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MATERNAL PLASMA VISFATIN IN PRETERM LABOR

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Abstract

Objective: Visfatin, a novel adipokine with diabetogenic and immunomodulatory properties, has been implicated in the pathophysiology of insulin resistance, as well as in various acute and chronic inflammatory disorders. We have previously reported that amniotic fluid concentrations of visfatin are higher in patients with preterm labor and intra-amniotic infection than in patients with preterm labor without inflammation. The aim of this study was to determine whether spontaneous preterm labor (PTL) with intact membranes and intra-amniotic infection/inflammation (IAI) is associated with changes in maternal plasma circulating visfatin concentrations.

Study design: This cross-sectional study included patients in the following groups: 1) normal pregnant women (n=123); 2) patients with an episode of preterm labor and intact membranes without IAI who delivered at term (n=57); 3) preterm labor without IAI who delivered preterm (n=47); and 4) preterm labor with IAI who delivered preterm (n=57). Plasma visfatin concentrations were determined by ELISA. Non parametric statistics were used for analysis.

Results: 1) Preterm labor with IAI leading to preterm delivery was associated with a higher median maternal plasma concentration of visfatin than normal pregnancy; 2) among patients with preterm labor, those with IAI had the highest median maternal concentration of visfatin; 3) the changes in maternal plasma visfatin remained significant after adjusting for maternal age, body mass index, gestational age at sampling, and birth weight.

Conclusion: 1) Preterm labor with IAI is characterized by high maternal circulating visfatin concentrations; 2) these findings suggest that visfatin plays a role in the regulation of the metabolic adaptations to insults resulting in preterm labor in the context of IAI.

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Keywords

Visfatin; Adipokines; Pregnancy; Preterm labor; Intra-amniotic infection; Inflammation; Chorioamnionitis; Preterm delivery; Energy Requirements; Energy Expenditure; Preterm Birth; Metabolism

Introduction

Infection and/or inflammation has been implicated as a mechanism of disease responsible for preterm parturition, as well as fetal injury.[1–14] Moreover, infection/inflammation is the only pathologic processes for which a solid causal link with preterm parturition has been established.[10;15] Indeed, there is experimental, epidemiologic and clinical evidence linking intra-amniotic infection and/or inflammation and preterm parturition.[2–5;8;10;11;15–58] In addition, a large body of evidence supports the same cause and effect relationship between systemic infection/inflammation and preterm parturition: 1) systemic administration of microbial products to pregnant mice can result in spontaneous preterm labor and preterm birth;[33;59;60] 2) preterm labor and preterm birth can be induced by the administration of IL-1 to pregnant mice[61] and exposure of these mice to IL-1 receptor antagonist abrogates parturition;[62] 3) systemic infection (e.g. malaria,[63–65] pyelonephritis,[66–70] pneumonia[71–73] and periodontal disease[74–83]) have been associated with preterm birth; and 4) disorders characterized by a chronic inflammatory state such as systemic lupus erythematosus,[84;85] inflammatory bowel diseases,[86;87] asthma,[88;89] and morbid obesity[90–92] have been associated with preterm parturition.

Adipose tissue has emerged as a highly active endocrine organ[93–96] that can orchestrate a metabolic response to insults, but also an inflammatory response via the production of soluble factors known as adipocytokines. Indeed, adipocytokines have been implicated in the pathophysiology of inflammatory disorders including asthma,[97;98] ulcerative colitis,[99;100] Crohn's Disease,[99] rheumatoid arthritis,[101;102] multiple sclerosis[103;104] and obesity.[105–114] Moreover, these highly active peptide and proteins have immunoregulatory effects on the innate (e.g. resistin,[58;115;116] visfatin[57;117;118]) adaptive or both limbs of the immune response (e.g. leptin,[119–122] adiponectin[123–126]). Importantly, adipokines have also been implicated in the adaptation to gestation and complications of pregnancy.[57;108;110;111;113;114;127–134]

