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Omentin-1 and vaspin are present in the fetus and neonate, and perinatal concentrations are similar in normal and growth-restricted pregnancies

Despina D. Briana[a], Maria Boutsikou[a], Stavroula Baka[a], Dimitrios Gourgiotis[b], Antonios Marmarinos[b], Sofia Liosi[a], Dimitrios Hassiakos[a], Ariadne Malamitsi-Puchner[a,*]

[a]*Neonatal Division, 2nd Department of Obstetrics and Gynecology, Athens University Medical School, 10682 Athens, Greece*
[b]*Research Laboratories, 2nd Department of Pediatrics, Athens University Medical School, 10682 Athens, Greece*

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Abstract

The aim of this study was to investigate circulating concentrations of omentin-1 and vaspin (adipocytokines predominantly secreted by visceral adipose tissue and not yet investigated in perinatal life) in maternal, fetal, and neonatal samples from intrauterine growth-restricted (IUGR; associated with altered development of adipose tissue) and appropriate-for-gestational-age (AGA) pregnancies and to correlate them with the respective insulin concentrations. Serum omentin-1 and vaspin concentrations were determined by enzyme immunoassay in 40 mothers and their 20 IUGR and 20 AGA singleton full-term fetuses and neonates on postnatal day 1 (N1) and day 4 (N4). Both hormones were detectable in fetal and neonatal blood (omentin-1 [mean ± SD, in nanograms per milliliter]: AGA vs IUGR group—fetal: 11.32 ± 1.88 vs 10.47 ± 1.30, N1: 10.74 ± 1.42 vs 10.46 ± 1.54, and N4: 10.90 ± 2.72 vs 11.35 ± 3.92; vaspin [median, minimum-maximum; in nanograms per milliliter]: AGA vs IUGR group—fetal: 0.39 [0.04-19.06] vs 0.40 [0.05-1.34], N1: 0.40 [0.04-16.70] vs 0.44 [0.23-3.34], and N4: 0.49 [0.02-8.89] vs 0.55 [0.06-3.92]). No significant differences in omentin-1 or vaspin concentrations were observed between IUGR and AGA groups, whereas fetal and N1 insulin concentrations were lower in the former ($P = .025$ and $P = .027$, respectively). In both groups, fetal omentin-1 concentrations were higher ($P \leq .018$), whereas vaspin concentrations were lower ($P \leq .001$), than maternal ones. Furthermore, maternal vaspin concentrations were higher in cases of cesarean delivery ($P = .024$). Omentin-1 and vaspin concentrations did not correlate with the respective insulin ones. In conclusion, omentin-1 and vaspin are present in the fetus and neonate. Perinatal concentrations of omentin-1 and vaspin are similar in IUGR cases and AGA controls—despite lower insulin concentrations in the former—and do not correlate with the respective insulin concentrations. Higher omentin-1 concentrations in the fetus may be crucial to enhance a growth-promoting effect, whereas lower maternal vaspin concentrations in cases of vaginal delivery may be attributed to spontaneous term delivery inflammation.

1. Introduction

Adipose tissue—previously ascribed only the role of fat storage depot—secretes a number of hormones, collectively called *adipocytokines*, currently considered as new potential mediators of insulin resistance [1,2]. Several recent studies have explored the role of adipocytokines in fetal growth because many of them are known to be produced within the intrauterine environment [3-6].

Omentin and vaspin are newly identified adipocytokines, predominantly expressed and secreted by visceral adipose tissue [7,8]. Omentin is capable of enhancing insulin-mediated glucose uptake in human adipocytes; and thus, it presents with insulin-sensitizing properties [9]. Furthermore, plasma omentin-1 levels (the major circulating isoform in human plasma) were inversely correlated with obesity and insulin resistance [10]. Similarly, vaspin, a serine protease inhibitor, has been shown to improve glucose tolerance and reverse the altered expression of insulin resistance–relevant genes [11]. However, elevated serum vaspin concentrations have been demonstrated in obesity and impaired insulin sensitivity in both children and adults, probably representing

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The Ethics Committee of our teaching hospital approved the study protocol.

* Corresponding author. Tel.: +30 6944443815; fax: + 30 2107233330.
E-mail addresses: amalpu@aretaieio.uoa.gr, amalpu@otenet.gr (A. Malamitsi-Puchner).

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a compensatory mechanism [12,13]. Recently, vaspin expression has been documented in the human placenta [14]. Nevertheless, to our knowledge, there is no currently available information relating to circulating omentin and vaspin concentrations in the perinatal period.

