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Low cord blood serum levels of vitamin D: cause or effect of fetal macrosomia?

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Summary

Aim: The aim of the study was to compare cord blood vitamin D levels of macrosomic large for gestational age (LGA) and appropriate gestational age (AGA) newborns. *Materials and Methods:* Seventy-nine healthy, normal term newborns were included in the study. They were divided by birth weight into two groups: 37 in the LGA group above 4,000 g, and 42 newborns in the AGA group birth weight between 3,000 g and 4,000 g. Cord blood samples from groups were collected. Circulating 25(OH)D was measured as 25 hydroxyvitamin D3 (25(OH)D3) by high-performance liquid chromatography (HPLC) in serum using a kit. *Results:* Maternal characteristics (age, body mass index [BMI], and gestational age) did not differ between the AGA and LGA groups. Cord blood 25 OH vitamin D levels were significantly low in neonates with LGA ($p = 0,02$). *Conclusions:* The authors found that macrosomic infants had low levels of vitamin D. Providing vitamin D supplements to pregnant women may prevent macrosomia. Randomized controlled trials are needed to prove this assertion.

Key words: Vitamin D; Fetal macrosomia; Large for gestational age (LGA).

Introduction

Fetal macrosomia, commonly defined as a birth weight above the 90th centile for gestational age (GA), is associated with increased risks for the mother, including cesarean section and trauma to the birth canal, and for the baby, including shoulder dystocia and consequent brachial plexus or facial nerve injuries, fractures of the humerus or clavicle, and birth asphyxia [1–6]. The prevalence of macrosomia in developed countries is between 5% and 20%; however, an increase of 15–25% has been reported in the past two to three decades [7-9].

Vitamin D deficiency is an increasing public health concern [10]. Though most commonly associated with rickets in childhood or osteomalacia in later adult life, but also a lack of vitamin D has potential health consequences that reach far beyond disordered calcium regulation and bone mineralization [11]. Vitamin D receptors are distributed in a variety of tissues throughout the body [12]. In pregnancy, vitamin D deficiency has been shown to be associated with complications such as preeclampsia, gestational diabetes mellitus, and primary caesarian section, and it has been hypothesized to also induce increased risk of multiple sclerosis, heart disease, and cancer later in life [13-19]. Low serum levels of 25(OH)D have been linked through observational studies to the pathophysiology of obesity, diabetes mellitus, and metabolic syndrome. Vitamin D receptor is highly expressed in adipocytes and is responsive to activation by 1,25-(OH)2D [20-22]. Also vitamin D is fat soluble and can be stored in adipose tissues [23, 24]. Large cohort studies have shown that an increased percentage body fat and high body mass index (BMI) are strongly and inversely correlated with serum 25(OH)D concentrations, particularly in Caucasians [25, 26]. There is also strong evidence that 1,25-(OH)2D modulates intracellular ionized calcium signaling in the adipocyte, which in turn promotes increased lipogenesis and decreased lipolysis, possibly through the inhibition of uncoupling protein-2 (UCP2) [27].

Although some studies have shown a relationship between vitamin D deficiency and small for gestational age (SGA) infants. All of the studies compared with SGA and appropriate for gestational age (AGA) infants for vitamin D levels. Until now, no firm data have answered the question of whether fetal macrosomia is related to vitamin D deficiency. The aim of the study was to compare cord blood vitamin D levels of macrosomic (large for gestational age – LGA) and AGA infants.

