Exp Biomed Res 2023; 6(3): 230-237 **DOI: 10.30714/j-ebr.2023.187**

Experimental Biomedical Research *Original article*

Evaluation of newborns with vitamin D deficiency: A single-center experience

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ABSTRACT

Aim: To evaluate the demographic, clinical, and laboratory characteristics (primarily phosphorus, calcium (Ca), and alkaline phosphatase (ALP) levels of newborns with low 25-OHD levels.

Methods: In this retrospective study, babies whose 25-OHD levels were determined during hospitalization were evaluated. The newborns were classified as stated by their serum 25-OHD levels as follows: severely deficient, <5 ng/mL (group 1); deficient, 5–20 ng/mL (group 2); and insufficient, 20 to 30 ng/mL (group 3). In addition to the newborns' serum 25-OHD levels, their serum Ca, phosphorus, parathormone (PTH), and alkaline phosphatase levels and their mothers' 25-OHD levels were also measured.

Results: A total of 568 newborns were included. Serum 25-OHD level was severely deficient in 112 patients (19.7%). The mothers of the babies in group 1 were younger than those of the babies in the other groups. First PTH level ($F_{3,1}$, p = 0.04) and maternal ALP level were highest in group 1. In all the groups, the maternal 25-OHD level was <30 ng/mL. Vitamin D supplementation rate during pregnancy was found to be significantly lower in the severely deficient and deficient groups than in the insufficient group ($F_{1,84}$, p = 0.01).

Conclusion: 25-OHD deficiency continues to be a problem among pregnant women and their babies in Turkey despite the introduction of a supplementation program. This study emphasizes the need to improve maternal 25-OHD status to support maternal and infant health.

Key words: Newborn, hypocalcemia, pregnancy, vitamin D.

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Received: 2023-04-01 / Revisisons: 2023-06-04
Accepted: 2023-06-25 / Published online: 2023-07-01

Introduction

Vitamin D (25-OHD) as a hormone has many significant functions in the body. During the intrauterine period and early infancy, 25-OHD has an essential role in bone development and the growth and maturation of tissues such as those of lungs, endocrine system, and brain [1]. The fetus is dependent on maternal 25-OHD. Maternal 25-OHD levels are the main determinant of infants' 25-OHD and calcium levels [2].

In addition to ensuring placental integrity, maternal 25-OHD levels are measured as the main determinant of placental calcium and phosphorus transfer to the baby [3]. Maternal serum 25-OHD status during pregnancy is also important for 25-OHD to cross the fetus by placenta, and the level measured in cord blood at birth depends on the mother's condition and is

80% of the mother's value on average [4]. 25-OHD level is also the primary determinant of the infant's serum calcium (Ca), phosphorus (P), and 25-OHD levels in the early postnatal period. The classic outcomes of 25-OHD deficiency during pregnancy and in newborns are late hypocalcemia and nutritional rickets [2].

The goal of this study was to determine the demographic, symptomatological, clinical, and laboratory findings (primarily calcium, phosphorus, and alkaline phosphatase) of newborns with low vitamin D levels. In addition, we aimed to compare maternal and infant 25-OHD levels in patients whose maternal vitamin D levels were determined during hospitalization.

Materials and metods

In our retrospective study, data from the medical files of the patients hospitalized in our clinic between June 2010 and June 2020 were evaluated. In our clinic, 25-OHD levels are usually studied for patients with hypocalcemia, but the decision to do so is made by the attending consultant. All babies whose 25-OHD levels were determined during hospitalization were evaluated. The medical records of all the babies with 25-OHD levels < 30 ng/mL were evaluated. Patients with missing data in their files were excluded from the study, and those with complete medical information were included. The demographic, symptomatological, clinical, and laboratory characteristics (primarily calcium, phosphorus, and ALP levels) of the patients were recorded from an electronic database. Maternal 25-OHD levels were determined.

Serum 25-OHD levels were assessed using tandem mass spectrometry coupled to liquid chromatography (LC-MS/MS) with the APPLIED 3200 Biosystem device (DPC Cirrus Inc., Diagnostic Products Corporation, Los Angeles, CA). The 25-hydroxyvitamin D (25-OHD) values were used for the serum 25-OHD levels. 25-OHD values > 30 ng/mL was determined as sufficient; 20 to 30 ng/mL, as insufficient; <20 ng/mL, as deficient; and <5 ng/mL, as severely deficient [5,6]. The intended 25-OHD level is >30 ng/mL [7]. The classification according to serum 25-OHD levels were as follows: >30 ng/mL sufficient, 20 to 30 ng/mL insufficient, <20 ng/mL deficiency, <5 ng/mL severe deficiency [5].