Intense research has recently focused on early programming of adult diseases and has shown that asymmetric intrauterine growth restriction (IUGR) is independently associated with an increased propensity to visceral obesity, insulin resistance, type 2 diabetes mellitus, and other features of the metabolic syndrome later in life [15,16]. Although the underlying mechanisms remain unclear, several pieces of evidence support the implication of an impaired fetal development of adipose tissue in the emergence of IUGR-related insulin resistance [17,18].

This study was based on the hypothesis that, if present, circulating concentrations of omentin-1 and vaspin might differ between IUGR cases and appropriate-for-gestational-age (AGA) controls because the former are characterized by reduced fat mass and changes of endocrine/metabolic mechanisms, predisposing them to visceral obesity–related metabolic disorders in later life [15-19].

Therefore, we aimed to determine and compare, for the first time, to our knowledge, serum omentin-1 and vaspin concentrations in IUGR and AGA mother/infant pairs at time points characteristic of intra- and extrauterine life and investigate the association of these data with sex, parity, mode of delivery, and adjusted birth weight (customized centiles). In addition, a possible correlation of omentin-1 and vaspin concentrations with the respective insulin ones was investigated.

2. Methods and procedures

The Ethics Committee of our teaching hospital approved the study protocol. All included mothers provided signed informed consent before recruitment. Forty parturients consecutively giving birth either to 20 AGA or 20 IUGR full-term singleton infants (birth weight ≤fifth customized centile) were included in the study. The Gestation Related Optimal Weight computer-generated program [20] was used to calculate the customized centile for each pregnancy, taking into consideration significant determinants of birth weight, such as maternal height and booking weight, ethnic group, parity, gestational age, and sex [20]. Gestational age was estimated using the date of the last menstrual period and early antenatal ultrasound. Birth weight was measured with an electronic scale.

Irrespective of etiology, all IUGR cases presented with small (weights ranging from 240 to 450 g [21]) placentas. Furthermore, amniotic fluid, assessed by the largest fluid column on the vertical plane, was diminished (<2 cm) in all IUGR cases.

In the AGA group, mothers were healthy; and placentas were normal in appearance and weight [21].

Table 1
Demographic data for AGA and IUGR neonates and their mothers

	AGA	IUGR	*P*
	Mean (SD)	Mean (SD)	
Birth weight (g)	3280 (333)	2511 (261)	<.001
Birth weight centile	46 (24.7)	2.95 (1.9)	<.001
Gestational age (wk)	39.2 (0.83)	38.5 (1.2)	NS
Sex			NS
Male	10 (50%)	7 (35%)	
Female	10 (50%)	13 (65%)	
Maternal age (y)	30 (4.8)	32.7 (4.3)	NS
Parity			NS
Primigravida	14 (70%)	11 (55%)	
Other	6 (30%)	9 (45%)	
Mode of delivery			NS
Vaginal	15 (75%)	10 (50%)	
Cesarean	5 (25%)	10 (50%)	

NS indicates nonsignificant.

Tests for congenital infections were negative in all women of both groups, and their offspring had no symptoms of intrauterine infection or signs of genetic syndromes. One- and 5-minute Apgar scores were in all cases and controls greater than or equal to 8. All neonates were breastfed. Demographic data of participating subjects are listed in Table 1.

Prefeeding blood samples were collected in pyrogen-free tubes from (1) the mothers during the first stage of labor or before receiving anesthesia in cases of elective cesarean delivery; (2) the umbilical cords after double clamping, reflecting fetal state; and (3) the neonates on postpartum day 1 (N1) and day 4 (N4), characterizing transition and stabilization to extrauterine life, respectively. Serum was separated by centrifugation after clotting and was kept frozen at −80°C until assay.

The determination of serum omentin-1 concentrations was performed by enzyme immunoassay (EIA) (Apotech, Epalinges, Switzerland). The minimum detectable concentration and the intra- and interassay coefficients of variation were 0.4 ng/mL, 5.02%, and 4.19%, respectively.

Serum vaspin concentrations were determined by enzyme immunoassay (AdipoGen, Seoul, Korea). The minimum detectable concentration and the intra- and interassay coefficients of variation were 12 pg/mL, 3.8%, and 5.9%, respectively.

In addition, prefeeding circulating insulin concentrations were measured. The determination of insulin concentrations was performed by immunoradiometric assay (Immunotech, Prague, Czech Republic). The minimum detectable concentration and the intra- and interassay coefficients of variation were less than 1 μU/mL, 4.1%, and 5.3%, respectively.

