, the findings reported herein support a role for adiponectin in the intricate interface between pregnancy, inflammation and metabolism.

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