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Adiponectin and vitamin D-binding protein are independently associated at birth in both mothers and neonates

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Short title: VDBP and adiponectin in mothers and neonates

Key terms: adipokines; adiponectin; irisin; neonates; vitamin D; vitamin D-binding protein.

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Abstract

Context: Adult body fat is associated with birth anthropometry suggesting a role for metabolic regulators including vitamin D and the adipokines - adiponectin and irisin – which have been reported to interact but, as yet, data remain controversial.

Objective: To study (i) the relationship between vitamin D, its binding protein (VDBP) and the adipokines, adiponectin and irisin in mothers and neonates at birth and (ii) their effects on neonate anthropometric outcomes.

Design: Cross-sectional study for healthy mothers with full-term and uncomplicated births.

Setting: Primary care.

Subjects: Seventy pairs of newly delivered neonates and their mothers.

Main Outcomes Features: Biochemical markers from maternal and cord: VDBP, adiponectin, irisin, calcium, albumin, parathyroid hormone, 25OHD, $1,25(OH)_2D$. Maternal demographic and social characteristics and neonate anthropometric parameters were recorded.

Results: Maternal VDBP levels (364.1±11.9 μg/ml) demonstrated a strong positive correlation with maternal adiponectin (4.4 ± 0.4 μg/ml) and irisin (308.8 ± 50.8 ng/ml) concentrations which remained significant ($p<0.001$ and $p<0.041$, respectively) after adjustment with multiple parameters, including weeks of

gestation, maternal age, BMI. The finding of a strong association of VDBP (355.3 ± 29.2 μg/ml) and adiponectin (11.9 ± 2.0 μg/ml) but not irisin (174.4 ± 26.0 ng/ml), was also evident in neonates (p=0.03 and p=0.94, respectively). No association was observed in both maternal and neonatal vitamin D, adiponectin and irisin.

Conclusions: The main findings of this study are i) the perspective of a potential independent interaction of VDBP and adiponectin in both mothers and neonates and ii) the lack of a causative model effect of both maternal/neonatal vitamin D status and adipokine profile on neonatal anthropometry at birth, as a surrogate marker of future metabolic health of the offspring.

Precis

In mother-neonate pairs at birth, adiponectin is independently associated vitamin D binding protein but not vitamin D status or significant anthropometric indices.

1. Introduction

Vitamin D, recognised as essential for maintaining bone homeostasis and calcium absorption (1,2), has been recently established as a biological contributor in different cells and tissues (3-5). Despite having endogenous and dietary sources, hypovitaminosis D insufficiency and deficiency is common in all ages (6-8).

Numerous studies have investigated the association between vitamin D and disease onset or remission in a range of conditions including obesity, inflammation and insulin resistance (9-12). Recent advances in analytical capability have led to increasing interest in the roles of a wider range of molecules in the vitamin D metabolome (13,14). These advances, including accurate measurements of vitamin D forms, extend to the role of vitamin D-binding protein (VDBP), which primarily contributes to the transportation in the bloodstream of vitamin D metabolites (1). VDBP binds up to 80% of circulating vitamin D, playing a key role in regulating bioavailability and bioactivity of vitamin D, increasing its plasma half-life and modulating its distribution to target tissues. Therefore, its measurement along with vitamin D concentrations seems to be of importance (15). Moreover, VDBP has been hypothesized to exert regulatory immunological and metabolic actions (16).

Prior studies have investigated the relationship between vitamin D and adipokines. Adiponectin, secreted from adipose tissues, has key functions in energy homeostasis, including insulin action, food intake and metabolism (17). A proteomic study identified downregulation of adiponectin in vitamin D deficient obese children, and importantly a 12-month vitamin D_3 supplementation course increased adiponectin levels (17). In isolated adipocytes, 1,25-$(OH)_2D_3$ increased adiponectin (17). On the other hand, vitamin D supplementation did not increase adiponectin levels in a recent meta-analysis of 9 randomized controlled trials (RCTs) (18). Taken together, the

interaction between vitamin D and adiponectin may be condition-specific and affected by a number of mechanisms, including adipogenic gene expression and adipocyte apoptosis (19).

Irisin, a myokine secreted primarily by skeletal muscle, is inversely correlated with vitamin D levels in small gestational age newborns (20). Previous reports linked irisin with circulating vitamin D levels (21). To date, there have been no reports of associations between adiponectin or irisin and VDBP.

VDBP concentrations are known to increase in pregnancy. In addition, body weight and adipokine profile at birth, have been recently associated with fat mass in late childhood and adolescence, respectively (22). The potential role of VDBP as a mediator, confounder or neither in the metabolic regulation of maternal and offspring adipokine profile has not been investigated so far.

The primary aim of this study was to explore the association between adiponectin, irisin and VDBP concentrations in both mothers and neonates at birth of full-term and uncomplicated pregnancies. Secondary aims were to investigate the associations between neonatal anthropometric parameters, and maternal and neonatal adiponectin, irisin, VDBP, 25OHD and $1,25(OH)_2D$. The results of this study may provide insight in the physiological associations of VDBP beyond vitamin D, and possibly provide the basis for further research.

2. Patients and methods

2.1. Study population

This was a cross-sectional study of pregnant women and their neonates, conducted from April 2014 until October 2015. Recruitment was discontinued from November 2014 to March 2015 to minimize significant seasonal variation of study findings with

regard to maternal and neonatal vitamin D status. Pregnant women were recruited from the Maternity Unit of the First Department of Obstetrics and Gynaecology, Aristotle University, Thessaloniki, Greece, with latitude of 40°N. All women were fair skinned. Inclusion criteria were age>18 years, body mass index (BMI)≤30 kg/m^2 and full-term pregnancy (37-42th gestational week). Maternal non-inclusion criteria were BMI ≥30 kg/m^2, primary hyperparathyroidism, secondary osteoporosis, osteomalacia, liver disease, hyperthyroidism, nephrotic syndrome, inflammatory bowel disease, rheumatoid arthritis, morbid obesity, gestational or pre-existing diabetes, active infection and use of medications affecting calcium or vitamin D homeostasis. Neonatal non-clusion criteria were prematurity ≤37 weeks of gestation, being small and large-for-gestational age neonates and the presence of severe congenital anomalies, as a result of one or more genetic, infectious, nutritional or environmental factors including heart and neural tube defects and Down syndrome. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Medical School of Aristotle University of Thessaloniki. All mothers provided written informed consent for themselves and for their neonates.