3. Statistical analysis

Omentin-1 data were normally distributed (Kolmogorov-Smirnov test); thus, parametric tests (analysis of variance for repeated measures, paired-samples *t* test with Bonferroni

correction for multiple comparisons, Student *t* test) were applied in the analysis.

Vaspin and insulin data did not present with normal distribution (Kolmogorov- Smirnov test); therefore, non-parametric procedures (Mann-Whitney *U* test and Wilcoxon signed rank test) were used.

Spearman or Pearson correlation coefficient—whichever is appropriate—was applied to detect any positive or negative correlations. A $P < .05$ was considered statistically significant.

4. Results

Both hormones were detectable in all fetal and neonatal blood samples. Concerning omentin-1, serum values were as follows (mean ± SD): AGA group—maternal: 10.19 ± 2.78, fetal: 11.32 ± 1.88, N1: 10.74 ± 1.42, and N4: 10.90 ± 2.72; IUGR group—maternal: 9.29 ± 1.61, fetal: 10.47 ± 1.30, N1: 10.46 ± 1.54, and N4: 11.35 ± 3.92. Concerning vaspin, serum values were as follows (median, minimum-maximum): AGA group—maternal: 1.75 (0.19-24.6), fetal: 0.39 (0.04-19.06), N1: 0.40 (0.04-16.70), and N4: 0.49 (0.02-8.89); IUGR group—maternal: 2.19 (0.68-28.20), fetal: 0.40 (0.05-1.34), N1: 0.44 (0.23-3.34), and N4: 0.55 (0.06-3.92). No significant differences in serum omentin-1 or vaspin concentrations were observed between AGA and IUGR groups in maternal, fetal, and neonatal day 1 and 4 samples, whereas fetal and N1 insulin concentrations were significantly lower in the IUGR group ($P = .025$ and $P = .027$, respectively).

In both groups, fetal omentin-1 concentrations were significantly higher and positively correlated with maternal ones ($P = .014$ and $r = .880$, $P < .001$, respectively, in the AGA; $P = .018$ and $r = .447$, $P = .048$, respectively, in the IUGR group). In a combined group, N1 omentin-1 concentrations positively correlated with N4 ones ($r = .389$, $P = .013$). In the IUGR group, fetal omentin-1 concentrations positively correlated with N1 ones ($r = .538$, $P = .014$). The effect of birth weight, infants' customized centiles, sex, parity, gestational age, delivery mode, and maternal age on circulating omentin-1 concentrations was not significant.

On the other hand, fetal vaspin concentrations were in both groups significantly lower compared with maternal ones ($P < .001$ in the AGA and $P < .001$ in the IUGR group). In a combined group, maternal vaspin concentrations were positively correlated with fetal, N1, and N4 ones ($r = .322$, $P = .048$; $r = .348$, $P = .035$; and $r = .472$, $P = .003$, respectively). Similarly, fetal vaspin concentrations were positively correlated with N1 and N4 ones ($r = .423$, $P = .010$ and $r = .388$, $P = .019$, respectively). Furthermore, maternal vaspin concentrations were significantly higher in cases of delivery by cesarean delivery ($P = .024$). In the AGA group, maternal vaspin concentrations were positively correlated with N4 ones ($r = .567$, $P = .014$); fetal vaspin concentrations were positively correlated with N1 and N4 ones ($r = .671$, $P = .002$ and $r = .556$, $P = .020$, respectively); and N1 vaspin concentrations were positively correlated with N4 ones ($r = .528$, $P = .024$). Lastly, in the IUGR group, N1 vaspin concentrations were significantly higher in females ($P = .015$).

Circulating vaspin concentrations were not associated with birth weight, infants' customized centiles, parity, and gestational age.

Finally, no significant correlations were observed between serum omentin-1, as well as vaspin concentrations and the respective insulin ones, in either group.

5. Discussion

The results of this study show, for the first time, the presence of the novel adipocytokines omentin-1 and vaspin in the fetus and neonate.

Thus, both hormones were detectable in the serum of all recruited infants. The source of omentin-1 and vaspin in cord blood is unknown. Our findings suggest that they mainly derive from fetal and/or maternal tissues. Thus, a positive correlation between maternal and fetal omentin-1 and vaspin concentrations was found, implying a transplacental transport of both adipocytokines. In addition, the placenta most probably does not contribute to circulating concentrations of these hormones, as their concentrations do not decline after placental elimination.

