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Evidence for differential regulation of the adipokine visfatin in the maternal and fetal compartments in normal spontaneous labor at term

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Abstract

Objective—Visfatin, a novel adipokine with metabolic and immunoregulatory properties, has been implicated in the regulation of fetal growth, as well as in preterm labor. A gap in knowledge is whether spontaneous labor at term is associated with changes in the maternal and fetal concentrations of visfatin. The aim of this study was to determine if the presence of labor at term is associated with alterations in maternal and neonatal plasma visfatin concentrations.

Study design—This cross-sectional study included 50 normal pregnant women at term and their appropriate-for-gestational age (AGA) neonates in the following groups: 1) 25 mother-neonate pairs delivered by elective cesarean section without spontaneous labor, and 2) 25 mother-neonate pairs who delivered vaginally following spontaneous labor. 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 higher in umbilical cord plasma of neonates born following a spontaneous labor at term than that of those who were born by an elective cesarean section (p=0.02); 2) in contrast, the median maternal plasma visfatin concentration did not differ significantly between patients with and without labor (p=0.44); and 3) there was a significant correlation between umbilical cord plasma concentration of visfatin and both maternal visfatin concentration (r= 0.54, p=0.005) and gestational age at delivery (r= 0.58; p=0.002) only in the absence of labor.

Conclusion—Term labor is associated with increased fetal, but not maternal, circulating visfatin concentrations. Previous reports indicate that preterm labor leading to preterm delivery is characterized by an increase in maternal plasma concentrations of visfatin. The observations reported herein support the view that there are fundamental differences in the endocrine and metabolic adaptations in normal labor at term and preterm labor.

Keywords

adipokine; cytokine; pregnancy; parturition; cord blood; neonate; energy demands; metabolism; BMI; overweight; obesity

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Introduction

Parturition is a high energy-consuming process. This is evidenced by increased concentrations of circulating maternal glucose [30, 32, 86, 87, 104], free fatty acids [20, 104], ketone bodies [18], and lactic acid [44] during parturition. Moreover, there is a 3- to 4-fold increase in whole body glucose utilization during labor and delivery and the energy expenditure of the parturient women in the second stage of labor is 40% higher than that of patients in the first stage [6]. In addition, myometrial glycogen storage, which is significantly increased at term [69], is almost completely depleted during labor [40], further supporting the notion that parturition imposes an increase energy demand on the laboring woman. Similarly, a compelling body of evidence suggests that the energy requirements of the fetus also increase during labor and delivery. Indeed, parturition is associated with an increased fetal blood glucose [86, 87] and the concentrations of this nutrient is significantly higher in the umbilical vein than in umbilical arteries [36], suggesting enhanced fetal usage of this fuel during labor.

However, while the metabolic alterations that accompany labor and delivery are well established, the specific mechanism regulating this physiological response is not completely clear. The conventional view is that labor and delivery can be viewed as a moderate exercise [6, 30] and that similar, albeit not identical, mechanisms are governing the metabolic adaptation to parturition [6, 46, 93]. These mechanisms include non-insulin dependent glucose uptake, increased maternal circulating epinephrine and norepinephrine, enhanced hepatic gluconeogenesis and direct sympathetic nervous system stimulation [6, 46, 93].

It is now well-established that adipokines - hormones produced exclusively and/or abundantly by adipose tissue - play a major role in energy homeostasis during physiologic and pathologic conditions [28, 91], as well as during intense and/or acute physical activities [45, 85]. Adipokines, such as adiponectin [9, 58, 60, 62, 64, 75, 97], resistin [77] and visfatin [65] have been implicated in metabolic adaptations to normal gestation, as well as in complications of pregnancy such as preeclampsia [3, 12, 13, 22, 27, 29, 35, 67, 68, 72, 78, 84, 88, 95, 98, 102], SGA [39, 56, 103] preterm labor and others [38, 52-55, 57, 59, 61, 63, 64, 67, 76, 101].

Visfatin, a newly discovered 52 kDa adipokine, has been implicated in the regulation of glucose hemostasis [94] and it has been proposed that this hormone can play a role in fetal growth [7, 8, 25, 43, 47, 48, 51]. Recently, we have reported that preterm labor is associated with increased maternal circulating concentrations of visfatin [53]. However, it is unknown whether spontaneous labor at term is associated with changes in the maternal and fetal concentrations of visfatin. This study was conducted to address this question.