2.2. Methods

2.2.1. Demographic and anthropometric data

At enrolment, demographic and social characteristics were recorded. Maternal pre-pregnancy BMI was either normal (18–25 kg/m^2) or overweight (25-30 kg/m^2). We collected maternal, infant, and labor data from the medical records, collected umbilical cord blood samples at the time of delivery, and stored aliquots of plasma and serum at -70^{o}C until assays were performed. We also evaluated neonatal

anthropometry at birth. All neonatal anthropometric measurements were performed by the same trained nurse, between 12h and 72h of age according to standard techniques (23,24). The following measurements were recorded: birth weight, height, neck-rump, upper arm, femur and knee heel lengths; head, chest, abdominal, upper arm and middle thigh circumferences, and abdominal skinfold thickness.

The birth weight of the neonates was measured on regularly calibrated scales. Knee-heel length was measured with a hand-held BK5 infant knemometer (Force Technology, Brondby, Denmark). Instrument software calculated the mean of 10 sequential readings and generated a printed report of all readings and the calculated mean. We also measured neonatal height to the nearest millimeter using an Ellard newborn lengthboard (Ellard Instrumentation Ltd., Seattle, WA). Abdominal, upper arm and middle thigh head, mid-upper arm, and maximal head circumferences were measured using a plastic encircling tape (Child GrowthFoundation, London, UK). Abdominal, skin fold was measured using Holtain calipers (Holtain, Crymych, UK).

2.1.2. Biochemical and hormonal assays

Blood samples were obtained from mothers by antecubital venipuncture 30–60 minutes before delivery. Umbilical cord blood was collected immediately after clamping, from the umbilical vein**.** Calcium (mg/dl), albumin, parathyroid hormone (PTH) (pg/mL, 25OHD (ng/ml) 1,25$(OH)_2$D (pg/ml), VDBP (μg/ml) adiponectin (μg/ml) and irisin (ng/ml) were measured in one batch at the end of the study. Corrected calcium was calculated based on total calcium and albumin concentrations using standard equation [Corrected calcium= 0.8 ×(4 − serum albumin)]. Biochemical analysis of total calcium and albumin were performed with standard methods using the Cobas INTEGRA clinical chemistry system (D-68298; Roche Diagnostics,

Mannheim, Germany). PTH was measured with electro-chemiluminescence immunoassay (ECLIA; Roche Diagnostics GmbA, Mannheim, Germany). The reference range for PTH was 15 - 65 pg/ml, functional sensitivity 6.0 pg/ml, within-run precision 0.6 - 2.8% and total precision 1.6 - 3.4%. VDBP, irisin and adiponectin were measured with enzyme-linked immunosorbent assay (ELISA) on a Synergy H1 Hybrid reader and Gen5 software (BioTek, Winooski, VT, USA): Gc-Globulin/VDBP (AssayPro, St. Charles, MO, USA); irisin (MyBioSource, San Diego, CA, USA); adiponectin (R&D Systems, Minneapolis, MN, USA). 25OHD and $1,25(OH)_2D$ were measured by radioimmunoassay using commercial kits obtained from DiaSorin Corporation (Stillwater MN, USA). Intra-assay and inter-assay variance was 5% and 11% for 25(OH)D and 8% ,< 12% for $1,25(OH)_2D$, respectively). Intra-assay and inter-assay variance was <8% and <10% for adiponectin and <8% and <10% for irisin ,respectively. Detection limits for assays were 0.098 μg/ml for VDBP, 3.12 ng/ml for irisin,0.039 μg/ml for adiponectin, 5 ng/ml -100 ng/ml for 25OHD and 7.5-100 pg/ml for $1,25(OH)_2D$.

Vitamin D status (25OHD) was classified as sufficient or insufficient according to consensual Institute of Medicine criteria [sufficiency: 20-40 ng/ml (50-100 nmol/L); insufficiency < 20 ng/ml (50 nmol/L) (25).

2. 2. 3. Statistical Analysis

Continuous data are presented as mean ± standard error of the mean (SEM). Categorical data are presented as absolute numbers and/or frequencies. Kolmogorov-Smirnov test was used to check the normality of distributions of continuous variables. Chi-square test was used for between group comparisons, in case of categorical variables. Independent samples t-test or Mann-Whitney test was used for between

group comparisons, in case of continuous variables. Spearman's coefficient (r_s) was used for binary correlations. Multiple linear logistic regression analysis (method "enter") was used to identify independent associates for adiponectin, irisin levels or other parameters when needed. For the need of regression analysis, any of the included variables that did not follow normal distribution was logarithmically transformed. Statistical analysis was performed with SPSS 21 for Macintosh (IBM Corp., Armonk, NY). Significance was set at $p<0.05$ in all the tests.

3. Results

3.1. Description of the cohort and comparative data

Seventy pairs of newly delivered neonates and their mothers were included in this study. The demographic and anthropometric characteristics of the cohort are presented in Table 1. As selected, all women were non-obese (pre-pregnancy) and apparently healthy. Their educational level was elementary in 52 (74.3%) and secondary in 14 (20%), and unknown in 4 (5.7%) women. Eleven (15.7) women had previously given birth to one child; eight (11.4%) to two; one (1.4%) to three; and one (1.4%) to four children.