Visfatin, a 52 kDa newly discovered adipokine, has already been identified more than a decade ago as a growth factor for early B cell, termed pre-B cell colony-enhancing factor (PBEF).[117;118;135–137] The re-discovery of visfatin as an adipokine that is preferentially produced by visceral adipose tissue,[138–140] has facilitated the investigation of its metabolic and immunoregulatory effects. Indeed, in addition to its insulin-mimicking effects,[139;141] visfatin plays a role as a regulator of the innate immune response[117;137;142] as well as in inflammation associated with infection.[143] Recently, we have reported that intra-amniotic infection/inflammation (IAI) is characterized by elevated amniotic fluid concentrations of adipocytokines.[57;58] Specifically, amniotic fluid concentrations of visfatin were higher in patients with preterm labor and infection than those with preterm labor without infection.

Currently, there are no reports concerning maternal plasma visfatin in the presence of preterm labor or infectious disease. Thus, the aim of this study was to determine whether spontaneous preterm labor (PTL) with intact membranes and intra-amniotic infection/inflammation (IAI) is associated with changes in maternal plasma circulating visfatin concentrations.

Materials and methods

Study design and population

A cross-sectional study was designed by searching our clinical database and bank of biological samples, including 284 patients in the following groups: 1) normal pregnant women (n=123); 2) patients with an episode of preterm labor and intact membranes without IAI who delivered at term (n=57); 3) preterm labor without IAI who delivered preterm (<37 weeks gestation) (n=47); and 4) preterm labor with IAI who delivered preterm (n=57).

All women provided written informed consent prior to enrollment and the collection of blood and amniotic fluid. The collection and utilization of blood and amniotic fluid for research purposes was approved by the Institutional Review Boards of the Sotero del Rio Hospital (Chile), the 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.

Clinical Definitions

Patients were considered to have a normal pregnancy if they had a singleton gestation, a normal oral glucose challenge test,[144;145] and if they did not have any medical, obstetrical, or surgical complications, and delivered a term neonate (≥37 weeks) of appropriate birth weight for gestational age [146;147] without complications. Spontaneous preterm labor was defined by the presence of regular uterine contractions occurring at a frequency of at least two every 10 minutes associated with cervical change before 37 completed weeks of gestation that required hospitalization. Microbial invasion of the amniotic cavity was defined as a positive amniotic fluid culture for micro-organisms. Intra-amniotic inflammation was diagnosed by an amniotic fluid IL-6 concentration ≥2.6 ng/mL.[148]

Amniotic fluid collection

Amniotic fluid samples were obtained by trans-abdominal amniocentesis performed for evaluation of microbial status of the amniotic cavity. Samples of amniotic fluid were transported to the laboratory in a sterile capped syringe and cultured for aerobic/anaerobic bacteria and genital mycoplasmas. An amniotic fluid white blood cell (WBC) count, glucose concentration and Gram-stain were also performed shortly after collection as previously described.[149–151] The results of these tests were used for clinical management. Amniotic fluid IL-6 concentrations were used only for research purposes. Amniotic fluid not required for clinical assessment was centrifuged for 10 minutes at 4°C and the supernatant was aliquoted and stored at –70°C until analysis.

Maternal plasma sample collection and Human visfatin C-terminal immunoassay:

Maternal blood samples were collected immediately before or after the amniocentesis into vacutainer tubes. Blood was centrifuged at 1300 × g for 10 minutes at 4°C. The plasma obtained was stored at −80°C until analysis. 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 manufacturer 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

Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Since plasma visfatin concentrations were not normally distributed, non-parametric tests were used for analyses. Kruskal–Wallis tests with post-hoc analysis by Mann-Whitney U tests were used for comparisons of continuous variables. Comparison of proportions was performed by Chi-square test. Spearman rank correlation was utilized to assess correlations between maternal plasma concentration of visfatin, amniotic fluid WBC count, and amniotic fluid concentrations of glucose IL-6. Multiple linear regression analysis was used to determine which factors were significantly and independently associated with maternal plasma visfatin concentrations (after log transformation). The following parameters were included in the model: maternal age, gestational age at sampling, birth weight, first trimester body mass index (BMI) and the presence of IAI. A p value <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 preterm labor are displayed in Table I. There was no significant difference in the median first trimester body mass index (BMI) or parity between the four groups. Women with a normal pregnancy had a lower gestational age at sampling than those with preterm labor without IAI who delivered preterm (p=0.02) but not than patients with preterm labor and IAI (p=0.4) or those with preterm labor who delivered at term (p=0.051). Women with a normal pregnancy had a higher median birth weight than any of the three preterm labor groups (p<0.001 for all comparison). Comparison of the demographics and clinical characteristics among patients with preterm labor is presented in Table I.

Maternal plasma visfatin concentration in normal pregnant women and those with preterm labor

The median maternal plasma visfatin concentration was higher in patients with preterm labor with IAI than in those with preterm labor without IAI who delivered either preterm (median: 15.5 ng/mL, interquartile range [IQR] 14.2–19.0 vs. 14.4 ng/mL, IQR 11.3–15.9; p<0.001, Figure 1) or at term (15.5 ng/mL, IQR 14.2–19.0 vs. 14.4 ng/mL, IQR 12.2–17.2; p=0.002, Figure 1). Similarly, the median maternal plasma visfatin concentration was higher in patients with preterm labor with IAI than in those with a normal pregnancy (15.5 ng/mL, IQR 14.2–19.0 vs. 15.1 ng/mL, IQR 12.1–17.7; p=0.002, Figure 1).

Maternal plasma visfatin concentration in normal pregnant women and those with preterm labor without IAI

The median maternal plasma visfatin concentration did not differ significantly between patients with preterm labor without IAI who delivered preterm and those who delivered at term (p=0.3). In addition, there was no significant difference in the median maternal plasma visfatin concentration between women with a normal pregnancy and those with preterm labor without IAI who delivered either preterm (p=0.6) or at term (p=0.07).

Multiple regression analysis was employed to examine the relationship between the plasma concentrations of visfatin and preterm labor adjusting for maternal age, maternal first trimester body mass index, gestational age at blood sampling, birthweight and the presence of IAI. The final regression model suggested that the presence of IAI (p=0.001) and birthweight (p=0.04) was independently associated with a higher maternal plasma visfatin concentration. In addition, gestational age at blood sampling (p=0.001) was independently associated with a lower maternal plasma visfatin concentrations.

A significant correlation was observed between maternal plasma concentrations of visfatin and amniotic fluid concentrations of IL-6 (Spearman rho coefficient: 0.2, p=0.008).

Discussion

Principal findings of the study:

1) Patients with preterm labor with IAI leading to preterm delivery had a significantly higher median maternal plasma concentration of visfatin than those with normal pregnancy; 2)

among patients with preterm labor, those with IAI had the highest median maternal concentration of visfatin; 3) There was a relationship between the maternal plasma concentration of visfatin and the amniotic fluid concentration of IL-6.

What is the physiologic role of visfatin?

Visfatin, a 52 kDa molecule, was originally reported to enhance the effect of IL-7 and stem cell factor on pre-B-cell colony formation, thus named pre-B-cell enhancing factor (PBEF).[136] Subsequently, visfatin was reported to be produced by adipose tissue,[139;152–156] preferentially by visceral fat depot,[138;139;157] as well as in the placenta, fetal membranes,[118;158–164] myometrium,[165] bone marrow, liver, muscle,[136] heart, lung, kidney,[136] macrophages,[166] and neutrophils.[117;136;137]

The physiologic role of visfatin in humans has not been completely elucidated, however, a growing body of evidence suggests that this adipokine plays a regulatory role in energy homeostasis and in the inflammatory response. The evidence concerning the immunoregulatory role of visfatin includes: 1) treatment of human monocytes with visfatin results in an increased secretion of. IL-6, TNF-α, IL-1β in a dose dependent manner;[167] 2) acute lung injury in humans[137] and animals[142] is associated with increased visfatin expression from cells retrieved by bronchoalveolar lavage from the affected subjects; 3) visfatin expression increases in neutrophils retrieved from septic patients;[168] and 4) chronic inflammatory disorders (e.g. inflammatory bowel disease,[167] rheumatoid arthritis[169]) have associated with a higher circulating visfatin concentrations than normal subjects.