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 50 pregnant women and their neonates in the following groups: 1) 25 normal pregnant women at term in labor and their appropriate-for-gestational age (AGA) neonates; and 2) 25 normal pregnant women at term, who underwent elective cesarean delivery, and their AGA neonates.

Maternal plasma, umbilical cord blood and demographic and clinical data were retrieved from our bank of biological samples and clinical databases. Many of these samples were previously employed to study the biology of inflammation, hemostasis, angiogenesis

regulation, adipokines and growth factor concentrations in normal pregnant women and those with pregnancy complications.

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 (Santiago, Chile) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; 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 between the 10^{th} and the 90^{th} percentile [19]; 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 [2].

Spontaneous labor was defined as the presence of regular uterine contractions associated with cervical change, occurring at a frequency of at least two every 10 minutes. The body mass index (BMI) was calculated according to the 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 World Health Organization (WHO)[1].

Sample collection and Human Visfatin C-terminal immunoassay

Maternal blood samples were collected after the diagnosis of labor or before the onset of cesarean delivery. 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. 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 and the detailed description of the assay has been previously published [53, 63, 65, 66]. 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, Mann-Whitney U tests were used for comparisons of continuous variables between the different groups and Wilcoxon signed-rank test for comparison of visfatin concentrations between mother-neonate pairs. Comparison of proportions was performed by Fisher's exact test. Spearman rank correlation was utilized to assess correlations between umbilical cord blood visfatin concentrations and birthweight, gestational age at delivery, maternal plasma visfatin concentration, as well as 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 1. There were no significant differences in the demographic and clinical characteristics between the two groups.

Umbilical cord blood visfatin concentrations in labor vs. no labor

The median visfatin concentration was higher in umbilical cord plasma of neonates born following a spontaneous labor at term than in those who were born by an elective cesarean delivery (4.8 ng/ml, interquartile range [IQR] 4.2-5.3 vs. 3.8 ng/ml, IQR: 3.3-4.7; p=0.02, Figure 1A).

Maternal plasma visfatin concentrations in labor vs. no labor

The median visfatin concentration in maternal plasma did not differ significantly between patients with spontaneous labor at term and that of those who underwent an elective cesarean delivery (8.5 ng/ml, IQR: 6.4-10.3 vs. 9.1 ng/ml, IQR: 7.6-10.0; p=0.44, Figure 1B).

Comparison between maternal plasma and umbilical cord blood visfatin concentrations

The median maternal plasma visfatin concentration was significantly higher than that of umbilical cord blood regardless of the presence ($p<0.001$, Figure 2A) or absence ($p<0.001$, Figure 2B) of spontaneous labor.

Maternal-neonatal difference in plasma visfatin (defined as maternal plasma visfatin concentration - umbilical cord blood visfatin concentration) was comparable between mother-neonate pairs in labor and those not in labor (4.4 ng/ml, IQR: 2.4-5.8 vs. 3.8 ng/ml, IQR: 2.6-5.4; p=0.8). In a pooled analysis (including neonates born following spontaneous labor and by cesarean section), there was no significant difference in the median umbilical blood visfatin concentration between males and females (4.4 ng/ml, IQR: 3.5-4.9 vs. 4.4 ng/ml, IQR: 3.9-5.3; p=0.8).

There was a significant correlation between umbilical cord blood concentrations of visfatin and maternal visfatin concentration (r= 0.54, p=0.005), as well as gestational age at delivery (r=0.58; p=0.002) only in the absence of labor. There was no significant correlation between umbilical cord plasma visfatin concentration and birthweight.

Discussion

Principal findings of the study

1) The median visfatin concentration was higher in umbilical cord plasma of neonates born following spontaneous labor at term than in those who were born by an elective cesarean delivery; 2) in contrast, the median maternal plasma visfatin concentration did not differ significantly between patients with and without labor; and 3) there was a significant correlation between umbilical plasma visfatin concentration and both maternal visfatin concentration and gestational age at delivery only in the absence of labor.