Thirty-seven (52.9%) women had received calcium supplementation during pregnancy, either 500 mg (n=30) or 1000 mg (n=7). None received vitamin D supplementation during pregnancy. Serum 25OHD levels were insufficient in 55 (78.5%) women [27 (38.6%) women had levels between 10-19.9 ng/ml and 28 (40%) women had levels 5-9.9 ng/ml]. Maternal 25(OH) D levels were negatively correlated with elementary educational level (p=0.03) and height (p=0.04), but not with maternal BMI.

Comparative biochemical and hormonal data between mothers and neonates are presented in Table 2. As expected, the neonates had lower PTH and higher corrected calcium levels compared with mothers. On the other hand, 25OHD, $1,25(OH)_2D$ and VDBP levels were not different between groups, with $1,25(OH)_2D$ only marginally not reaching the level of statistical significance (p=0.057). Interestingly, adiponectin levels were higher, whereas irisin levels were lower in neonates than mothers.

When maternal and neonatal serum parameters [PTH, 25OHD, $1,25(OH)_2D$, VDBP, adiponectin and irisin] were compared according to the weeks of gestation (<37 vs. ≥37), maternal irisin levels were lower in the former group compared with the latter (153.3 vs. 402.5 ng/ml; p=0.006). When the median neonate weight (3205 g) was used as a cut-off, no statistically significant difference was observed in maternal and neonatal serum parameters between groups.

3.2. Correlations of maternal parameters

A correlation matrix for maternal parameters only is presented in Table 3. As expected, corrected calcium was inversely correlated with PTH levels, and positively with 25OHD and $1,25(OH)_2D$; 25OHD levels also were positively correlated with $1,25(OH)_2D$ and height. PTH, 25OHD and $1,25(OH)_2D$ levels were not correlated with VDBP, adiponectin or irisin levels. Notably, VDBP levels were positively correlated with adiponectin and irisin levels, whereas inversely with age. Adiponectin levels were inversely correlated with weight and BMI at term, and irisin levels positively with weight (Table 3).

After sequential adjustment for weeks of gestation (model 1), weeks of gestation and maternal age (model 2), weeks of gestation, maternal age and BMI

(term) (model 3), maternal adiponectin and irisin levels remained significantly positively associated with VDBP levels (Table 4 and 5, respectively). However, weeks of gestation did not remain significantly associated with irisin levels (Table 5).

3.3. Correlations of neonatal parameters

A correlation matrix for neonatal parameters only is presented in Table 6. Corrected calcium was inversely correlated with PTH levels, but not with 25OHD and $1,25(OH)_2D$ levels. 25OHD levels were positively correlated with $1,25(OH)_2D$ levels and upper arm length. VDBP levels were positively correlated with adiponectin, but not irisin levels. Irisin levels were inversely correlated with PTH levels and knee-heel length.

After sequential adjustment for weeks of gestation (model 1), weeks of gestation and neonate gender (model 2), weeks of gestation, neonatal gender and weight (model 3), neonatal adiponectin levels remained significantly positively associated with VDBP levels (Table 7). Neonatal irisin remained non-significantly associated with VDBP levels, after similar sequential adjustment.

3.4. Correlations between maternal and neonatal parameters

A correlation matrix between maternal and neonatal parameters is presented in Table 8. Maternal PTH levels were inversely correlated only with neonatal 25OHD levels. Maternal 25OHD levels were positively correlated with neonatal 25OHD and $1,25(OH)_2D$ levels, and upper arm length. Maternal $1,25(OH)_2D$ levels were inversely correlated with neonatal irisin levels and positively with abdominal skin fold. Maternal VDBP levels were inversely correlated with neonatal height and upper arm length, but not adiponectin or irisin levels. Maternal adiponectin levels were inversely

correlated, albeit marginal, with neonatal weight. Maternal irisin levels were inversely correlated with neonatal $1,25(OH)_2D$ levels and positively with knee-heel length. Notably, apart from 25OHD levels that were highly correlated between mothers and neonates, there was no correlation between maternal and neonatal levels of PTH, $1,25(OH)_2D$, VDBP, PTH, adiponectin and irisin (Table 8).

Neonatal adiponectin and irisin remained non-significantly associated with maternal VDPB, after sequential adjustment for weeks of gestation (model 1), weeks of gestation and maternal age (model 2), weeks of gestation, maternal age and BMI (term) (model 3), weeks of gestation and neonatal gender (model 4), weeks of gestation, neonatal gender and neonatal weight (model 5).

Since upper arm length was associated with both maternal and neonatal 25OHD and knee-heel length was associated with both maternal and neonatal irisin, we performed additional regression analyses with knee-heel length or upper arm length as dependent variables. Neonatal upper arm length remained significantly positively associated with maternal 25OHD after sequential adjustment for weeks of gestation (model 1), weeks of gestation and maternal age (model 2), weeks of gestation, maternal age and BMI (term) (model 3), and weeks of gestation, maternal age, BMI (term) and maternal VDBP (model 4; Table 9). On the other hand, neonatal upper arm length did not remain significantly associated with neonatal 25OHD after sequential adjustment for weeks of gestation, neonatal gender and neonatal weight and VDBP. Neonatal knee-heel length did not remain independently associated with maternal irisin levels after sequential adjustment for weeks of gestation, maternal age and BMI, or with neonatal irisin levels after sequential adjustment for weeks of gestation, neonatal gender and weight.

4. Discussion

This is the first study to investigate potential associations between vitamin D metabolites, VDBP and adiponectin (adipokine) and irisin (myokine) in mother-neonate pairs and the associations between neonatal anthropometry and maternal-neonatal vitamin D, adiponectin and irisin at birth. To the best of our knowledge, we provide here the first evidence of an association between VDBP and adiponectin levels in both mothers and neonates. On the other hand, no association was observed in both maternal and neonatal vitamin D metabolites, adiponectin and irisin.

