Published in final edited form as:
*J Matern Fetal Neonatal Med*. 2010 October ; 23(10): 1119–1128. doi:10.3109/14767050903572190.

# Maternal and Neonatal Circulating Visfatin Concentrations in Patients with Preeclampsia and a Small-For-Gestational Age Neonate

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## Abstract

**Objective—**Maternal circulating visfatin concentrations are higher in patients with a small-for-gestational-age (SGA) neonate than in those who delivered an appropriate-for-gestational age AGA neonate or in those with preeclampsia. It has been proposed that enhanced transfer of visfatin from the fetal to maternal circulation may account for the high concentrations of maternal visfatin observed in patients with an SGA neonate. The aims of this study were: 1) to determine whether cord blood visfatin concentrations differ between normal neonates, SGA neonates and newborns of preeclamptic mothers; and 2) to assess the relationship between maternal and fetal circulating visfatin concentrations in patients with an SGA neonate and those with preeclampsia.

**Study design—**This cross-sectional study included 88 pregnant women and their neonates, as well as 22 preterm neonates in the following groups: 1) 44 normal pregnant women at term and their AGA neonates; 2) 22 normotensive pregnant women and their SGA neonates; 3) 22 women with preeclampsia and their neonates; and 4) 22 preterm neonates delivered following spontaneous preterm labor without funisitis or histologic chorioamnionitis, matched for gestational age with infants of preeclamptic mothers. Maternal plasma and cord blood visfatin concentrations were determined by ELISA. Non-parametric statistics were used for analyses.

**Results—**1) The median visfatin concentration was lower in umbilical cord blood than in maternal circulation, in normal pregnancy, SGA and preeclampsia groups ($p<0.001$ for all comparisons); 2) the median cord blood visfatin concentrations did not differ significantly between term AGA or SGA neonates, infants of mothers with preeclampsia and their gestational-age-matched preterm AGA neonates; 3) maternal and cord blood visfatin concentrations correlated only in the normal term group ($r= 0.48$, $p=0.04$).

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**Conclusion—**Circulating visfatin concentrations are lower in the fetal than in the maternal circulation and did not significantly differ between the study groups. Thus, it is unlikely that the fetal circulation is the source of the high maternal visfatin concentrations reported in patients with an SGA neonate.

### Keywords

visfatin; adipokines; cytokine; pregnancy; fetal growth restriction; AGA; umbilical cord blood

## Introduction

Preeclampsia and delivery of a small-for-gestational age (SGA) neonates, two of the "great obstetrical syndromes"[1], share several mechanisms of disease including failure of physiologic transformation of the spiral arteries [2,3], an anti-angiogenic state [4–18], endothelial cell dysfunction [19–21], and an increased maternal intravascular inflammatory response [15,22–32]. Despite these similarities, preeclampsia and pregnancies complicated by an SGA neonate have different clinical manifestations. While preeclampsia is characterized by hypertension, proteinuria and organ damage [33,34], SGA is usually defined as a birthweight below the $10^{th}$ percentile for gestational age at birth according to the birth weight distribution of a particular population [35]. Hypertension, proteinuria and organ damage are not clinical features of pregnancies with isolated SGA.

Several explanations have been proposed to reconcile this apparent disparity including exposure to infection during pregnancy [36,37], differences in the profile of angiogenic and anti-angiogenic response to intrauterine insults [13,17], altered activity of the coagulation system [38], and changes in the concentrations of placental growth hormone [39] and pro-inflammatory chemokines (CXCL10/IP-10) [15]. Ness and Sibai [19] have proposed that the presence of altered metabolic states (e.g. obesity, insulin resistance, dyslipidemia) predisposes pregnant women to develop preeclampsia, while the absence of these metabolic derangements will result in an SGA neonate.

Visfatin, a newly discovered 52 kDa adipokine, has been implicated in the regulation of glucose homeostasis [40], Type-2 diabetes mellitus (Type-2 DM) [41], gestational diabetes mellitus (GDM) [42–46], as well as in fetal growth [47]. Recently, we have reported that patients with an SGA neinate, but not those with preeclampsia, had a higher maternal plasma visfatin concentration than those with a normal pregnancy [48] suggesting that perturbation of visfatin homeostasis may be implicated in the phenotypic distinction between preeclampsia and SGA. Nevertheless, the source of the higher maternal circulating visfatin concentrations in patients with an SGA neonate has not yet been determined. It has been hypothesized that enhanced transfer of visfatin from the fetal to the maternal circulation can account for the high concentrations of maternal visfatin reported in patients with an SGA neonate. Thus, the aims of this study were: 1) to determine whether cord blood visfatin concentration differ between normal neonates, SGA neonates and newborns of preeclamptic mothers; and 2) to assess the relationship between maternal and fetal circulating visfatin concentrations in patients with an SGA neonate and those with preeclampsia.