The physiological role of visfatin

Visfatin was originally identified as a growth factor for early B cell and thus was termed Pre-B cell colony-enhancing factor (PBEF) [92]. Subsequently, this protein was identified as a 52 kDa adipokine that is preferentially produced by visceral fat depot [94] and the name “visfatin” was coined. The expression of visfatin/ PBEF is not limited to adipose tissue; indeed, its expression has been determined in placenta, fetal membranes [33, 34, 49, 73, 74, 79-82], myometrium,[15] bone marrow, liver, muscle [92], heart, lung, kidney [92], macrophages [14], and neutrophils [26, 92].

Visfatin has been implicated in the regulation of glucose homeostasis, as well as in inflammatory response[94, 100]. Several lines of evidence support the role of this adipokine in metabolic regulation: 1) adipocytes secrete visfatin in response to treatment with glucose

[21]; 2) visfatin deficient mice have an impaired glucose tolerance [89]; and 3) a visfatin promoter polymorphism is associated with susceptibility to type-2 diabetes mellitus [106]. The evidence supporting a role for visfatin as an immunomodulator includes the following findings: 1) visfatin synergizes with interleukin (IL)-7 and stem cell factors to promote the growth of B cell precursors; 2) treatment of human monocytes with visfatin results in an increased secretion of IL-6, TNF-α and IL-1β in a dose dependent manner [71]; and 3) chronic inflammatory disorders such as inflammatory bowel disease [71] and rheumatoid arthritis [83] are associated with a higher circulating visfatin concentration than normal subjects.

Maternal visfatin in normal gestation and in complications of pregnancy

Adipokines have been implicated in the regulation of metabolic adaptations to gestation, as well as in complications of pregnancy [38, 53-56, 58-64, 67, 75-77, 97]. Normal pregnancy is associated with alterations in maternal circulating visfatin concentrations [24, 31, 50, 65, 70, 99]. In addition, gestational diabetes mellitus [5, 11, 37, 42, 66], preeclampsia [4, 17, 24, 107], large–for-gestational-age neonate [66], fetal growth restriction [16, 47] and preterm labor [53] were linked to changes in circulating maternal visfatin concentrations when compared to normal pregnant women. Consistent with these findings, patients with intra-amniotic infection/inflammation have a higher amniotic fluid concentration of visfatin than those without intra-amniotic infection/inflammation [63].

Umbilical cord visfatin in normal gestation and its association with maternal concentrations of this adipokine

Umbilical cord blood visfatin concentrations have been reported in only a few studies [25, 43, 47, 48]. The results reported herein are in agreement with those of Malamitsi-Puchner et al.[47, 48] who found positive correlation between maternal and fetal visfatin concentrations, as well as those of Ibánez et al.[25] who found no gender disparity in umbilical cord visfatin concentrations. Our findings are also in agreement with López-Bermejo et al.[43] who reported lack of association between umbilical cord blood visfatin concentrations and indices of neonatal size.

The present study indicates that the median maternal visfatin concentration is higher than that determined in the umbilical cord blood regardless of the presence of labor. This finding is in contrast to the reports by Malamitsi-Puchner et al.[47, 48] in which comparable concentrations in the maternal and fetal circulation were detected. Differences in study design can account for the apparent inconsistencies among the studies. Specifically, the ethnic origin, maternal age, and birthweight varied among the studies. We recognize that the cross-sectional nature of our study precludes comment on causality in the association between maternal and fetal circulating visfatin concentration. Nevertheless, several explanations can account for the higher maternal visfatin concentration. As this adipokine is produced by adipose tissue, the mother's high total fat mass can produce more visfatin. An additional explanation can be differential secretion of placental visfatin between maternal and fetal circulation. Visfatin is expressed in a considerable amount in term human placenta [31, 70]. It is possible that this adipokine is released preferentially into the maternal systemic circulation. Such pattern has been demonstrated for other adipokines produced by the placenta such as leptin [23].

Spontaneous labor at term, in contrast to preterm labor, is not associated with alterations in maternal circulating visfatin

The findings reported herein demonstrate, for the first time, that labor is not associated with significant alterations in maternal visfatin concentrations. Recently, we reported that preterm labor with intra-amniotic infection/inflammation leading to preterm delivery is associated

with a higher median maternal plasma concentration of visfatin than normal pregnancy [53]. A possible explanation for this difference is that the metabolic and hormonal changes that characterize spontaneous term labor are different from those of preterm labor. In addition, we have likened increased circulating maternal visfatin concentrations to an inflammatory process in addition to metabolic response. The basis for this hypothesis is that among patients with preterm labor, those with intra-amniotic infection/inflammation had the highest circulating maternal visfatin concentrations [53]. Infection and inflammation are more prevalent as a cause for preterm than term parturition [90, 96]. Thus, the disparity in maternal visfatin concentration between term and preterm labor may reflect etiological differences between these two conditions.

