

## THE INFLUENCE OF MATERNAL LEVELS OF VITAMIN D AND ADIPONECTIN ON ANTHROPOMETRICAL MEASURES AND BONE HEALTH IN OFFSPRING

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### ABSTRACT

**Background:** From the conception onward, certain parameters associated with maternal health may affect foetal body composition, growth and bone mineral content.

The objective of the study was to determine the association between maternal vitamin D and adiponectin status with the anthropometrical measures of newborns, and bone health status measured by Quantitative Ultrasound (QUS) at birth.

**Methods:** Circulating 25OHD and adiponectin concentration were measured in 73 pregnant women. Correlations with the anthropometrical measures and bone health status in their infants were studied. Bone health was evaluated using QUS with the measurements of speed of sound (SOS, in m/s) and Z score on the right tibia.

**Results:** There was no significant association between maternal 25OHD and newborn's anthropometrical measures at birth (weight  $p=0.35$ , length  $p=0.59$  and head circumference  $p=0.47$ ). There was a significant negative correlation between a maternal serum adiponectin and a) weight of infants at birth ( $R=-0.37$ ,  $p=0.002$ ); b) birth length ( $R=-0.31$ ,  $p=0.008$ ) and c) head circumference ( $R=-0.29$ ,  $p=0.014$ ). There was no significant correlation between maternal 25OHD blood levels during pregnancy and SOS in newborns ( $p=0.48$ ). Additionally, a correlation between maternal adiponectin concentration during pregnancy and SOS in newborns was not significant ( $p=0.82$ ).

**Conclusion:** Although a high prevalence of low 25OHD level among pregnant women was found, maternal vitamin D status did not influence growth and bone health of their offspring at birth. Maternal adiponectin levels in plasma showed an inverse relationship with anthropometrical measures of infants at birth, while no correlation with the newborn's bone health was found.

**Keywords:** adiponectin, bone mineral density, newborns, pregnant women, vitamin D

### INTRODUCTION

From the conception onward, a child is developing under the influence of a series of biological events which enable maturation of tissues, growth and adaptation. This multi-factorial process repre-

sents the interplay between genetic, environmental and dietary influences [1, 2]. Certain parameters associated with the mother, such as a vitamin D deficiency and circulating levels of adiponectin, may

affect the body composition, bone mass, and the physiology of the child [2, 3].

In the last decade, various studies have enabled researchers to establish a link between vitamin D status in pregnant women and the outcome of pregnancy, the health of the foetus and the newborn, as well as the health of offspring in their childhood and adulthood [2, 3]. Many studies have shown an association between maternal vitamin D status, foetal skeletal development and foetal growth. Maternal vitamin D deficiency induces inadequate skeletal mineralization in utero, which may manifest as osteopenia in newborn infants, craniotabes or congenital rickets. According to Weiler et al., vitamin D deficient full-term newborns had lower whole-body mineral content relative to body weight [4], which could be explained with autocrine/paracrine actions of vitamin D on osteoblast differentiation and skeletal homeostasis [5]. The exact mechanisms of maternal vitamin D deficiency or sufficiency action on foetal growth indices are not clear. It is plausible that vitamin D could influence size at birth via bone mineral accrual of the foetus [6]. There is no consistent relationship between the maternal vitamin D status and the presence or absence of bone disease as well as with anthropometric measurements at birth in the literature [7-11].

It is a well-known fact that the birth weight is positively correlated with maternal pre-pregnancy body mass index, as well as with maternal circulating adiponectin. Overweight pregnant women are reported to have lower plasma concentrations of adiponectin compared to non-obese pregnant women [12]. Adiponectin is an adipocyte-derived signalling molecule that is produced in adipose tissue [13]. Serum levels of maternal adiponectin correlate negatively with the birth weight of the offspring. The hypothesis is that the maternal adiponectin plays a causative role in regulating the foetal growth by modulating placental nutrient transport [12]. Two observational studies have showed that adiponectin is present also in amniotic fluid, where its levels increase with the weeks of gestation and that there also might be a production of adiponectin in placenta [14, 15]. However, there are several studies that have not confirmed these findings, which makes it possible to suggest that adiponectin, influencing placental function, originates predominantly from maternal adipose tissue [15, 16]. To the best of our knowledge, the influence of maternal adiponectin on offspring bone health has not been described.

The aim of the present study was to determine the association between maternal vitamin D and se-

rum adiponectin status with the bone health (BH) and anthropometrical measures of newborns at birth.