## Materials and Methods

### Study Population

A case-control study was conducted by searching our clinical database and bank of biological samples, and included 88 pregnant women and their neonates, as well as 22 preterm neonates, in the following groups: 1) 44 normal pregnant women at term and their

appropriate-for-gestational age (AGA) neonates; 2) 22 normotensive pregnant women and their SGA neonates; 3) 22 women with preeclampsia and their neonates; and 4) 22 preterm AGA neonates delivered following spontaneous preterm labor without funisitis or histologic chorioamnionitis, matched for gestational age with neonates of the preeclampsia group.

Maternal plasma, umbilical cord blood and clinical and demographic data were retrieved from our bank of biological samples and clinical database. Many of these samples have previously been employed to study the biology of inflammation, homeostasis, angiogenesis regulation and adipokines concentrations in normal pregnant women and those with pregnancy complications. Maternal visfatin concentrations for the patients included in the present study have been previously reported [48] and were included in this study in order to provide a complete picture to the reader.

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 the Sotero del Rio Hospital (Santiago, Chile) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH/DHHS, Bethesda, Maryland, USA).

## Definitions

The inclusion criteria for normal pregnancy were: 1) no medical, obstetrical or surgical complications; 2) intact membranes; 3) delivery of a term neonate (>37 weeks) with a birth weight above the $10^{th}$ percentile;[49] and 4) a normal oral 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation based on the World Health Organization (WHO) criteria [50].

Preeclampsia was defined as the presence of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours to 1 week apart) first occurring after 20 weeks of gestation in a woman with previously normal blood pressure, and proteinuria (≥300 mg in a 24-hours urine collection or at least one dipstick measurement ≥1+) [51]. The diagnosis of SGA was based on ultrasonographic estimated fetal weight and confirmed by a birth weight below the $10^{th}$ percentile for gestational age [49]. The body mass index (BMI) was calculated according to the following formula: weight (kg)/height ($m^2$). Normal weight women were defined as those with a BMI of 18.5–24.9 kg/$m^2$ according to the definition of the WHO [52]. Ponderal Index was calculated according to the following formula: weight (kg)/height ($m^3$).

## Sample collection and Human Visfatin C-terminal immunoassay

Maternal blood samples were collected during clinical visits and umbilical cord blood was obtained from the umbilical vein at the time of delivery. Blood was centrifuged at 1300 × *g* for 10 minutes at 4°C. The plasma obtained was stored at −80°C until analysis.

Comparison between maternal and fetal circulating visfatin concentrations, as well as correlation analysis was conducted only in cases in which the time interval between maternal blood sampling and delivery was less than 48 hours. The 48 hours interval was chosen to maintain a meaningful temporal relationship of visfatin concentrations between umbilical cord blood and maternal blood.

Concentrations of visfatin in maternal and fetal plasma were determined using specific and sensitive enzyme immunoassays (Phoenix Pharmaceuticals, Inc. Belmont, CA, USA). An initial assay validation was performed in our laboratory prior to the conduction of this study. A detailed description of the assay has been previously published [46,53–55]. 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 was calculated to be 0.04 ng/ml.

### Statistical analysis

Normality of the data was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since maternal plasma and umbilical cord blood visfatin concentrations were not normally distributed, Kruskal–Wallis tests with post-hoc analysis by Mann-Whitney U tests were used for comparisons of continuous variables between the different groups. Comparison of proportions was performed by Fisher's test. Wilcoxon Signed ranks test exact test was used to compare visfatin concentrations between mather-neonate pairs. Spearman rank correlation was utilized to assess correlations between umbilical cord blood visfatin concentrations and birthweight, Ponderal Index, gestational age at delivery, maternal plasma visfatin concentration and maternal BMI. 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 the study groups are presented in Table I. The median gestational age at delivery (i.e. gestational age at cord blood sampling) was significantly lower in neonates of mothers with preeclampsia than in normal term AGA and SGA newborns. There was no significant difference in the median gestational age at delivery between neonate of mothers with preeclampsia and those with preterm labor (Table I).