Maternal VDBP levels demonstrated a positive association with maternal adiponectin and irisin concentrations, which remained significant after adjustment for multiple potential confounders. VDBP and adiponectin, but not irisin, also were independently associated in neonates. This finding raises consideration regarding the role of VDBP as a carrier protein or regulator of biological activity of adiponectin and irisin during pregnancy. The expected rise of VDBP in the pregnant state might also distort the association, but this finding was observed in neonates as well, at least for adiponectin. Mechanistic studies are required to elucidate whether VDBP plays a carrier or regulatory role for adiponectin and/or irisin during pregnancy.

This study also confirmed data from previous observational studies (26, 27) showing that cord blood adiponectin levels were higher than those observed in adults. This finding could be explained by the observed increase in adiposity with aging. The increase in adiposity is most evident in visceral adipose tissue, while there may be decreases in subcutaneous adipose tissue. being most evident in visceral adipose tissue, while there may be decreases in subcutaneous adipose tissue. This age-associated change in body composition, where adiposity increases throughout midlife but decreases once late-life is reached, has been consistently found in several different

ethnic groups and may be influenced by dietary intake however, unlike many adipocyte derived factors, circulating adiponectin levels decrease with increasing adiposity (26,27).On the other hand, irisin concentrations were lower in neonates than mothers, a finding which has been previously observed in pathological conditions, including diabetes and obesity, as well as in uncomplicated pregnancy (28). Differences in neonate and adult muscle mass could explain the increased concentrations of maternal irisin compared to neonatal ones ,in this study.

As previously reported (29), there was no correlation between maternal circulating VDBP and PTH, 25OHD and $1,25(OH)_2D$ concentrations. A high estrogen status such as pregnancy (29) is associated with high serum VDBP concentrations.

Of note, a negative correlation of VDBP with age, was evident. Previous findings demonstrated, that serum VDBP concentrations are lower in post- than premenopausal women which could potentially be attributed to differences in estrogen status (30). However, the finding of age related of VDBP according to age within the same pregnant cohort warrants further investigation.

Vitamin D metabolites were also not correlated with adiponectin and irisin in both mothers and neonates, although previous results, reported an association of adiponectin, advanced oxidation protein products and advanced glycation end-products, with vitamin D status (31,32). However, as aforementioned, a recent meta-analysis did not indicate any significant effect of vitamin D supplementation on adiponectin profile in the general non-pregnant population (18).

Our results are in accordance with recent findings by McManus et al. (33), who reported no correlations between maternal and neonatal 25OHD and adipokine concentrations at birth in both controls and women with gestational diabetes. Unlike the present population, McManus et al. population was vitamin D sufficient (33).

Although further studies are necessary, this finding may imply that vitamin D metabolites are not correlated with adiponectin irrespective of vitamin D status.

Regarding correlations between maternal and neonatal parameters, contrary to our findings, Luo et al. observed a positive correlation in adiponectin levels of maternal and fetal circulation (34). In our study however, no such association was observed for adiponectin and irisin across maternal-neonatal pairs, which possibly implies that neonatal adiponectin and irisin at birth are not substantially affected by maternal ones. The study of Luo et al. (34), investigated adiponectin concentrations in maternal (at 24-28 and 32-35 weeks of gestation) and fetal circulations, whereas our study assessed these adiponectin levels at birth. This difference in the time point of maternal-neonatal sampling might be the reason for the differences between the two studies. Similar to our findings, other authors observed no correlation between maternal and umbilical cord adiponectin concentrations (35), suggesting that adiponectin in cord blood is possibly of fetal origin. With regard to potential gender differences for adipokines in neonates, no significant differences in adiponectin levels were found between female and male neonates in a previous study (35).

Upper arm length was the only anthropometric parameter associated with both maternal and neonatal 25OHD, although this association attenuated for neonates after adjustment for potential confounders. Although lower mean neonatal knee-heel length at birth has been associated with lower maternal 25OHD levels at 28–32 weeks' gestation (36), we were not able to confirm this association at birth. No consistent correlations were evident between maternal and neonatal adiponectin or irisin and neonatal anthropometry as well.

Although the present study was not designed for this purpose, it reported maternal and neonatal hypovitaminosis D in a sunny European area, with none receiving

vitamin D supplementation according to current guidelines (37). These results are consistent with previous larger scale findings from the same region (38,39). Of note, a similar pattern of distribution of hypovitaminosis D between maternal and neonatal 25OHD concentrations was observed in both mothers and neonates being at insufficiency range (40-42).The lack of maternal vitamin D status with BMI could be attributed to the small study sample .In addition, previous findings on the association of maternal vitamin D levels and educational status (43), were also observed in this study.

The main strength of our study relies on its originality. The absence of prior reports on associations between VDBP and adiponectin warrants further mechanistic research on the role of VDBP in bioavailability and bioactivity of adiponectin. This study, however, has certain limitations. First, while the sample size was relatively small, it was sufficiently powered to show significant differences regarding the main aim of the study. Second, the cross-sectional design of the study cannot prove a causal relationship. Third, all women were Caucasian, so our results cannot be safely generalized to other ethnicities, known to differ at least in adiponectin levels. Furthermore, multiple comparisons render some correlations prone to a false positive error. However, the association between VDBP and adiponectin and irisin remained robust after adjustment for potential confounders. Finally calcium intake was based on self-reporting and we did not systematically assess calcium intake with a validated questionnaire.

In conclusion, our study reports that neonatal anthropometry at birth was not associated with maternal or neonatal vitamin D concentrations, but suggests an independent association between VDBP and adiponectin in both mothers and

neonates, and between VDBP and irisin only in mothers. These findings warrant further research on the potential role of VDBP in regulating adiponectin and irisin.