Materials and Methods

This case control cross-sectional study was conducted between December and February 2013 in the Department of Perinatology at Zekai Tahir Burak Women's Teaching and Research Hospital in Ankara, Turkey. In this hospital there are approxi-

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Table 1. — *Comparison between AGA and LGA newborns cord blood vitamin D, birth weight and, maternal data.*

Variables	AGA newborns N=42	LGA newborns N=37	*p* value
Maternal age (years)	27.2 (±4.2)	27.6 (±6.5)	0.7
Gravida	1.8 (±0.89)	2 (±1.1)	0.5
Gestational age (days)	275 (±9.1)	278 (±6.9)	0.07
BMI (kg/m^2)	29.8 (±4.3)	31.2 (±2.5)	0.16
25OH vitamin D_3 (µg/l)	26.4 (±17.6)	15.1 (±6.9)	0.02
Log 25OH vitamin D_3	1.3 (±0.33)	1.1 (±0.18)	0.008

mately 1,000 births in a month. Cases were consecutive births between this period. Seventy-nine healthy, normal term newborns were included in the study. They were divided by birth weight into two groups: 37 in the LGA group above 4,000 g, and 42 newborns in the AGA group birth weight between 3,000 g and 4,000 g. Cord blood samples from groups were collected. The umbilical cord was double clamped and blood samples were collected from the umbilical vein by needle puncture just after delivery. All blood samples were taken from mothers with low-risk, term (37 weeks or more gestation) pregnancies without a history of hypertension, diabetes mellitus, chronic respiratory or cardiovascular diseases, pre-eclampsia/eclampsia, oligohydramnios, intrauterine growth restriction, poor biophysical profile, smoking or vitamin D using. Age, BMI, gestational age, gravidity, parity, maternal fasting blood glucose, levels of vitamin D in newborn cord blood, and birth weight were recorded. Because of seasonal variation of vitamin D levels, study were conducted in winter time. Gestational age at delivery was calculated according to the last menstrual period and confirmed by ultrasound examination during the first trimester or early second trimester. Gestational diabetes was ruled out by normal glucose tolerance test (GCT) or normal oral glucose tolerance test (OGTT) in cases when GCT was abnormally high. These tests were performed between 25 to 29 gestation weeks.

Laboratory methods

Umbilical cord blood samples were taken into vacutainer tubes and centrifuged. Serum samples were then stored in aliquots at -80°C until the testing period. Circulating 25(OH)D was measured as 25 hydroxyvitamin D3 (25(OH)D3) by high-performance liquid chromatography (HPLC) in serum using a kit. The intra-assay coefficients of variation for serum vitamin D was 2.6% and the inter-assay coefficients of variation for serum Vitamin D was 4%. The reference interval was 25-150 nmol/l (10-60 µg/l) for winter time.

Statistical analysis

When the macrosomic birth weight prevalence of 20% among term deliveries [7-9] 95% confidence interval, a = 0.05 and 85% power, the sample size was calculated as 36 cases and 36 controls. A total of 37 cases and 42 controls were evaluated in the present study.

Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS). Vitamin D data was log transformed before statistical analysis by the independent samples *t*-test. A Mann–Whitney *U*-test was used to compare the other variables. Statistical significance was set at $p < 0.05$. The study was approved by the local ethics committee and all of the patients gave informed consent for participation in the study.

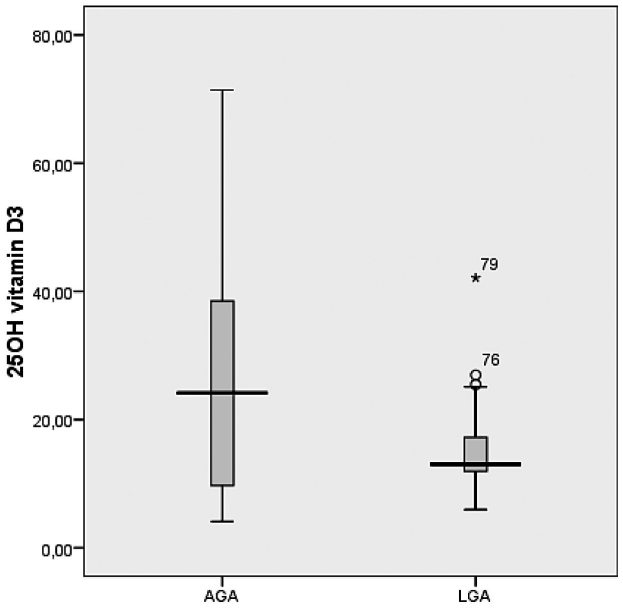

Figure1. — Cord blood 25 OH vitamin D_3 levels of newborns.