The simultaneous serum Ca, phosphorus, parathormone (PTH), and alkaline phosphatase (ALP) levels with serum 25-OHD levels were noted. The control serum P, Ca, PTH, and ALP levels were also measured. Synchron D×C 800 pro Coulter Beckman was used to measure the serum P, Ca, ALP, and PTH levels. Normal range for inorganic phosphate levels was 5.2 to 8.4 mg/dL for babies 0 to 5 months old and 2.5 to 4.5 mg/dL for adult women. Upper normal limits for ALP level were 420 and 130 IU/L for infants and non-pregnant women, respectively [8]. Serum PTH levels < 67 pg/mL were considered normal, and those with > 67 pg/mL were considered high [9].

Hypocalcemia was identified as a total serum Ca level < 8 mg/dL (2 mmol/L) or an ionized Ca level < 4.4 mg/dL (1.1 mmol/L) for term infants or preterm infants weighing >1500 g at birth and a total serum calcium level < 7 mg/dL (1.75 mmol/L) [10].

Neonatal hypocalcemia is usually asymptomatic. Clinical findings such as hypotonia, high-pitched crying, lethargy, apnea, jitterines, stridor, laryngospasm, cyanosis, feeding difficulty, vomiting, irritability, and seizures may be observed in symptomatic infants [11,12].

This study was ethically approved by the ethics committee of the Dr. Sami Ulus Obstetrics, Child Health and Diseases Training and

Research Hospital (No. E-21/04-157). The data used in this study were anonymous; therefore, informed consent was not required.

Statistical analysis was work out using SPSS 23.0. Categorical variables were presented as percentages, and continuous variables were denoted as mean ± standard deviation. Analysis of variance (ANOVA) was used to compare the means between the three groups. Variables found significant in the ANOVA were subjected to post hoc tests to identify significant pairs. *P* values of < 0.05 were considered statistically significant.

Results

During the study period, 14,631 newborn babies were hospitalized. In our neonatal intensive care unit over a 10-year period. 25-OHD deficiency was detected in 622 (4.2%) of these patients. Ninety-six patients with missing data were excluded from the study, and 568 newborns were included. Of the patients, 356 (62.7%) were male and 212 (37.3%) were female. The mean gestational week was 37.64±2.47 weeks, the median age at hospitalization was 5 (1-56) days, and the mean birth weight was 3013.72±636.26 grams. The mean maternal age was 27.8±5.3 years and the mean maternal serum 25-OHD level was 9.7±5.5 ng/mL. 25-OHD supplements during pregnancy was used by 78 (13.7%) of mothers.

The clinical presentations of all patients with 25-OHD deficiency are given in Table 1. The most common clinical finding was hypocalcemia in 135 (23.7%) newborns. 25-OHD supplementation was started for all newborn babies whose 25-OHD was found to be below 30 ng/mL, and calcium supplementation was given to 160 (28,1%) patients with accompanying hypocalcemia. Newborns were classified as severe deficiency <5 ng/mL (group 1), 5-20 ng/mL deficiency (group 2), and insufficient 20

Table 1: Demographic and clinic presentation of all newborns

Gestastional age (weeks)	37.64±2.47
Birhtweight (gram)	3013.72±636.26
Sex	
Male	356 (62.7%)
Female	212(37.3%)
Maternal vitamin D supplementation during pregnancy	
Yes	78 (13.7%)
No	490 (86.3%)
Season	
Winter	125 (22%)
Spring	184 (32.4%)
Summer	169 (29.8%)
Autum	90 (15.8%)
Clinic symptom	
Hypocalcemia	135 (23.7%)
Congenital Rickets	75 (13.2%)
Seizure	13 (2.28%)
Jitterness	5 (0.88%)
Fracture	3 (0.5%)
None	337 (59.3%)

