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Association between umbilical cord vitamin D levels and adverse neonatal outcomes

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Abstract

Objective: We investigated the associations between cord blood concentration of 25-hydroxyvitamin D [25(OH)D], neonatal outcomes, and the risk of hospitalization during the first year of life.
Methods: A total of 402 newborn infants and their mothers were prospectively enrolled and divided in four groups according to season of the year. We determined 25(OH)D serum concentrations from maternal–neonatal pairs at delivery by electrochemiluminescence immunoassay. Cut-offs at 25, 50, and 75 nmol/L defined vitamin D status, corresponding to deficiency, insufficiency, and sufficiency, respectively. Crude odds ratio (cOR) and 95% confidence intervals (CI) were estimated using logistic regression.
Results: Vitamin D severe deficiency (i.e., <25 nmol/L) was present in 18% of newborns. Cord blood severe deficiency was associated with an increased risk of preterm birth (cOR 3.6, 95% CI: 1.1–12.2), neonatal respiratory distress syndrome (cOR 5.9, 95% CI: 1.1–33.2), and increased risk of hospitalization during the first year of life because of acute respiratory infection (cOR 3.9, 95% CI: 1.4–10.6) or acute gastroenterocolitis (cOR 5.2, 95% CI: 1.4–19.1).
Conclusion: Cord blood vitamin D deficiency is associated with increased risk of preterm birth, neonatal respiratory distress syndrome, and hospitalization during the first year of life.

Keywords

25-Hydroxyvitamin D, cord blood, vitamin D deficiency, neonatal outcome, respiratory infection, gastroenterocolitis

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Introduction

The role of vitamin D beyond its classical function in bone and muscle health has been of increasing interest in recent years. A significant amount of research has shown a potential impact of vitamin D deficiency in pregnant women on maternal, fetal, and neonatal health. The findings from several studies suggest an increasing prevalence of vitamin D deficiency in pregnancy and associated adverse maternal and fetal outcomes, such as gestational diabetes mellitus, preeclampsia, small for gestational age (SGA) and preterm births, among others.[1–3] Although some of the studies found improvement in pregnancy outcomes with vitamin D supplementation, others have not shown any association.[2,4,5] The primary reason for no improvement in pregnancy outcomes with vitamin D supplementation is that trials were based on vitamin D doses, not baseline and achieved 25-hydroxyvitamin D [25(OH)D] levels.[3,6–8]

Vitamin D cord blood status is directly dependent on maternal levels of 25(OH)D.[9–12] Several maternal risk factors contribute to low maternal–fetal 25(OH)D concentrations.[13] Vitamin D insufficiency in the mother results in neonatal insufficiency, which may negatively affect the anthropometric parameters in the neonate, skeletal health, the immune system, and neurological development, and might increase the risk of asthma and type 1 diabetes in later life.[2,12,14,15] Based on the potent immunomodulatory effect of vitamin D, several studies have linked maternal vitamin D deficiency to an increased risk of respiratory tract infections in infants, but only a few studies have examined cord blood vitamin D status.[2,12,16,17]

There is no consensus regarding the optimal level of 25(OH)D in pregnant women or neonates. The US Institute of Medicine defines 25(OH)D levels of 50 nmol/L as adequate,[18] whereas others advocate a threshold of 75 nmol/L[19] and up to 100 nmol/L as optimal during pregnancy.[20] Recently developed recommendations define vitamin D deficiency and insufficiency as <30 and 30 to 50 nmol/L, respectively.[21] Because of the lack of consensus in the literature, more studies are needed to establish the exact 25(OH)D level that can be deemed sufficient for improved maternal and neonatal health.

We published our own data recently that showed a high prevalence of vitamin D deficiency among pregnant women at the time of delivery in Slovenia, especially in the months following autumn and winter and in those who did not take supplements containing vitamin D.[22] The aim of this study was to analyze, in a maternal–infant cohort, the association between cord blood concentration of 25(OH)D and neonatal outcomes as well as risk of hospitalization during the first year of life related to different levels of 25(OH)D.

Material and methods

Study design

Data were analyzed from a population-based prospective birth cohort study, conducted in the Department of Perinatology, Maribor University Medical Centre, Slovenia, in September 2013, December 2013, March 2014, and June 2014. September was the month chosen for the summer group, December for the autumn group, March for the winter group, and June for the spring group, as these are the months at the end of four temperature seasons in the continental climate that prevails in this region.

The study was approved by our institution's ethics committee (No. 138/13, April 19, 2013). Written informed consent was obtained from all participants.