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Figure legends

Figure 1. Scatter plot between adiponectin and vitamin D-binding protein in mothers (A) and neonates (B). A significant correlation is shown in both.

Table 1. Maternal and neonatal demographic and anthropometric characteristics.

Maternal	
Number (n)	70
Age (years)	31.9 ± 0.7
Height (cm)	164.9 ± 0.7
Weight; pre-pregnancy (kg)	67.6 ± 1.8
Weight; term (kg)	81.4 ± 1.8
BMI; pre-pregnancy (kg/m^2)	24.9 ± 0.6
BMI; term (kg/m^2)	29.6 ± 0.7
Weeks of gestation (n)	38.8 ± 0.2
Smoking [n (%)]	10 (14.3)
Alcohol consumption [n (%)]	8 (11.4)
Previous live births [n (%)]	21 (30.0)
Daily Calcium Supplementation [n (%)]	37 (52.9)
Daily Calcium Supplementation (mg)	423 ± 44
Neonatal	
Number (n)	70
Gender; Males [n (%)]	38 (54.3)
Height (cm)	50.5 ± 0.2
Weight (g)	3292 ± 51
Head Circumference (cm)	34.4 ± 0.3
Chest Circumference (cm)	31.0 ± 0.2
Abdominal Circumference (cm)	28.1 ± 0.3

Skin fold; abdominal (cm)	3.0 ± 0.2
Upper Arm Circumference (cm)	9.8 ± 0.1
Middle thigh Circumference (cm)	13.4 ± 0.1
Upper Arm Length (cm)	13.7 ± 0.1
Femur Length (cm)	9.9 ± 0.1
Knee-Heel Length (cm)	9.2 ± 0.1

Data are presented as mean ± standard error of the mean (SEM) for continuous variables and frequencies [numbers (%)] for categorical variables.

Abbreviations: BMI, body mass index.

Table 2. Comparative maternal and neonatal biochemical and hormonal parameters

	Mothers	**Neonates**	**p-value ***
Corrected Calcium (mg/dl)	10.1 ± 0.1	11.7 ± 0.1	<0.001
PTH (pg/ml)	27.2 ± 1.6	6.4 ± 0.2	<0.001
25OHD (ng/ml)	18.3 ± 1.2	16.3 ± 1.0	0.217
$1,25(OH)_2D$ (pg/ml)	51.9 ± 2.4	43.8 ± 3.6	0.057
VDBP (μg/ml)	364.1 ± 11.9	355.3 ± 29.2	0.780
Adiponectin (μg/ml)	4.4 ± 0.4	11.9 ± 2.0	<0.001
Irisin (ng/ml) [#]	308.8 ± 50.8	174.4 ± 26.0	0.041

Data are presented as mean ± standard error of the mean (SEM) for continuous variables.

* Independent sample t-test or Mann-Whitney test were used for between group comparisons.

[#] n=61 for mothers; n= 42 for neonates

Abbreviations: $1,25(OH)_2D$, $1,25(OH)_2$-Vitamin D; 25OHD, 25(OH)-Vitamin D; PTH, parathyroid hormone; VDBP, Vitamin D-binding protein.

Table 3. Correlations of maternal parameters.

	PTH (pg/ml)	**25OHD (ng/ml)**	**1,25(OH)$_2$D (pg/ml)**	**VDBP (µg/ml)**	**Adiponectin (µg/ml)**	**Irisin (ng/ml)$^{\#}$**
Age (years)	0.15 (0.22)	-0.08 (0.51)	-0.05 (0.68)	-0.26 (0.04)*	-0.23 (0.08)	-0.06 (0.64)
Height (cm)	-0.08 (0.51)	0.26 (0.04)*	-0.17 (0.16)	0.10 (0.40)	-0.12 (0.35)	0.02 (0.83)
Weight; pre-pregnancy (kg)	-0.06 (0.61)	0.09 (0.46)	0.06 (0.06)	-0.08 (0.51)	-0.21 (0.09)	0.13 (0.31)
Weight; term (kg)	0.03 (0.81)	-0.01 (0.92)	0.01 (0.89)	-0.04 (0.73)	-0.28 (0.03)*	0.27 (0.047)*
BMI; pre-pregnancy (kg/m^2)	-0.08 (0.53)	0.03 (0.76)	0.11 (0.11)	-0.11 (0.39)	-0.17 (0.18)	0.10 (0.43)
BMI; term (kg/m^2)	-0.03 (0.83)	-0.07 (0.59)	0.01 (0.92)	-0.12 (0.33)	-0.27 (0.04)*	0.17 (0.21)
Weeks of gestation (n)	-0.10 (0.49)	0.12 (0.41)	0.19 (0.19)	-0.14 (0.33)	0.05 (0.72)	0.28 (0.06)
Corrected calcium (mg/dl)	-0.46 (<0.001)*	0.38 (0.002)*	0.28 (0.002)*	0.13 (0.28)	-0.07 (0.55)	-0.02 (0.85)
PTH (pg/ml)	-	-0.46 (<0.001)*	0.00 (0.97)	-0.03 (0.77)	0.17 (0.15)	0.10 (0.43)
25(OH)D (ng/ml)	-	-	0.49 (<0.001)*	0.01 (0.92)	0.10 (0.39)	0.00 (0.98)
1,25(OH)$_2$D (pg/ml)	-	-	-	0.21 (0.07)	0.08 (0.51)	0.25 (0.05)
VDBP (µg/ml)	-	-	-	-	0.41 (0.001)*	0.30 (0.02)*

Adiponectin (µg/ml)	-	-	-	-	-	0.04 (0.73)

Data are presented as Spearman's correlation (p-value).

*: Statistically significant correlation.

[#] n=61

Table 6. Correlations of neonatal parameters.