The presence of spontaneous labor at term is associated with high umbilical cord blood visfatin concentrations

The median umbilical cord blood visfatin concentration was higher in neonates born following spontaneous labor than that of those who were delivered by cesarean section in the absence of labor. This is a novel finding and several explanations can be offered: labor imposes metabolic challenge not only on the parturient woman, but also on the fetus. Glucose, the most important fuel for the fetus [10, 93], is subject to dynamic metabolic change during the course of labor. Indeed, parturition is associated with an increased fetal blood glucose [86, 87]. Moreover, umbilical vein concentrations of glucose are lower [36] and those of lactate are higher [93] than in the umbilical artery, suggesting enhanced fetal consumption of glucose during labor. Of note, umbilical cord blood concentrations of glucose, insulin and cortisol are higher in neonates born after spontaneous labor than in neonates born by cesarean delivery in the absence of labor [41], further supporting the notion that labor is an energy consuming state for the fetus.

Visfatin has been implicated in the regulation of glucose homeostasis. Specifically, it has been proposed that visfatin can induce the uptake of glucose into cells [70] and that it can exert other insulinomimetic properties [21, 105]. Furthermore, Haider et al.[21] have demonstrated in a randomized, double blind, placebo-controlled, crossover study, that circulating visfatin concentrations are increased by hyperglycemia in humans. Thus, it is tempting to postulate that the increase in circulating umbilical cord blood visfatin is part of the metabolic adaptations of the fetus during labor aimed to meet the increased demands for glucose.

In conclusion, alterations in circulating maternal visfatin concentrations, previously reported in patients with preterm labor, were not observed in term parturient women thus highlighting the fundamental differences between these two conditions. In contrast, labor is associated with high umbilical cord blood visfatin concentrations suggesting that visfatin may play a role in fetal metabolic adaptations to the increased energy demand associated with labor.

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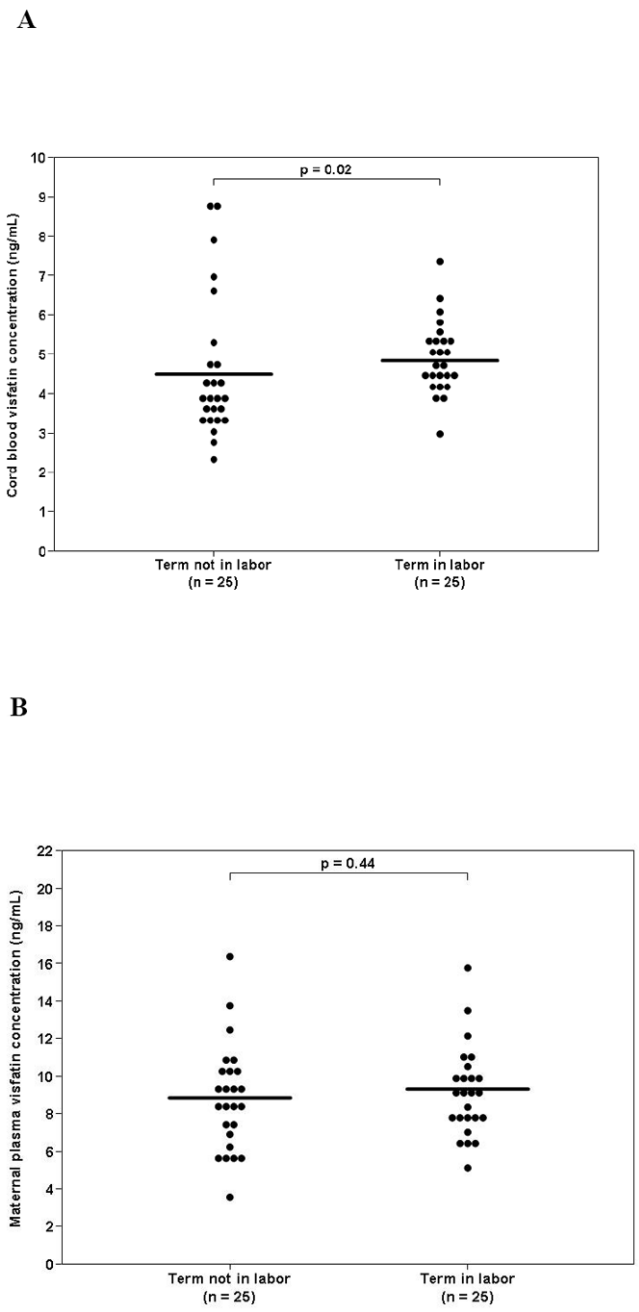
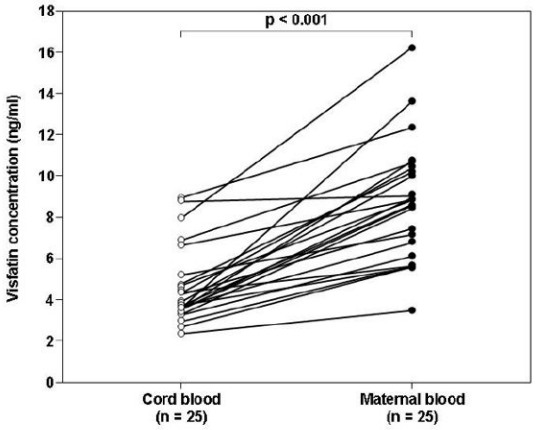