The following findings support the role of visfatin in metabolic regulation: 1) treatment of adipocytes with glucose results in increased secretion of visfatin.[170] Consistent with this observation, administration of glucose to human subjects results in increase circulating visfatin concentration;[170] 2) obesity is associated with increased circulating visfatin concentration,[117;152;171–175] 3) human serum concentration of visfatin are positively correlated with the amount of intra-visceral fat;[175] 5) patients with type-2 DM[175–178] or metabolic syndrome[179;180] have higher plasma concentrations of visfatin.

Visfatin in normal gestation and in complications of pregnancy:

Visfatin also plays a role in normal gestation, as well as in pregnancy complications. The evidence for that includes: 1) normal pregnancy is associated with altered maternal circulating visfatin concentrations;[114;181–183] 2) gestational diabetes mellitus (GDM) is associated with higher maternal concentrations of visfatin[113;184;185] than non-diabetic pregnant women ; 3) preeclampsia[186] and fetal growth restriction[187] are associated with higher concentrations of visfatin than normal pregnancy; and 5) IAI is associated with higher amniotic fluid concentrations of visfatin than the absence of infection.[57] Collectively, these data support a role for visfatin in the physiologic adaptations to pregnancy as well as in metabolic- and inflammatory-associated complications of pregnancy.

Intra amniotic infection/inflammation is characterized by high circulating maternal visfatin concentrations:

Preterm labor with IAI was associated with a higher maternal plasma visfatin concentration that preterm labor without IAI either with preterm or term delivery. Preterm labor with IAI was also associated with a higher maternal plasma visfatin than normal pregnant women. These findings are novel. Indeed, to date, there are no reports concerning the association between visfatin and preterm labor or any other infection-related conditions during pregnancy. The findings reported herein are consistent with our previous study in which median amniotic fluid concentration of visfatin found to be in patients with preterm labor with IAI, as well as with those reported by Bryant-Greenwood group in which expression and secretion of visfatin from amniotic epithelial were increased in response to various inflammatory stimuli.[118;161;163;164;188;189]

There are paucity of data concerning the association between visfatin and acute infection and/or inflammation.[190] Transcription of the visfatin gene is increased in neutrophils obtained from critically ill, septic patients. Moreover, this increased transcription is mitigated through the use of an antisense oligonucleotide. Of note, neutrophils harvested from the circulation of septic patients are characterized by a marked inhibition of the apoptosis and enhanced respiratory burst capacity.[190;191] Jia et al.[117] have proposed that visfatin plays a crucial role in these processes. This suggestion is supported by the finding that incubation of non-activated neutrophils (taken from healthy subjects) with visfatin results in dose-dependent inhibition of apoptosis.[117] Anther acute condition in which the role of visfatin was investigated is acute lung injury. Ye et al.[137;142] reported that there is an increased expression of visfatin in cells retrieved by bronchoalveolar lavage from patients with this condition[137] and in lung tissue of animals with acute lung injury.[142] Moreover, 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.[192]

Why is preterm labor with IAI associated with increased maternal plasma concentrations of visfatin?

We can not ascertain from the current study whether increased maternal concentration of visfatin is causally related to preterm labor with IAI due to the cross-sectional nature of this report. However, several possibilities can be entertained to explain the increased concentration of visfatin, including the presence of labor along with the increased metabolic burden associated with infection.