### Umbilical cord blood visfatin concentrations in preeclampsia, SGA and preterm labor

The median umbilical cord plasma concentrations did not differ significantly between AGA (7.2 ng/ml, interquartile range [IQR]: 5.8–8.0), SGA newborns (7.1 ng/ml, IQR: 5.7–9.5) and infants of patients with preeclampsia (7.4 ng/ml, IQR: 5.6–8.2) (p=0.8, Kruskal-Wallis; Figure 1).

Since gestational age at umbilical cord sampling was significantly lower in neonate of mothers with preeclampsia, circulating visfatin concentrations were determined in 22 preterm AGA neonates delivered following spontaneous preterm labor without funisitis or histologic chorioamnionitis, matched for gestational age with the infants of patients with preeclampsia. The median umbilical cord visfatin plasma concentrations did not differ significantly between neonates of patients with preeclampsia and those born preterm without preeclampsia (7.4 ng/ml, IQR: 5.6–8.2 vs. 7.1 ng/ml, IQR: 6.4–7.7, p=0.9, Figure 1).

In contrast, the median maternal plasma visfatin concentrations differed significantly among groups (p=0.04, Kruskal-Wallis). The median maternal plasma concentration of visfatin was significantly higher in patients with an SGA neonate than in those with either normal pregnancy (18 ng/ml, IQR: 16.2–23.3 vs. 16.1 ng/ml, IQR: 11.2–20.3; p=0.02) or those with preeclampsia (15.9 ng/ml, IQR: 13–22; p=0.04). The median maternal plasma visfatin concentration did not differ significantly between patients with preeclampsia and those with a normal pregnancy (p=0.7).

### Comparison between maternal plasma and umbilical cord blood visfatin concentrations

Comparison between maternal and fetal circulating visfatin concentrations was conducted only in cases in which the time interval between maternal and umbilical cord blood sampling was less than 48 hours. Using this cut-off, maternal-neonatal paired samples were available for 18 patients in the normal pregnancy group, 20 in the SGA group and 19 in the preeclampsia group. The median plasma visfatin concentration was significantly higher in

the maternal than in the umbilical blood in the normal pregnancy group (18.7 ng/ml, IQR: 12.7–21.3 vs. 7.3 ng/ml, IQR: 6.1–7.9, p<0.001; Figure 2A), SGA group (18 ng/ml, IQR: 16.4–23 vs. 6.7 ng/ml, IQR: 5.7–8.5, p<0.001; Figure 2B),and in the preeclampsia group (16.5 ng/ml, IQR: 13.1–22.6 vs. 7.6 ng/ml, IQR: 6.4–8.2, p<0.001; Figure 2C).

The median umbilical cord plasma visfatin concentration did not differ significantly between male and female neonates in a pooled analysis (p=0.1) or within normal neonates (p=0.5), SGA newborns (p=0.8), neonates of mothers with preeclampsia (p=0.1) or preterm neonates (p=0.9, data not shown).

Maternal and cord blood plasma visfatin concentrations correlated only in the normal term group (r= 0.48, p=0.04; Figure 3), but not in the SGA (r= 0.2, p=0.3) or preeclampsia group(r= 0.5, p=0.1). No significant correlation was found between cord blood visfatin concentrations and birthweight, Ponderal Index or gestational age at delivery.

## Discussion

### Principal findings of the study

1) The median plasma visfatin concentration was significantly lower in cord blood than in the maternal circulation in normal pregnancy, SGA and preeclampsia; 2) the median cord blood visfatin concentrations did not differ significantly between term AGA, SGA and neonates of patients with preeclampsia; 3) maternal and cord blood visfatin concentrations correlated only in the normal term group.

### The physiological role of visfatin

Visfatin, also known as Pre-B cell colony-enhancing factor (PBEF), was originally identified as a growth factor for early B cell [56]. Subsequently, it was recognized as a novel adipokine which is preferentially produced by the visceral fat depot.[40] Visfatin/PBEF has been implicated in the regulation of glucose homeostasis. Indeed, *in vitro*, adipocytes secrete visfatin in response to treatment with glucose[57] and this protein can exert insulin-mimicking effects [58]. *In vivo*, visfatin-deficient mice have impaired glucose tolerance[59] and a polymorphism in the human visfatin gene promoter is associated with a susceptibility to type-2 DM [60]. Moreover, high circulating concentrations of this adipokine characterize patients with insulin resistance [44–46,61,62].