## METHODS

### *Study Design*

The study was a part of the My-MILK project “The role of human milk in development of breast fed child’s intestinal microbiota” (My-MILK; [www.moje-mleko.si/en](http://www.moje-mleko.si/en)). The study protocol was approved by The National Medical Ethics Committee of the Republic of Slovenia (32/07/10, 38/02/12). All participant women signed a written informed consent. The study was registered at ClinicalTrials.gov (NCT01548313). All data of participants were coded and all information kept confidential.

### *Study population*

The target population of the survey comprised volunteer pregnant Slovenian women during the third trimester of gestation, in the period from December 2010 to October 2012 recruited in Ljubljana, and their newborns. Seventy-three women were recruited to participate in the study. Their vitamin D status and adiponectin level were measured. The newborns underwent anthropometrical measurements and bone health status assessment at birth.

### *Blood samples for 25 (OH)D concentrations*

Blood samples of approximately 5 ml were collected by venepuncture in tubes with no added anticoagulant in the third trimester of gestation in pregnant women. He collected blood samples were processed (centrifuged at 2,000 x g, aliquoted) at the Biochemical Laboratory of the University Medical Centre Ljubljana and stored at -80°C until the analysis. The analyses for the quantitative determination of circulating 25-hydroxyvitamin D [25OHD] were performed with radioiodine (125I)-based radioimmunoassay (RIA). Vitamin D status was defined according to the 25OHD blood levels as follows: deficiency (< 50 nmol/L), insufficiency (50–75 nmol/L) and sufficiency (75–125 nmol/L).

### *Serum samples for adiponectin analysis*

Adiponectin serum concentrations were measured in duplicate on microplate reader (Tecan, Männedorf, Switzerland) using human ELISA Kits for adiponectin (BioVendor, Lab. Med. Inc.,

Brno, Czech Republic). Kits are sandwich ELISA kits that use anti-human adiponectin antibodies that recognize adiponectin in serum. The microplate provided is coated with an antibody that captures adiponectin in standards and samples when added to the plate. After non-bound proteins are removed, the biotinylated detecting antibody is added and binds to a second site on the adiponectin. The plate is then washed and streptavidin-horseradish peroxidase is added. The enzyme-substrate reaction generates a colorimetric signal that is measured on a plate reader at 450 nm minus the absorbance at 550 nm. The absorbance is proportional to the amount of human adiponectin in the standard or sample. Assay sensitivity was 10 pg/mL for adiponectin. Interassay and intraassay CVs were less than 10%.

#### *Bone health status*

Speed of Sound (SOS) was measured at the right tibia of newborns in the first 48 hours after birth using the Sunlight Omnisense 7000P (Sunlight Medical Ltd, Tel Aviv, Israel). The site of measurement on the right tibia was determined by identifying the midpoint between the plantar aspect of the flexed foot and the dorsal aspect of the flexed knee (midshaft of the tibia), using an eyeliner pencil provided by the manufacturer. Ultrasound gel was applied to the leg and to the probe. The CS probe for newborn infants was used, aligned along and parallel to the bone and moved in a semi arc over the circumference of the site of measurement until a reliable estimate of the SOS was measured. A set of at least three repeated measurements was obtained. The software used the three most consistent measurements to compute the result. This is expressed in meters per second (m/sec), and displayed together with a z score (units of standard deviations relative to the mean for age- and sex-matched population reference values) based on a cross-sectional reference range for term and preterm infants that was included with the software and reported by Littner et al [17].

#### *Anthropometrical measurements*

A midwife attending the birth performed the newborn's anthropometrical measurements at birth including weight, length and head circumference. Body mass was measured with a certified medical scale to the nearest 0.1 kg, and body height to the nearest 0.5 cm (Seca digital scale 769, Germany).

#### *Statistical Analysis*

A descriptive analysis of the variables was carried out. Frequencies and percentages for categorical variables and the mean, median and standard deviation (SD) for numerical variables were calculated. The strength of bivariate linear correlation between dependent variable maternal 25 (OH) D and adiponectin serum concentration and independent variables newborn's body mass, length, head circumference, SOS and Z score was determined based on Pearson's bivariate correlation. In all statistical analyses, p values of <0.05 was considered to show statistically significant effects. Statistical analysis was performed with IBM SPSS 20.0 (Chicago, IL). [18]

## RESULTS

73 healthy pregnant women and their infants were recruited to the survey from 2010 to 2012. The age of mothers at delivery was 30.6 ± 4.2 years, 60 % of them were in the first pregnancy, and 78% had a higher level of education (completed university education). 73 infants enrolled in this study included males (54 %) and females (46 %) with mean gestational age 39.3 ± 1, 2 weeks, mean birth weight 3.346 ± 459.4 (range 2,070 - 4,490), mean length 50.9 ± 2.1 (range 46 - 56) and head circumference 34.7 ± 1.2 (range 31.5 - 37.5) [Table 1].