Labor is associated with a dramatic increase in energy demands as manifested by increased maternal blood glucose,[193;194] free fatty acids,[195] ketone bodies[196], high glucose turnover.[197] It is possible that the acute nature of preterm labor requires prompt metabolic rearrangements to ensure constant flux of macronutrients to the fetus and the mother. Visfatin has been implicated in the pathophysiology of insulin resistance. It is tempting to suggest that the high maternal concentration of visfatin is part of the metabolic adaptation to preterm labor associated with infection. Indeed, the median maternal visfatin concentrations did not differ between patients in labor (albeit preterm) and those not in labor. Thus, *prima*

facia, it seems that increased circulating visfatin is not associated to the labor *per se* rather than to the state of infection. However, the median gestational age of patients with preterm labor without IAI was significantly higher that this of those with normal pregnancy (not in labor). In addition, acute infection/inflammation is associated with hypermetabolism, enhanced energy expenditure, and insulin resistance.[198–200] Thus, it is likely that the presence of IAI (independent of labor) is associated with increased metabolic demands. Increase in production and/or secretion of visfatin may be part of the adaptive response to the metabolic dysregulation associated with the state of infection.

An additional explanation can be that the alterations in circulating maternal visfatin concentration are aimed at regulating the immune response. Compelling evidence suggests that visfatin has an important role in the regulation of the innate immune limb. *In vitro,* visfatin induces, in a dose dependent manner, the production of proinflammatory cytokines (e.g. IL-6, TNF-α, IL-1β) by human monocytes.[167] Moreover, the following pro-inflammatory mediators were reported to increase visfatin expression: TNF-α in monocytes, [166] macrophages[201] and neutrophils,[117] IL-6 in synovial[202] and amniotic epithelial cells[162] and IL-8 and granulocyte/macrophage colony stimulating factor in neutrophils.[117] Similarly, expression of visfatin can be induced by endotoxin/LPS from neutrophils[117] amniotic epithelial cells[162] and lung microvascular endothelial cells.[142] Thus, we hypothesize that the increased concentrations of visfatin in patients with preterm labor and IAI can be part of the innate immune response (i.e. inflammation).

In conclusion, the present study is the first to demonstrate that maternal plasma visfatin concentrations are higher in patients with preterm labor and intra-amniotic infection. The findings reported herein together with our previous report focusing on amniotic fluid visfatin suggest that this adipokine may have a role hitherto unrecognized in the pathogenesis of preterm labor associated with infection. The data of the present study do not allow us to determine whether the increase in maternal visfatin concentration is secondary to preterm labor with IAI or whether it is present already before establishment of the disease. However, since visfatin has been implicated in the regulation of metabolic adaptations to insults, as well as in the regulation of the innate immune limb, we suggest that the perturbation in visfatin homeostasis is an adaptive response to the insult imposed by preterm labor with IAI.