In addition to its metabolic effects, visfatin has pro-inflammatory properties. *In vitro*, visfatin synergizes with interleukin (IL)-7 and stem cell factors to promote the growth of B-cell precursors and treatment of human monocytes with visfatin results in an increased secretion of IL-6, tumor necrosis factor-α and IL-1β in a dose-dependent manner.[63] In addition, patients with chronic inflammatory disorders such as inflammatory bowel disease [63] and rheumatoid arthritis [64] have a higher circulating visfatin concentration than normal subjects.

### Visfatin in normal gestation and in complications of pregnancy

The rationale to study visfatin concentrations in human pregnancy rests on the association between alterations in adipokines concentrations and adaptations to gestation [55,65–73], as well as with complications of pregnancy such as preeclampsia [48,74–77], preterm labor [53,78], intra-amniotic infection/inflammation [54,79–81], delivery of an SGA neonate [82,83], macrosomia [84,85], GDM [84] and pyelonephritis [86]. Moreover, visfatin is expressed in the placenta, fetal membranes [87–94] and the myometrium [95]. Normal pregnancy is associated with high maternal circulating visfatin concentrations [55,96–100]. In addition, GDM is characterized by alterations in maternal concentrations of this adipokine

[42,44–46,101]. Recently, we have reported that intra-amniotic infection/inflammation is associated with higher amniotic fluid concentrations of visfatin than in the absence of infection [54], and that preterm labor is characterized by high maternal circulating concentrations of this adipokine [53].

### Visfatin concentrations are lower in the fetal than in the maternal circulation

Only several studies have addressed umbilical cord blood visfatin concentrations [102–106], and a comparison between maternal and neonatal concentrations of this adipokine was included in only two reports [104,105]. The results of the present study indicate that circulating visfatin concentrations are lower in the fetal than in the maternal circulation. This novel finding was demonstrated in all study groups, including normal neonates, SGA newborns and neonates of mothers with preeclampsia. The results reported herein are in contrast to the report by Malamitsi-Puchner et al.[105] in which there was no significant differences between maternal and neonatal circulating visfatin concentrations. Ethnic origin, clinical definitions, and gestational age at enrollment varied between the studies and may account for this discrepancy.

It is not clear why visfatin concentrations are lower in the fetal than in the maternal circulation. Increased production by the larger maternal fat depot compared to the newborn is a plausible explanation. In addition, visfatin, which is expressed in a considerable amount in the term human placenta [97], may be preferentially released into the maternal systemic circulation. Disparity in placental secretion of adipokines into the maternal and fetal circulation has been demonstrated for other adipokines such as leptin [107].

Our findings indicate that maternal and cord blood plasma visfatin concentrations were correlated only in the normal term group. This finding is in agreement with the reports by Ibánez et al.[102] and Malamitsi-Puchner et al.[104,105] we found no gender disparity in umbilical cord visfatin concentrations. Our findings are also in agreement with López-Bermejo et al.[103] who found no association between umbilical cord blood visfatin concentrations and anthropometric indices of the newborn. The present study extends the aforementioned reports by demonstrating these finding not only to term or AGA neonates but also to those of mother with preeclampsia and premature neonates.

### The fetal circulation is not the source for the elevated visfatin concentrations of mother with a small-for-gestational-age neonate

Two studies, conducted by Fasshauer et al.[108] and Malamitsi-Puchner et al.[104] have reported higher maternal circulating visfatin concentrations in patients with an SGA neonate than in those who delivered an AGA neonate. In accordance with these findings, we have recently reported that patients with an SGA neonate, but not those with preeclampsia, had a higher maternal plasma visfatin concentration than those with a normal pregnancy suggesting differential involvement of visfatin in SGA and preeclampsia [48]. However, the mechanism by which an SGA neonate affects maternal visfatin circulation is not clear. It has been proposed that enhanced transfer of visfatin from the fetal to the maternal circulation can account for the high concentrations of maternal visfatin reported in patients with an SGA neonate [48]. The results of the present study suggest that the fetal circulation is not the source for the increased maternal visfatin concentrations in patients with an SGA neonate as no significant differences were documented between the cord blood concentrations of the different study groups.