**Table 1.** *Clinical characteristics and measures of bone health in newborns in the first week and levels of maternal concentrations of 25(OH) D and adiponectin during pregnancy (n=73)*

I Newborn infants	Mean ± SD
Gestational age, weeks	39.3 ± 1.2
Birth weight, g	3346 ± 459.4
Length, cm	50.97 ± 2.1
Head circumference, cm	34.7 ± 1.2
Male gender, n (%)	39 (54%)
Tibial bone SOS, m/s	3043 ± 120.6
Z score	-0.33 ± 1.0
II. Pregnant women	Mean ± SD
Maternal 25(OH)D, nmol/L	81.67 ± 28.6
Maternal adiponectin, µg/ml	14.5 ± 11.6
Vaginal delivery, n (%)	58 (80.8)

Continuous data presented as means ± SD. Categorical variables presented as percentages (%).

SOS, bone quantitative ultrasound speed of sound; Z-score

Mean value of 25 (OH)D in blood of pregnant women was 81.67±28.6 nmol/L (range

33.9-169.9). Vitamin D deficiency was present in 14.4%, while insufficiency was present in 40.9% of women. The risk for vitamin D inadequacy was significantly higher in pregnant women older than 30 years ( $\chi^2 = 8.118$ ,  $p = 0.01$ ), in those with less frequent outdoor physical activity ( $\chi^2 = 7.196$ ,  $p = 0.01$ ) and in pregnancies during the low sun exposure season ( $\chi^2 = 4.005$ ,  $p = 0.04$ ).

#### *Maternal vitamin D status, anthropometrical measures and bone status at birth*

Sensitivity analysis in the subset ( $n=73$ ) showed comparable findings, indicating no significant associations between maternal vitamin D status and birth weight ( $p=0.35$ ), length ( $p=0.59$ ) and head circumference ( $p=0.47$ ) at birth [Table 2]. Mean tibial bone SOS was  $3.043 \pm 120.6$  m/s (range 2,678-3,351) and mean Z score was  $-0.33 \pm 1.0$  (range -3.6 - +1.9). The Pearson's correlation coefficient between maternal serum 25(OH)D and infant's SOS and Z score at birth was statistically not significant ( $p=0.48$ ) and ( $p=0.43$ ) respectively [Table 2].

#### *Maternal adiponectin status, anthropometrical measures and bone status at birth*

Mean serum adiponectin in pregnant women was  $14.5 \pm 11.6$   $\mu\text{g/ml}$  (range 2.5-66.5). There was no statistically significant correlation between maternal adiponectin value and newborn tibial bone SOS ( $p=0.82$ ). There was a statistically significant negative correlation between maternal serum adiponectin values and newborn birth mass ( $p=0.002$ ,  $R = -0.37$ ); length ( $p=0.008$ ,  $R = -0.31$ )

and head circumference ( $p=0.014$ ,  $R = -0.29$ ) at birth [Table 2].

## DISCUSSION

Vitamin D is involved in maintaining normal glucose homeostasis, human chorionic gonadotropin expression and placental sex steroid production and might therefore have an important role in foetal growth, development and newborn outcomes [19]. As regards the role of vitamin D on foetal growth, several biological mechanisms have been suggested, including the interaction of vitamin D with parathyroid hormone, calcium homeostasis and by that on bone growth [20, 21]. A study by Belenchia et al. on mice offspring suggests that exposure to vitamin D deficiency during the perinatal period can directly affect genes involved in the development of adipose tissue that led to leaner mice offspring [22]. There is also a study by Chen et al. that suggests that the vitamin D deficiency changes placental amino acid transportation and therefore alters foetal growth [23]. It has also been suggested that vitamin D receptors and 1,25-dihydroxyvitamin D [1,25(OH)2D] regulate a placental secretion of human placental lactogen and other hormones that affect maternal glucose and fatty acid metabolism, which provides energy for foetal needs [19, 23].