	PTH (pg/ml)	25(OH)D (ng/ml)	1,25(OH)$_2$D (pg/ml)	VDBP (µg/ml)	Adiponectin (µg/ml)	Irisin (ng/ml)[#]
Height (cm)	0.04 (0.69)	0.06 (0.62)	0.16 (0.19)	0.05 (0.66)	-0.11 (0.40)	0.06 (0.69)
Weight (g)	0.08 (0.48)	0.00 (0.98)	0.03 (0.78)	0.21 (0.09)	0.01 (0.95)	-0.08 (0.64)
Head Circumference (cm)	-0.09 (0.43)	0.08 (0.52)	0.17 (0.17)	-0.01 (0.90)	-0.13 (0.32)	-0.29 (0.06)
Chest Circumference (cm)	-0.06 (0.63)	0.20 (0.12)	0.15 (0.22)	0.05 (0.69)	0.00 (0.98)	-0.11 (0.53)
Abdominal Circumference (cm)	-0.02 (0.83)	0.21 (0.11)	0.12 (0.33)	0.10 (0.42)	0.10 (0.42)	-0.17 (0.30)
Skin fold; abdominal (cm)	0.19 (0.11)	0.08 (0.54)	-0.04 (0.70)	-0.16 (0.22)	0.19 (0.14)	0.12 (0.45)
Upper Arm Circumference (cm)	0.09 (0.43)	-0.02 (0.85)	0.16 (0.20)	0.30 (0.02)*	0.10 (0.43)	-0.24 (0.13)
Middle thigh Circumference	0.04 (0.72)	0.16 (0.22)	0.03 (0.81)	0.08 (0.50)	0.03 (0.79)	0.00 (0.97)
Upper Arm Length (cm)	-0.11 (0.35)	0.30 (0.02)*	0.20 (0.11)	0.23 (0.07)	-0.06 (0.60)	0.05 (0.74)
Femur Length (cm)	0.01 (0.89)	0.04 (0.74)	0.06 (0.62)	0.05 (0.67)	-0.13 (0.32)	-0.06 (0.68)
Knee-Heel Length (cm)	0.00 (0.97)	-0.21 (0.10)	-0.07 (0.57)	0.02 (0.86)	-0.13 (0.32)	-0.34 (0.04)*
Corrected Calcium (mg/dl)	-0.32 (0.01)*	0.10 (0.42)	0.00 (0.96)	-0.16 (0.20)	-0.29 (0.02)*	0.06 (0.68)

PTH (pg/ml)	-	-0.19 (0.12)	-0.06 (0.63)	0.10 (0.41)	0.08 (0.51)	-0.31 (0.049)*
25(OH)D (ng/ml)	-	-	0.58 (<0.001)*	0.00 (0.96)	-0.03 (0.78)	0.07 (0.63)
1,25(OH)$_2$D (pg/ml)	-	-	-	0.11 (0.36)	0.03 (0.77)	-0.18 (0.24)
VDBP (µg/ml)	-	-	-	-	0.28 (0.03)*	0.01 (0.94)
Adiponectin (µg/ml)	-	-	-	-	-	-0.00 (0.97)

Data are presented as Spearman's correlation (p-value).

*: Statistically significant correlation

[#] n=42

Abbreviations: 1,25(OH)$_2$D, 1,25(OH)$_2$-Vitamin D; 25OHD, 25(OH)-Vitamin D; PTH, parathyroid hormone; VDBP, Vitamin D-binding protein.

Table 8. Correlations between maternal and neonatal parameters.

		Maternal parameters					
		PTH (pg/ml)	**25(OH)D (ng/ml)**	**1,25(OH)$_2$D (pg/ml)**	**VDBP (µg/ml)**	**Adiponectin (µg/ml)**	**Irisin (ng/ml)[#]**
Neonatal parameters	**Height (cm)**	0.00 (0.98)	0.14 (0.24)	0.11 (0.36)	-0.29 (0.04)*	-0.17 (0.18)	0.17 (0.18)
	Weight (g)	0.07 (0.57)	0.04 (0.72)	0.13 (0.28)	-0.15 (0.22)	-0.25 (0.049)*	0.05(0.66)
	Head Circumference (cm)	0.13 (0.29)	0.17 (0.18)	0.12 (0.31)	-0.11 (0.36)	0.06 (0.61)	0.20 (0.12)
	Chest Circumference (cm)	-0.10 (0.40)	0.22 (0.07)	0.10 (0.43)	-0.12 (0.31)	-0.21 (0.09)	0.12 (0.35)
	Abdominal Circumference (cm)	-0.04 (0.73)	0.13 (0.27)	0.08 (0.53)	-0.20 (0.10)	-0.15 (0.24)	0.06 (0.60)
	Skin fold; abdominal (cm)	0.05 (0.66)	0.16 (0.20)	0.28 (0.02)*	0.12 (0.32)	0.09 (0.47)	0.03 (0.80)
	Upper Arm Circumference (cm)	0.06 (0.62)	0.04 (0.73)	0.07 (0.54)	-0.05 (0.68)	-0.15 (0.24)	0.05 (0.70)
	Middle thigh Circumference (cm)	0.02 (0.89)	0.12 (0.33)	0.03 (0.77)	-0.04 (0.73)	-0.01 (0.91)	0.11 (0.38)
	Upper Arm Length (cm)	-0.11 (0.35)	0.36 (0.004)*	0.01 (0.88)	-0.31 (0.01)*	-0.19 (0.12)	0.10 (0.43)
	Femur Length (cm)	-0.02 (0.81)	0.03 (0.79)	0.10 (0.44)	0.05 (0.64)	-0.01 (0.97)	0.14 (0.27)
	Knee-Heel Length (cm)	0.02 (0.81)	0.01 (0.89)	0.19 (0.11)	0.11 (0.36)	-0.01 (0.91)	0.27 (0.04)*