The finding reported herein concerning the lack of difference in umbilical cord blood visfatin concentrations between SGA neonates and those with a normal pregnancy is in contrast to the report by Malamitsi-Puchner et al.[104] in which umbilical cord blood

visfatin concentrations were higher in SGA than in AGA neonates matched for gestational age. Differences in the definition of an SGA neonate and ethnic origin may account for this discrepancy. Specifically, in the study by Malamitsi-Puchner et al.[104] the SGA group included patients with preeclampsia, gestational hypertension, iron-deficiency anemia, gestational diabetes, hypothyroidism, as well as cardiac arrhythmias, whereas in the present study mothers with these conditions were excluded from the SGA group.

In conclusion, circulating fetal visfatin concentrations are lower than maternal plasma concentrations. Despite the association between the presence of an SGA neonate and high maternal circulating visfatin concentrations, comparable visfatin concentrations were detected in the umbilical cord blood of normal neonates, SGA newborns, infants of patients with preeclampsia and preterm neonates. Collectively, these observations suggest that fetal-maternal transport of visfatin is not likely to account for the high maternal visfatin concentrations in patients with an SGA neonate.

## Acknowledgments

This research was supported (in part) by the Perinatology Research Branch, Division of Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

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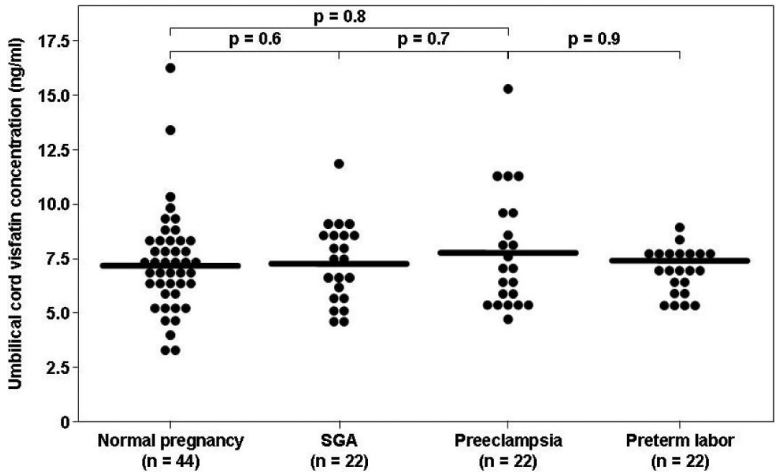
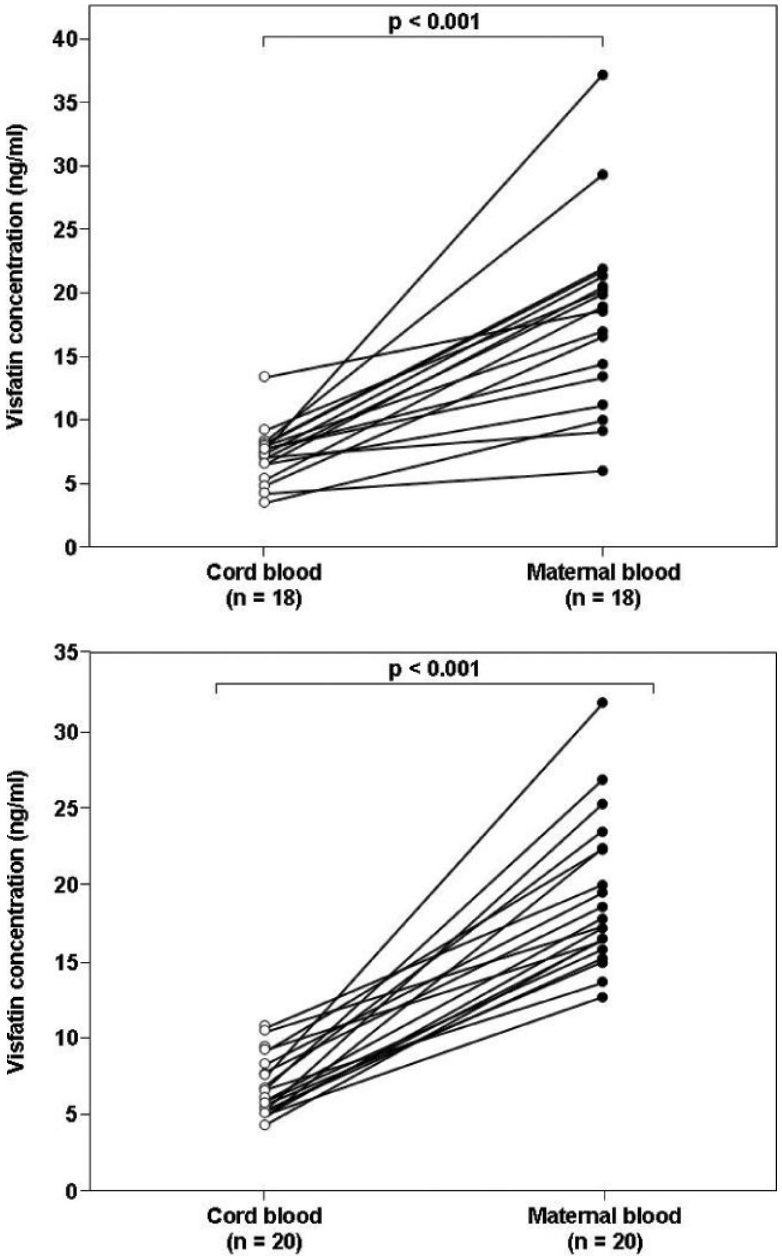