Results

All neonates were normal and did not suffer from any complication. Forty (50.6%) neonates were born by cesarean section (22 of AGA group and 18 of LGA group), and 39 (49,4%) by vaginal delivery (20 of AGA group and 19 of LGA group). Forty-four of the neonates were males (55.7%) and 32 (40.5%) were females. Maternal characteristics (age, BMI, and gestational age) did not differ between the AGA and LGA groups (Table 1). Cord blood 25 OH Vitamin D levels were significantly low in neonates with LGA ($p = 0.02$). Cord blood 25 OH vitamin D_3 levels of newborns are shown in Figure 1.

Discussion

This case–control study was undertaken to compare cord blood 25OH vitamin D values of LGA infants and AGA infants. The results showed that LGA infants had a significantly lower 25OH vitamin D levels compared to AGA infants.

The effects of vitamin D deficiency on birth size are inconsistent. The present results add to the evidence that cord blood 25(OH)D concentrations are negatively correlated with high birth weight as reported by other studies [28-30]. In contrast, some studies reported no such correlation [31] or even a positive association [32-33] between birth size and 25(OH)D level. These conflicting findings may be related to the varied populations studied or methods used. Variants in the vitamin D receptor gene may influence the associations between maternal 25(OH)D concentrations and birth size measurements.

It is now known that vitamin D has potent antiproliferative properties. The presence of vitamin D dampens proliferation and induces cells to exit the cell cycle via differentiation and, in certain circumstances, induces apoptosis [34, 35]. Therefore, its absence in the prenatal period could lead to inappropriately high cell numbers, which could subsequently influence the size of the offspring. Animal experiments indicate that these mechanisms do have an impact on fetal growth. For instance, the newborn offspring of normocalcemic rats deprived of vitamin D were significantly heavier than those of control animals [29]. Guinea pig fetuses exposed to low levels of vitamin D had expanded growth plates in their long bones [30]. If similar mechanisms operated in humans, the newborns with hypovitaminosis D should be heavier (due to increased cell number) and longer (due to wider growth plates in the lower limb bones).

Recent studies showed that adiposity, the expansion and growth of white adipose tissue (WAT) caused by hyperplasia and hypertrophy of adipocytes [36], is dependent on the neovascularization and dilatation of existing capillaries, respectively [36, 37]. Hence, hypertrophic adipocytes are typically found to possess low-oxygenmicroenvironments-hypoxia [38]. Similar to tumor growth, the inhibition of adipose tissue angiogenesis inhibits WAT growth and ultimately, the development of adiposity. Numerous studies showed 1α,25(OH)2D3 inhibited the proliferation of cultured endothelial cells and anti-angiogenesis in animal models [39, 40]. The hormone can also interrupt the angiogenic factor interleukin 8 signaling, leading to the inhibition of endothelial cell migration and tube formation [41]. It can be speculated that macrosomia may be related the low level of vitamin D and its antiangiogenic effects.

Environmental factors that have regular seasonal fluctuation influence both the size and shape of neonates. Animal experiments suggest that prenatal hypovitaminosis D may underlie greater limb length [30]. Fetal vitamin D requirements increase during pregnancy (related to the increased need for fetal calcium), thus maternal vitamin D levels tend to fall during the third trimester, especially if this occurs during winter [42]. Seasonal variation of vitamin D levels may be the cause of seasonal change of fetal weight.

There are some limitations of this study. First of all the authors did not evaluated levels of vitamin D in maternal serum at birth. For this reason they can not conclude that this lower levels of vitamin D in macrosomic infants only related with fetal vitamin D levels. In addition this limited number of patients included the study. In the next step, this study should be repeated with a larger number of patients and also maternal serum levels of vitamin D should be evaluated.

In conclusion, the authors found that macrosomic infants had low levels of vitamin D. Providing vitamin D supplements to pregnant women may prevent macrosomia. Randomized controlled trials are needed to prove this assertion.

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