Corrected Calcium (mg/dl)	-0.09 (0.46)	0.00 (0.97)	0.19 (0.11)	0.19 (0.11)	0.00 (0.96)	0.18 (0.16)
PTH (pg/ml)	0.16 (0.18)	-0.18 (0.15)	-0.03 (0.80)	0.09 (0.43)	0.22 (0.07)	-0.23 (0.06)*
25(OH)D (ng/ml)	-0.46 (<0.001)*	0.82 (<0.001)*	0.23 (0.07)	-0.14 (0.28)	0.22 (0.09)	-0.10 (0.44)
1,25(OH)$_2$D (pg/ml)	-0.22 (0.08)	0.54 (<0.001)*	0.23 (0.06)	0.01 (0.92)	0.20 (0.12)	-0.27 (0.04)*
VDBP (µg/ml)	0.19 (0.12)	-0.06 (0.66)	-0.12 (0.32)	0.01 (0.90)	0.14 (0.28)	-0.11 (0.39)
Adiponectin (µg/ml)	0.06 (0.59)	0.04 (0.72)	-0.14 (0.26)	-0.03 (0.82)	0.06 (0.61)	-0.12 (0.35)
Irisin (ng/ml)[#]	-0.01 (0.90)	-0.11 (0.47)	-0.44 (0.004)*	-0.10 (0.54)	0.00 (0.95)	-0.11 (0.48)

Data are presented as Spearman's correlation (p-value).

*: Statistically significant correlation

[#] n=61 for mothers; N= 42 for neonates

Table 4. Sequential models of linear logistic regression analysis evaluating independent associates of maternal adiponectin levels (μg/ml).

Variable	Unstandardized β	Standardized β	*p*-value	95% CI for β
Model 1				
Maternal VDBP (μg/ml)	0.02	0.41	0.005	0.01 – 0.03
Weeks of Gestation	1.01	0.14	0.31	-0.92 – 2.97
Model 2				
Maternal VDBP (μg/ml)	0.02	0.38	0.011	0.01 – 0.03
Weeks of Gestation	1.00	0.15	0.29	-0.92 – 3.00
Maternal age (years)	-0.07	-0.14	0.34	-0.22 – 0.08
Model 3				
Maternal VDBP (μg/ml)	0.02	0.35	0.026	0.01 – 0.03
Weeks of Gestation	0.74	0.10	0.47	-1.32 – 2.80
Maternal age (years)	-0.04	-0.07	0.64	-0.21 – 0.13
Maternal BMI; term (kg/m^2)	-0.07	-0.15	0.33	-0.23 – 0.08

Weeks of gestation was rated as 0 for <38, and 1 for ≥38, respectively.

Abbreviations: VDBP, Vitamin D-binding protein.

Table 5. Sequential models of linear logistic regression analysis evaluating independent associates of maternal irisin levels (ng/ml) [#].

Variable	Unstandardized β	Standardized β	*p*-value	95% CI for β
Model 1				
Maternal VDBP (μg/ml)	2.49	0.39	0.007	0.72 – 4.26
Weeks of Gestation	269.8	0.27	0.062	-14.5 – 554.1
Model 2				
Maternal VDBP (μg/ml)	2.29	0.36	0.016	0.44 – 4.13
Weeks of Gestation	263.2	0.26	0.07	-22.9 – 549.4
Maternal age (years)	-8.06	-0.12	0.42	-29.9 – 12.7
Model 3				
Maternal VDBP (μg/ml)	2.33	0.37	0.015	0.47 – 4.18
Weeks of Gestation	278.7	0.28	0.06	-7.1 – 564.6
Maternal age (years)	-14.31	-0.19	0.22	-37.7 – 9.08
Maternal BMI; term (kg/m^2)	2.72	0.04	0.79	-17.8 – 23.2

Weeks of gestation was rated as 0 for <38, and 1 for ≥38, respectively.

[#] n=61 for mothers

Abbreviations: VDBP, Vitamin D-binding protein.

Table 7. Sequential models of linear logistic regression analysis evaluating independent associates of neonatal adiponectin levels (μg/ml).

Variable	Unstandardized β	Standardized β	*p*-value	95% CI for β
Model 1				
Neonatal VDBP (μg/ml)	0.05	0.51	<0.001	0.02 – 0.07
Weeks of Gestation	7.41	0.19	0.15	-2.70 – 17.53
Model 2				
Neonatal VDBP (μg/ml)	0.05	0.55	<0.001	0.03 – 0.07
Weeks of Gestation	6.20	0.16	0.25	-4.61 – 17.01
Neonatal gender	7.31	0.20	0.16	-2.91 – 17.53
Model 3				
Neonatal VDBP (μg/ml)	0.05	0.54	<0.001	0.02 – 0.07
Weeks of Gestation	7.77	0.20	0.17	-3.51 – 19.04
Neonatal gender	5.16	0.14	0.35	-5.95 – 16.27
Neonatal weight (g)	-0.01	-0.14	0.32	-0.02 – 0.01

Weeks of gestation was rated as 0 for <38, and 1 for ≥38, respectively.

Boys were rated as 0, and girls as 1 within gender.