The findings by our cohort suggest that the maternal vitamin D deficiency during the mid-late trimester of pregnancy is not associated with anthropometrical measures of newborns at birth.

**Table 2.** Correlation between maternal concentrations of 25(OH) D and adiponectin with anthropometrical measures and bone status of newborns at birth (Pearson's bivariate correlation)

Maternal values	Anthropometrical measures of newborns at birth			Bone status of newborns at birth	
	Birth weight (g)	Length (cm)	Head circumference (cm)	SOS (m/sec)	Z-score
25(OH)D (nmol/L)	$p=0.35$	$p=0.59$	$p=0.47$	$p=0.48$	$p=0.44$
	$R = -0.12$	$R = -0.07$	$R = -0.09$	$R = -0.09$	$R = -0.10$
Adiponectin ( $\mu\text{g/ml}$ )	$p=0.002$	$p=0.008$	$p=0.014$	$p=0.82$	$p=0.91$
	$R = -0.37^{**}$	$R = -0.31^{**}$	$R = -0.29^*$	$R = -0.03$	$R = 0.01$

$p$ ,  $p$  value; SOS, bone quantitative ultrasound speed of sound (Pearson's bivariate correlation).

\*correlation is significant at level 0.05

\*\*correlation is significant at level 0.01

Although a link between maternal vitamin D concentrations and foetal development remains inconclusive in literature, our observation agrees with several cohort studies which reported a lack of influence of maternal vitamin D on anthropometric measures of newborns [14, 24, 26]. In these studies cut-offs for vitamin D deficiency in pregnant women were higher (37.5 to 80 nmol/L) [14, 25, 26], with a vitamin D deficiency prevalence that ranged from (20-66%) which is similar to our study. On the other hand, a recent meta-analysis reported an association between insufficient circulating 25OHD concentration and a risk of newborns small for gestational age and low birth weight newborns [27]. The association remained significant after stratified analysis and adjustment for confounders. Moreover, infants of mothers with a 25OHD concentration <37.5 nmol/l had a lower birth weight, while birth length and head circumference were not associated with maternal 25OHD concentration [27]. While our and other studies found no effect of the maternal level of serum vitamin D on foetal growth, others reported an improvement of foetal growth with high doses of vitamin D supplementation, i.e. 1,000 or even 4,000 IU of vitamin D/day [1, 8, 9, 28]. Higher doses of vitamin D intake are supposed to provide circulating 25OHD high enough to have impact on foetal growth [28].

Even though the importance of vitamin D for foetal and infant skeletal growth has been recognized for a long time, the exact mechanism remains unknown. Several studies suggest that 25OHD levels in plasma of pregnant mother increase by 2-fold in early pregnancy and reach a maximum in the third trimester of pregnancy and therefore enhance calcium transportation and fetal bone mineral accretion [21]. Placental calcium transfer and placental synthesis of active vitamin D is supposed to be activated by PTH-related peptide (PTHrP) which is produced in foetal parathyroid gland and the placental tissues [20].

Our results did not confirm the influence of maternal vitamin D on bone mineralization in our cohort of newborns. Similarly, Dror et al. also did not find any significant relation between bone mineral content and maternal vitamin D status, season of birth, feeding habits or sex, but found that it was most strongly influenced by various indices of infant size and factors determined to be in the pathway for predicting size (maternal pre-pregnancy BMI and infant age at the time of the scan). Additionally, Dror and Hollis in their

observational studies concluded that maternal vitamin D status and foetal bone mineral accretion are associated positively only when maternal serum 25OHD is above 80 nmol/l [29, 30]. Although maternal mean value of 25OHD in our study was above 80 nmol/l, we could not confirm any positive association between serum levels of 25OHD and bone health in newborns. Contrary to these findings, in the study of Weiler et al. both maternal and cord plasma level of 25(OH)D remained significant in a multivariate model predicting bone mineral content in term-born Canadian infants aged less than 15 days [4].

We additionally studied the influence of maternal circulating adiponectin levels and foetal growth and confirmed the results of previous studies that reported inverse association between maternal adiponectin and birth weight length and head circumference [31]. The underlying mechanisms remain unknown though the results from cell-lines and non-pregnant animal's studies strongly suggest that adiponectin enhances insulin sensitivity. Contrary to this data, recent findings suggest that adiponectin promotes insulin-resistance in placenta. Additionally, adiponectin regulates human placental function by limiting nutrient transporter expression and inducing apoptosis, resulting in foetal growth inhibition *in vivo*. Based on these studies, adiponectin inhibits the expression of the major glucose transporters and sodium-coupled neutral amino acid transporters, enhances total ATP production and stimulates cell death by enhancing the expression of the pro-apoptotic B-cell lymphoma-2 [32]. Regulation of placental function by adiponectin constitutes a novel physiological mechanism by which the endocrine functions of maternal adipose tissue influence foetal growth.