**Figure 1. Comparison between umbilical cord plasma visfatin plasma concentration in normal neonates, SGA newborns, infants of patients with preeclampsia and preterm neonate**

The median umbilical cord plasma concentrations of normal neonates (7.2 ng/ml, interquartile range [IQR] 5.8–8.0), SGA newborns (7.1 ng/ml, IQR: 5.7–9.5) and infants of patients with preeclampsia (7.4 ng/ml, IQR: 5.6–8.2) did not differ significantly (p=0.8, Kruskal-Wallis). Similarly, the median umbilical cord plasma visfatin concentrations did not differ significantly between neonates of patients with preeclampsia and those delivered preterm without preeclampsia matched for gestational age (7.4 ng/ml, IQR: 5.6–8.2 vs. 7.1 ng/ml, IQR: 6.4–7.7).



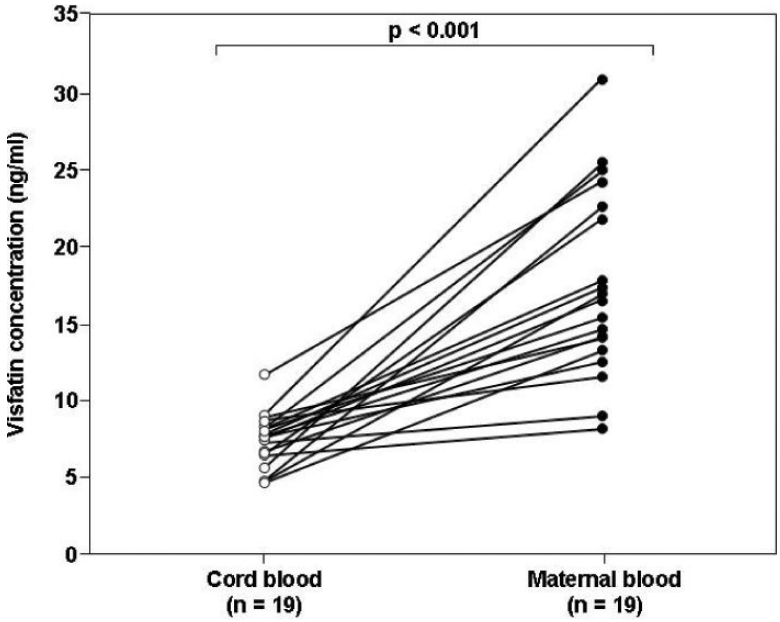



**Figure 2. Comparison between umbilical cord blood and maternal plasma visfatin concentrations in normal gestations (A), pregnancies complicated by an SGA neonate (B) or preeclampsia (C)**

The median maternal plasma visfatin concentration was higher than in the umbilical blood in the normal pregnancy group (18.7 ng/ml, IQR: 12.7–21.3 vs. 7.3 ng/ml, IQR: 6.1–7.9, respectively, $p<0.001$), SGA group (18.0 ng/ml, IQR: 16.4–23.0 vs. 6.7 ng/ml, IQR: 5.7–8.5, $p<0.001$),and in the preeclampsia group (16.5 ng/ml, IQR: 13.1–22.6 vs. 7.6 ng/ml, IQR: 6.4–8.2, $p<0.001$).