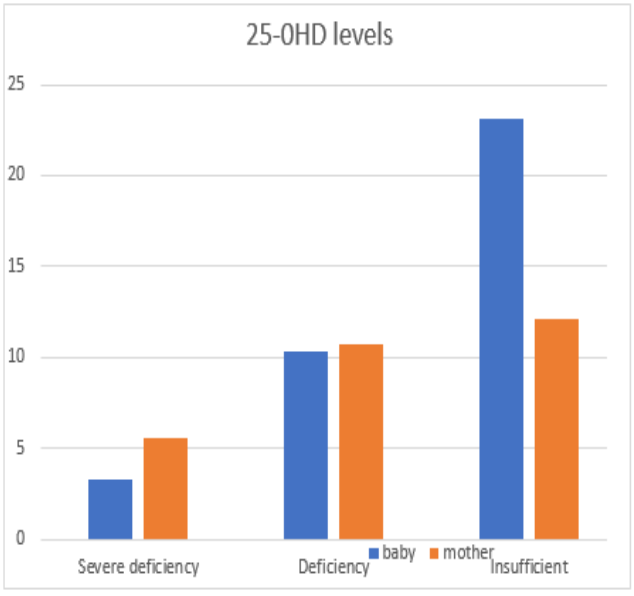

Figure 1. Mean serum 25-OHD levels (ng/mL) of mothers and their babies.

to 30 ng/mL (group 3) according to their serum 25-OHD levels. The mean serum 25-OHD levels of mothers and their babies are shown in Figure 1. Demographic and laboratory findings of all groups were given in Table 2. Serum 25-OHD levels were found to be severely deficient in 112 (19.7%) of the patients. The mothers of the babies in group 1 were younger than the other groups. The first PTH level is higher in group 1 (F:3,1; p:0,04). Mother's ALP levels are high in group 1. In all groups mother's 25-OHD levels are below 30 ng/mL. In addition, it was observed that the mothers in the group 1 had the lowest 25-OHD levels. 25-OHD supplementation during pregnancy was found to be significantly lower in severe deficiency and deficiency groups compared to the insufficient group (F:1,84; p: 0.01).

Table 2: Clinical characteristics of all subjects by study groups.

Parameters	Severe deficiency (Group 1) (n:112)	Deficiency (Group 2) (n:410)	Insufficient (Group 3) (n:46)	F	*p*
Mother age (year)	26,73±5,51	27,82±5,95	30,29±6,26	5,7	**0,003**
Gestational week (week)	38,3±1,8	37,5±2,48	37,1±3,36	5,9	**0,003**
Birth weight (gr)	3089,04±504,06	3012,02±652,24	2848,67±748,69	2,33	0,09
P(1^{st}) (mg/dL)	9,81±3,98	6,19±1,37	6,3±1,24	1,77	0,17
Ca (1^{st}) (mg/dL)	9,71±6,58	8,9±1,65	9,6±1,88	3,18	**0,042**
ALP(1^{st}) (ıu/l)	264,35±236,45	239,89±140,65	241,04±111,79	0,94	0,38
PTH (1^{st}) (pg/dL)	70,69±70,42	65,59±64,55	39,05±30,90	3,1	**0,044**
25-OHD (1^{st}) (ng/ml)	3,26±1,34	10,37±3,68	23,07±2,2	616	**<0,01**
P (2^{nd}) (mg/dL)	6,05±1,47	5,99±1,27	5,56±1,06	1,66	0,192
Ca(2^{nd}) (mg/dL)	9,92±0,86	10,14±5,24	9,94±0,75	0,09	0,91
ALP (2^{nd}) (ıu/l)	294,74±114,06	283,21±146,06	279,68±108,51	0,19	0,8
PTH (2^{nd}) (pg/dL)	40,06±35,37	48,7±42,05	52,65±33,20	0,54	0,58
25-OHD (2^{nd}) (ng/ml)	29,21±15,32	33,89±29,64	46,95±40,32	2,09	0,12
P (mother) (mg/dL)	4,46±0,59	4±0,81	4,3±0,33	1,71	0,87
Ca (mother) (mg/dL)	8,88±0,56	8,68±0,61	9,1±0,52	0,84	0,43
ALP (mother) (ıu/l)	148,4±62,19	126,09±44,18	95,12±38,13	3,36	**0,03**
PTH (mother) (pg/dL)	113,81±96,32	98,78±55,81	56,95±17,83	0,46	0,63
25-OHD (mother) (ng/ml)	5,6±2,96	10,77±5,19	12,14±9,33	14,1	**<0,01**
NICU stay, day	11,7± 3,58	15,11±5,39	20,77±4,29	1,56	0,21

25-OHD :25- hydroxycholecalciferol, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, PTH: parathormone, NICU: Neonatal intensive care unit.

Discussion

Vitamin D deficiency is a significant health problem worldwide. 25-OHD deficiency during pregnancy has been found to be associated with an increased incidence of adverse fetal and maternal outcomes, particularly gestational diabetes, preeclampsia, preterm births, and low birth weight [13–15]. For these reasons, 25-OHD levels are also important for newborns.