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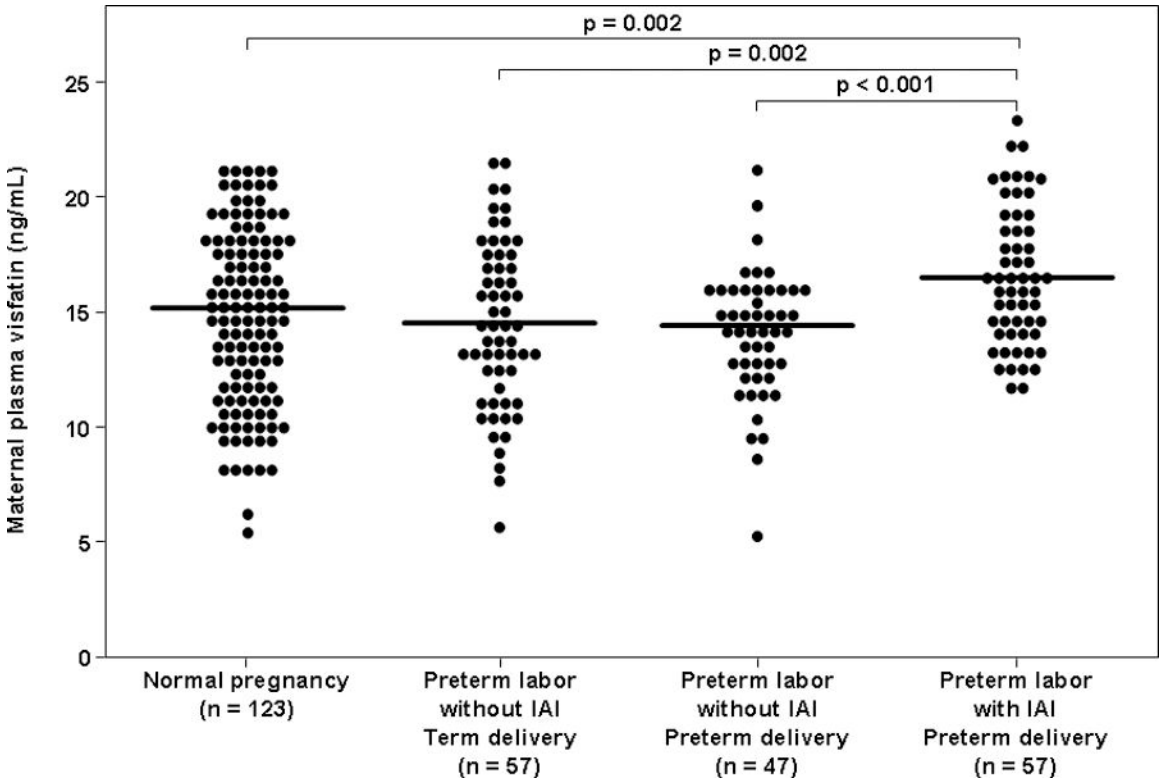

Figure 1. Comparison of the median maternal plasma visfatin between women with normal pregnancies and patients with spontaneous PTL.

The median maternal plasma visfatin concentration was higher in patients with preterm labor with IAI than those with preterm labor without IAI who delivered either preterm or at term. Similarly, the median maternal plasma visfatin concentration was higher in patients with preterm labor with IAI than those with a normal pregnancy. The median maternal plasma visfatin concentration did not differ significantly between patients with preterm labor without IAI who delivered preterm and those who delivered at term. In addition, there was no significant difference in the median maternal plasma visfatin concentration between women with a normal pregnancy and those with preterm labor without IAI who delivered either preterm or at term.

Table I.

Clinical and demographic characteristics of the study population

	Normal Pregnancy (n=123)	PTL without IAI Term delivery (n=57)	p^1	PTL without IAI Preterm delivery (n=47)	p^2	PTL with IAI Preterm delivery (n=57)	p^3
Maternal age (years)	25 (21–31)	22 (19–26)	NS	22 (19–27)	NS	24 (20–27)	NS
Parity	1 (0–2)	1 (0–2)	NS	1 (0–3)	NS	1 (0–3)	NS
First trimester BMI (kg/m^2)	23.3 (21.6–26.2)	23.1 (20.0–25.7)	NS	23.4 (21.3–25.6)	NS	24.8 (21.6–29.7)	NS
GA at blood sampling (weeks)	27.7 (21.5–32.2)	30.6 (26.3–32.7)	NS	31.0 (28.9–32.3)	<0.01	25.1 (23.9–31.6)	NS
GA at delivery (weeks)	39.8 (39.0–40.4)	38.6 (37.6–39.3)	<0.01	34.2 (32.9–35.3)	<0.01	27.5 (24.4–32.8)	<0.01
Birth weight (grams)	3470 (3220–3730)	2998 (2681–3250)	<0.01	2112 (1559–2358)	<0.01	920 (611–1742)	<0.01

p^1: comparison between preterm labor who delivered at term and preterm labor without IAI

p^2: comparison between preterm labor who delivered preterm without IAI and preterm labor with IAI

p^3: comparison between preterm labor who delivered at term and preterm labor with IAI

Values are expressed as median and interquartile (IQR) range; **PTL:** preterm labor; **GA:** gestational age; **BMI:** body mass index; **IAI:** intra-amniotic infection/inflammation **NS:** not significant