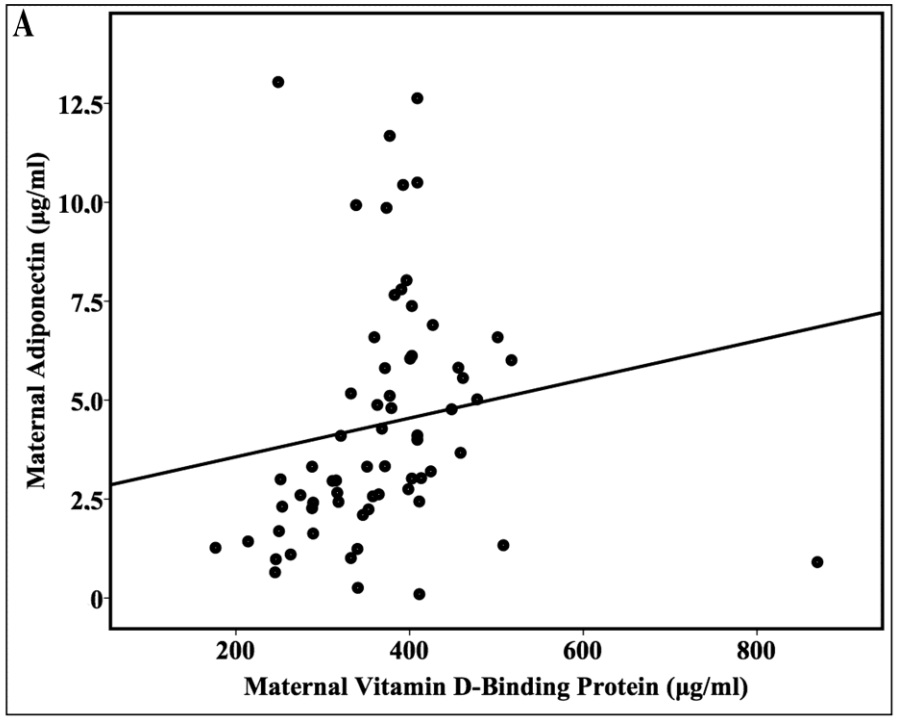
Abbreviations: VDBP, Vitamin D-binding protein.

Table 9. Sequential models of linear logistic regression analysis evaluating independent associates of neonatal upper arm length (μg/ml).

Variable	Unstandardized β	Standardized β	*p*-value	95% CI for β
Model 1				
Maternal 25OHD (ng/ml)	0.04	0.42	0.005	0.01 – 0.07
Weeks of Gestation	-0.05	-0.02	0.87	-0.68 – 0.58
Model 2				
Maternal 25OHD (ng/ml)	0.04	0.45	0.003	0.02 – 0.07
Weeks of Gestation	-0.08	-0.04	0.80	-0.71 – 0.55
Maternal age (years)	0.03	0.17	0.23	-0.02 – 0.07
Model 3				
Maternal 25OHD (ng/ml)	0.04	0.45	0.004	0.02 – 0.07
Weeks of Gestation	-0.04	-0.02	0.90	-0.71 – 0.63
Maternal age (years)	0.02	0.13	0.40	-0.03 – 0.08
Maternal BMI; term (kg/m^2)	0.01	0.05	0.72	-0.04 – 0.06
Model 4				
Maternal 25OHD (ng/ml)	0.04	0.45	0.005	0.01 – 0.07
Weeks of Gestation	-0.04	-0.02	0.92	-0.71 – 0.64
Maternal age (years)	0.02	0.14	0.38	-0.03 – 0.08
Maternal BMI; term (kg/m^2)	0.01	0.06	0.67	-0.04 – 0.06
Maternal VDBP (μg/ml)	0.001	0.05	0.73	-0.004 – 0.005

Weeks of gestation was rated as 0 for <38, and 1 for ≥38, respectively.

Abbreviations: 25OHD, 25(OH)-Vitamin D; VDBP, Vitamin D-binding protein.


A
Maternal Adiponectin (µg/ml)
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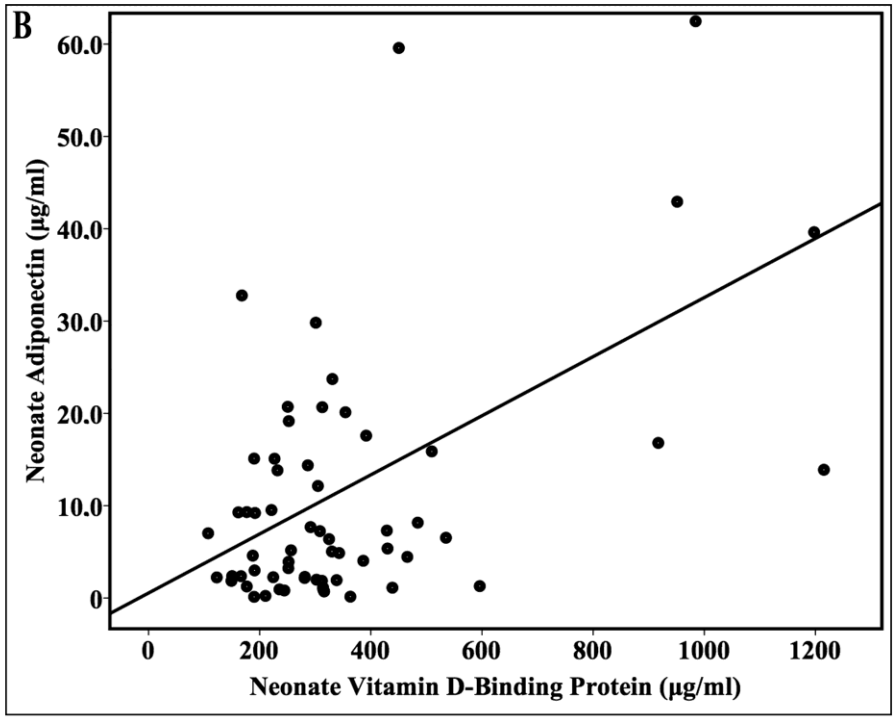
10.0
7.5
5.0
2.5
0
200
400
600
800
Maternal Vitamin D-Binding Protein (µg/ml)


B
Neonate Adiponectin (µg/ml)
60.0
50.0
40.0
30.0
20.0
10.0
0
0
200
400
600
800
1000
1200
Neonate Vitamin D-Binding Protein (µg/ml)