In Turkey, in accordance with a program initiated by the Ministry of Health in 2011, it is recommended that pregnant women be given 1200 IU (30 mcg; nine drops) of 25-OHD support daily from the twelfth week of pregnancy and that the support should be continued until the end of the sixth month after delivery [16,17]. However, studies from Turkey have shown that compliance with this program is low [2]. A thesis study showed that only 33.3% of pregnant women used 25-OHD supplements during pregnancy [18]. Only 13.7% of the pregnant women in our study received 25-OHD supplementation during pregnancy. This rate was even lower than the national average, and it was thought that this might be due to the inclusion of immigrant patients in our study. Sixty-two (10.9%) newborns were immigrants.

In a recent multicenter study in Turkey, the 25-OHD level in 86.5% of newborns with hypocalcemia was about 12 ng/mL [19]. Yılmaz and colleagues reported the prevalence of severe 25-OHD deficiency as 56% in neonatal hypocalcemia cases [2]. In a 2010 study, severe 25-OHD deficiency was determined in 64.3% of newborns [20]. Although there is no clear consensus on the level of 25-OHD deficiency, the International Society of Endocrinology recommends a 25-OHD level of < 20 ng/mL as the lower limit for 25-OHD deficiency [6]. In our study, serum 25-OHD level was evaluated as < 20 ng/mL deficiency, and <5ng/mL was classified as a severe deficiency. The serum 25-OHD levels of 112 (19.7%) of newborns with 25-OHD deficiency were <5 ng/mL, and these newborns were classified as having severe 25-OHD deficiency.

It was observed that mothers of newborns with severe 25-OHD deficiency were younger than the other groups. We speculate that young women may not use 25-OHD supplementation regularly. However, maternal serum 25-OHD levels were ≤ 12ng/mL in all groups. The lowest maternal D vitamin levels were seen in the severe deficiency group. The mean serum 25-OHD levels of all mothers in our study were 9.7±5.5 ng/mL. When compared with the study by Ergür et al., the serum 25-OHD levels of the mothers in our study were lower than those of nonpregnant women in the same age group. In addition, when we examined newborns according to groups in our study, serum 25-OHD levels of mothers in all three groups were lower than non-pregnant women in the same age group [20].

Vitamin D deficiency is correlated with the disturbance of Ca homeostasis, which results from hypocalcemia, hypophosphatemia, and elevated ALP and PTH levels. PTH elevation in response to low 25-OHD levels is uncommon in the neonatal age group [21]. Ozdemir et al. reported that they did not find any difference in Ca, P, and ALP levels between the 25-OHD deficient and insufficient groups of newborns and their mothers [22]. We found significantly higher ALP levels in mothers in the group with severe 25-OHD deficiency. In our study, the severe deficiency and deficiency groups' PTH levels were high, and the severe deficiency group had higher PTH levels. In a multicenter study conducted with late neonatal hypocalcemia cases; PTH levels were found to increase in only 45.8% of newborns at the time of diagnosis [19]. PTH is required to increase Ca absorption in pregnant women. There was no statistical

difference between the PTH levels of the mothers in the three groups in our study. In a study conducted in Turkey, no significant difference was found in PTH levels between trimesters of pregnancy and among nonpregnant women in the same age group. The women in the control group in this study and the mothers in our study had a similar mean age, and the PTH levels of the mothers in the severe deficiency and deficiency groups in our study were higher than those of the nonpregnant women [23]. In addition, our study found that calcium levels were in the normal range in the patient group with 25-OHD <30 ng/mL. This made us think that 25-OHD deficiency should not be considered only in cases with neonatal hypocalcemia.

Conclusions

In our study, the prevalence of hypocalcemia was 23%. In previous studies, similar to ours, the frequency of hypocalcemia in newborn babies with 25-OHD deficiency was determined to be 18.3% (2). In newborns, 25-OHD is of increasing importance today because it has important functions in the body during the newborn period. As in all age groups, 25-OHD deficiency is seen in newborns. The main source of 25-OHD in newborn babies is maternal 25-OHD. It has been observed that 25-OHD deficiency continues to be a problem for pregnant women and their babies in Turkey, despite the introduction of a supplementation program. In our study, we wanted to emphasize the need to improve maternal 25-OHD status in order to support maternal and infant health.

Funding: *The authors received no financial support for the research, authorship, and/or publication of this article.*

Conflict of interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *This study was ethically approved by the ethics committee of the Dr. Sami Ulus Obstetrics, Child Health and Diseases Training and Research Hospital (No. E-21/04-157).*

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