Figure 1. Comparison between visfatin circulating concentrations in the presence and absence of labor in cord blood (A) and maternal plasma (B)

The median visfatin concentration was higher in umbilical cord plasma of neonates born following spontaneous labor at term than in those who were born by an elective cesarean delivery (4.8 ng/ml, interquartile range [IQR] 4.2-5.3 vs. 3.8 ng/ml, IQR: 3.3-4.7; p=0.02). In contrast, the median visfatin concentration in maternal plasma was not significant different between patient with spontaneous labor at term and those who underwent an elective cesarean delivery (8.5 ng/ml, IQR: 6.4-10.3 vs. 9.1 ng/ml, IQR: 7.6-10.0; p=0.44, Figure 1B).

A



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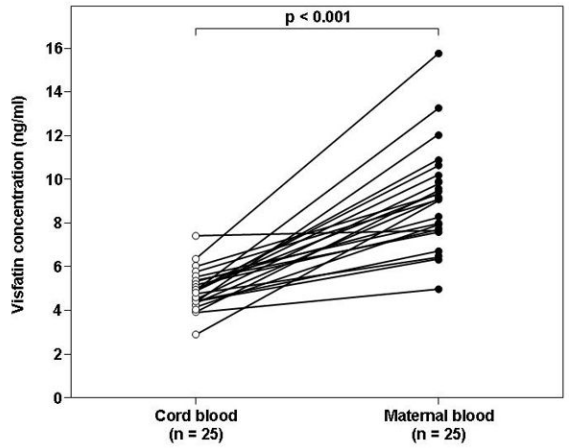

Figure 2. Comparison between umbilical cord blood and maternal plasma visfatin concentrations in the absence (A) and presence of labor (B)

The median maternal plasma visfatin concentration was higher than in the umbilical blood regardless of the presence or absence of spontaneous labor ($p<0.001$ for both comparisons).

Table 1

Clinical and demographic characteristics of the study population.

	Not in Labor (n=25)	Spontaneous Labor (n=25)	P
Maternal age (years)	32 (27 – 35)	26 (23 – 32)	0.06
Parity	1 (0 – 2)	1 (0 – 1)	0.8
Pre-gestational BMI (kg/m^2)	24.5 (22.7 – 27.0)	23.2 (22.3 – 26.0)	0.3
Overweight/Obese	11 (44)	8 (32)	0.3
Smoking	1 (4)	1 (4)	0.5
GA at delivery (weeks)	39.0 (38.1 – 40.5)	39.4 (38.7 – 40.1)	0.6
Birth weight (grams)	3560 (3165 – 3685)	3360 (3255 – 3490)	0.6
Female neonate	11 (44)	16 (64)	0.1

Values expressed as median (interquartile range) of number (%)
GA – Gestational Age; **BMI** – Body Mass Index