Moreover, we demonstrated the presence of markedly high concentrations of omentin-1 in umbilical serum samples. Given that several other adipokines (such as leptin and adiponectin) involved in energy metabolism are present in high concentrations during fetal life [5,22], it could be speculated that omentin-1 has a similar role in controlling energy homeostasis. During fetal growth, glucose is the main energy source of the fetus [23]. Insulin plays a significant role in increasing the uptake of circulating glucose by fetal muscle and adipose tissue [23]. Therefore, although no information is available regarding the role of omentin-1 in fetal growth, a high concentration in the fetus may be crucial to enhance a growth-promoting effect through its insulin-sensitizing action.

Alternatively, as reduced fat mass leads to up-regulation of omentin (implying a negative feedback of adipose tissue on omentin-1 production) and newborns have significantly lower body fat than children or adults [24], a possible explanation for the high omentin-1 concentrations in cord blood might be the lack of adipocyte hypertrophy in newborns [24]. However, in this study, no correlation between serum omentin-1 concentrations and birth weight or insulin concentrations was found. Nevertheless, the physiologic roles of omentin-1 remain largely unknown; and no data exist in the literature concerning its potential functions in the perinatal period.

In line with previous reports in adults, our results revealed higher vaspin concentrations in female neonates [12,25]. This sex difference in adults has been assumed to reflect an

effect of sex hormones [25]. Concerning the fetus, ovaries are regarded as hormonally inactive during the first part of pregnancy; but later, they may have steroidogenic capacity [26]. A sex-dependent regulation has also been demonstrated for adiponectin and leptin because of an inhibitory effect of androgens on expression of these adipocytokines [22,27]. However, whether this fact also applies to vaspin needs to be further investigated [25]. In addition, sex-dependent differences in adipose tissue mass and distribution [28] might contribute to increased circulating vaspin concentrations in female neonates.

Another finding of this study was the lack of significant differences in serum concentrations of omentin-1 and vaspin in the perinatal period between IUGR and AGA groups.

Although the mechanisms controlling intrauterine growth are poorly understood, adipose tissue may plausibly play a role in linking IUGR to the subsequent development of abdominal obesity and insulin resistance, the exact onset of which is not fully elucidated [15,16]. In this respect, the total amount of fat mass is strikingly reduced in IUGR neonates, attesting to an altered adipose tissue development [17,18]. Moreover, several studies [6,29-31], including the present one, have determined lower concentrations of insulin—a significant regulator of fetal adiposity—in IUGR fetuses and neonates on day 1 of life. However, newborns with low birth weight may have relatively increased visceral fat stores [32,33]. Furthermore, differential regulation of various adipocytokines has been described in the IUGR state, probably predicting the risk of adult disease occurrence [3].

Omentin and vaspin have recently been discovered as visceral fat–specific secretory proteins and have been postulated to play a significant role in the relationship between human obesity and its related metabolic disorders [7-12]. However, data regarding the metabolic function of these novel adipocytokines are sparse; and there is, at present, no clear proof of a causal link between omentin or vaspin and abdominal fat accumulation or insulin resistance [34,35].

Similarly, our data did not demonstrate any significant differences in maternal omentin-1 and vaspin concentrations between the IUGR and AGA groups. The development of insulin resistance in late gestation is a process common in all human pregnancies, being more exaggerated in IUGR [36,37]. Relatively, recent investigations have focused on the pathophysiologic role of various adipocytokines in the regulation of gestational insulin resistance and pointed to a differential secretion pattern of these hormones in pregnancy complications, including preeclampsia and IUGR [38]. Our results are in line with the ones of Stepan et al [39], who recently documented lack of significant differences in maternal vaspin concentrations between preeclamptic and normal pregnant women.

Lastly, an interesting observation in this study is that maternal vaspin concentrations are lower in cases of vaginal delivery. This finding may be attributed to spontaneous vaginal delivery inflammation [40] because vaspin expression may be altered in inflammatory states [25].

In conclusion, this study showed the presence of vaspin and omentin-1 in the fetus and neonate. Furthermore, omentin-1 and vaspin concentrations were similar in IUGR cases and AGA controls—despite lower insulin concentrations in the former—and did not correlate with the respective insulin ones. Because we are just beginning to understand the metabolic function of these novel adipocytokines in adults, it is rather difficult to speculate their role in fetuses and neonates. Data concerning the source and regulation of these hormones in the fetus, their physiologic function, and their putative implication in pathologic processes are yet to be clarified. Therefore, follow-up studies would be of great importance.

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