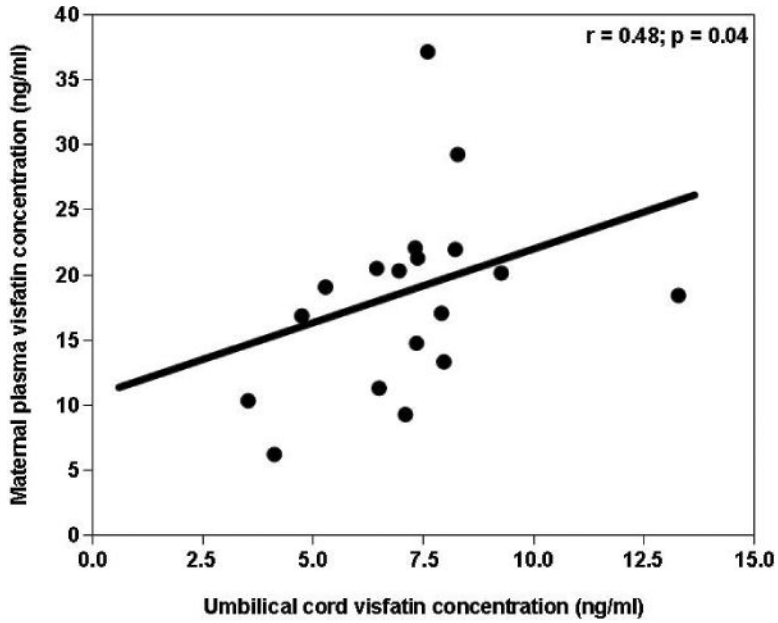



**Figure 3. Correlation between umbilical cord blood and maternal plasma visfatin concentrations in the normal gestation**

Maternal and cord blood plasma visfatin concentrations correlated only in the normal term group (r= 0.48, p=0.04)

**Table I**

Clinical and demographic characteristics of the study population.

| | Normal Pregnancy (n=44) | p | SGA (n=22) | $p^a$ | Preeclampsia (n=22) | $p^b$ | Preterm Labor (n=22) | $p^c$ |
|---|---|---|---|---|---|---|---|---|
| **Maternal age (years)** | 25 (21 – 33) | 0.8 | 28 (21 – 33) | 0.2 | 23 (20 – 29) | 0.3 | 23 (19 – 27) | 0.5 |
| **Parity** | 1 (0 – 2) | 0.7 | 1 (0 – 1) | 0.7 | 1 (0 – 1) | 0.8 | 1 (0 – 1) | 0.5 |
| **Pre-gestational BMI ($kg/m^2$)** | 23.4 (21.6 – 26.1) | 0.6 | 23.8 (22.6 – 27) | 0.7 | 23.4 (19.4 – 29.5) | 0.6 | 22.8 (21.1 – 24.1) | 0.6 |
| **GA at maternal blood sampling (weeks)** | 33.6 (27.9 – 38.5) | 0.007 | 38.1 (37.2 – 38.9) | 0.9 | 33.6 (32.4 – 37.7) | <0.001 | NA | NA |
| **GA at delivery (weeks)** | 38.6 (38.1 – 38.9) | 0.1 | 38.3 (38.0 – 38.7) | <0.001 | 34.0 (33.0 – 37.7) | 0.003 | 34.0 (33.0 – 34.7) | 0.1 |
| **Male Gender** | 25 (57%) | 0.4 | 10 (45%) | 0.6 | 11 (50%) | 0.9 | 10 (45%) | 0.9 |
| **Birth weight (grams)** | 3245 (3102–3500) | <0.001 | 2430 (1962–2595) | <0.001 | 2135 (1632–2575) | 0.2 | 2345 (2017–2547) | 0.3 |

Values expressed as median (interquartile range) or n (%)

**SGA**- Small-for-gestational-age**; GA** – Gestational Age; **BMI** – Body Mass Index; **NA** – Not available

**p**: comparison between normal pregnancy and the SGA group

$\mathbf{p^a}$: comparison between normal pregnancy and the preeclampsia group

$\mathbf{p^b}$: comparison between preeclampsia and the SGA group

$\mathbf{p^c}$: comparison between preeclampsia and the preterm labor group

*J Matern Fetal Neonatal Med*. Author manuscript; available in PMC 2012 August 07.