In accordance with this explanation, we additionally analysed the influence of maternal adiponectin level on bone health in offspring, which to our knowledge has not been studied yet. We demonstrated no significant influence of maternal adiponectin on bone status in newborns. A large number of studies relating adiponectin-circulating levels to bone parameters and in different populations have been published and found a consistent inverse association between serum adiponectin levels and bone mineral density [26]. Adipocytes and osteoblasts are both of mesoderm origin and mature cells express and secrete several common factors. Adiponectin stimulates osteoblast genesis and suppresses osteoclast genesis by direct en-

doctrine action through AdipoR1 and Adipo R2 receptors, autocrine/ paracrine action and indirect endocrine effects by interacting with other signalling pathways [33, 34]. In line with these findings, Cekmez et al. observed that adiponectin and vitamin D were positively associated with bone homeostasis although the exact mechanism is still subject of further studies [35]. Future studies will hopefully discover missing parts of the complex puzzle and further our understanding of the physiological role of mother adiponectin in bone biology, which is probably thought the placental function.

## CONCLUSION

Although a high prevalence of low vitamin D level among pregnant women was found, maternal vitamin D status did not influence growth outcomes of their offspring and had no influence on their bone health at birth. According to our results, maternal circulating adiponectin has inverse influence on newborns' measures at birth, but has no influence on bone health in newborns.

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## Резиме

### ВЛИЈАНИЕТО НА МАЈЧИНИТЕ НИВОА НА ВИТАМИН Д И АДИПОНЕКТИН ВРЗ АНТРОПОМЕТРИСКИТЕ МЕРКИ И ЗДРАВЈЕТО НА КОСКИТЕ КАЈ ПОТОМЦИТЕ

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**Вовед:** Со самото ембрионално зачнување, одредени параметри поврзани со здравјето на мајката може да влијаат на телесната структурата на фетусот, растот и минералниот состав на коските.

Целта на студијата беше да се утврди поврзаноста меѓу витаминот Д кај мајката и вредноста на адипонектинот со антропометричките мерки кај новороденчето, како и со минералниот состав на коските определен со квантитативен ултразвук по самото раѓање.

**Методи:** Серумската концентрација на 25ОНД и на адипонектинот беа измерени кај 73 бремени жени. Се проучуваше корелацијата меѓу антропометричките мерки и здравствената состојба на коските кај нивните новороденчиња. Минералниот состав на коските се определуваа со помош на користење на QUS со мерките од брзината на звукот (SOS и m/s) и Z резултатот на десната тибиа.

**Резултати:** Немаше значителна поврзаност меѓу 25ОНД кај мајката и антропометричките мерки кај новороденчето по раѓањето (тежина  $p=0,35$ , должина  $p=0,59$  и обем на главата  $p=0,47$ ). Постоеше значителен негативен сооднос меѓу адипонектичкиот серум на мајката и тежината на новороденче веднаш по раѓањето: а) ( $R= -0,37$ ,  $p=0,002$ ); б) должина на бебето при раѓање ( $R= -0,31$ ,  $p=0,008$ ) и в) обем на главата ( $R= -0,29$ ,  $p=0,014$ ). Не постоеше посебна поврзаност меѓу нивото на 25ОНД во крвта кај мајката за време на бременоста и SOS кај новороденчињата ( $p=0,48$ ). Дополнително, самата корелација меѓу концентрацијата на адипонектинот кај мајката за време на бременоста и SOS кај новороденчињата не е толку голема и значајна ( $p=0,82$ ).

**Заклучок:** Иако беше откриена висока застапеност на ниското ниво на 25ОНД кај бремените жени, нивото на витаминот Д кај мајките не влијае врз развојот и структурата на коските кај нивните бебиња при раѓањето. Нивото на адипонектинот кај мајката во плазмата покажува една обратна поврзаност со антропометричките мерки кај новороденчињата при раѓањето. Истовремено, не е откриена поврзаност со здравјето на коските кај новороденчињата.

**Клучни зборови:** адипонектин, минерална структура на коските, новороденчиња, бремени жени, витамин Д