Study population

The participants were consecutive Caucasian pregnant women who were admitted for delivery in the selected months and signed informed consent. Exclusion criteria were the presence of chronic renal disease, bone disease, or any kind of malabsorption syndrome. Mothers and neonates for whom we had no data on 25(OH)D serum concentrations were excluded (Figure 1). At admission, patients received a questionnaire on their lifestyle during pregnancy, including dietary habits, intake of nutritional supplements, and sunbathing. Vitamin D supplementation is not yet routinely recommended to pregnant women in Slovenia and it is an individual choice. At the time of the study, the only commercially available nutritional supplement for pregnant women contains 400 IU of vitamin D in one daily pill. Analyzed data obtained from the questionnaire were presented in our previous publication.[22] Information about complications or illnesses during pregnancy, anthropometric parameters, and health status of newborn at birth, as well as follow-up data in case of infant's hospitalization during the first

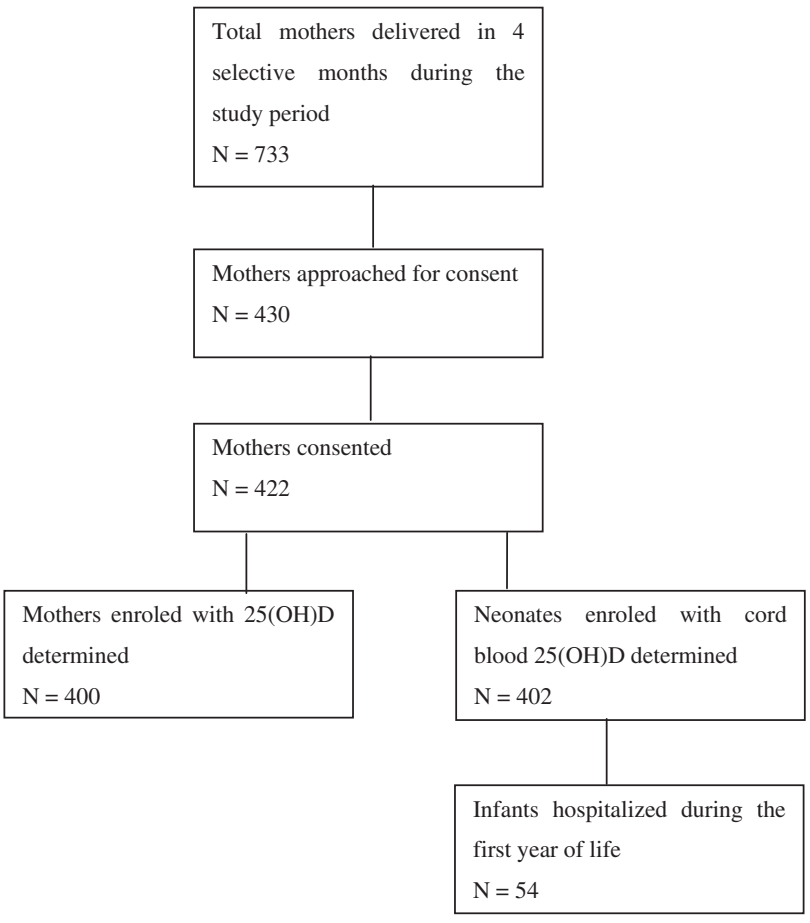

Figure 1. Flowchart showing the recruitment of study population.

year of life, were obtained from hospital records. Information about an infant's hospitalization was verified by telephone call with the mother 2 years after enrollment. All reasons for hospitalization were grouped in four categories: acute lower respiratory tract infection (ARI), acute gastroenterocolitis (GAE), allergic etiology, and others.

Sample analysis

A venous blood sample from each participating woman and from the umbilical vein of her neonate was taken at delivery to determine 25(OH)D concentration. Samples were immediately delivered to the hospital laboratory, and 25(OH)D concentrations were measured using an electrochemiluminescence immunoassay on the Cobas e 601 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Precision and accuracy of the test were performed in accordance with Clinical and Laboratory Standards Institute (CLSI) Protocol EP-15-12. PreciControl Varia Control Material (PC-V; Roche Diagnostics) and pooled serum samples were used. The values (coefficient of variation; CV) for precision were 11%, 8%, and 8%, respectively, for PC-V (levels 1, 2 and 3) and 11%, 5%, and 5%, respectively, for pooled sera (levels 1, 2 and 3). For accuracy, we determined mean relative bias of 1%, −3%, and 4% for PC-V Control Material levels 1, 2, and 3, respectively. The target values for 25(OH)D in PreciControl Varia 1, 2, and 3 were 44, 71, and 85 nmol/L, respectively. Vitamin D status was divided into four categories in accordance with the literature: >75 nmol/L (optimal concentration), 50 to 75 nmol/L (insufficiency), 25 to 50 nmol/L (deficiency), and <25 nmol/L (severe deficiency).[19]

Statistical analysis

Data were processed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). The results are presented as means ± standard deviation or by frequencies and percentages. ANOVA and the chi-square test were used for comparisons between groups. Pearson correlation coefficient was used to determine the strength of correlation between vitamin D concentrations in pregnant women and neonates. The association between cord blood 25 (OH)D levels and covariates was evaluated with logistic regression analysis. A p-value of <0.05 was considered statistically significant.

A total of 400 subjects was calculated to have >90% power to detect a significant association for logistic regression (using α of 0.05, medium odds ratio of about 2.5 to 1, and a minimum event proportion of 3%).[23,24] We calculated that 400 subjects would have >95% power to detect a significant association for one-way ANOVA (using α of 0.05, medium effect size of 0.25, and 4 groups).[25]

Results

A total of 400 pregnant women (i.e., 100 from each temperature season) and their 402 neonates (2 pairs of twins) were included in the study. Maternal and neonatal characteristics are presented in Table 1.

The average 25(OH)D concentration in women at delivery was 43 ± 24 nmol/L (range 5–166 nmol/L). Mean cord blood 25 (OH)D concentration was 56 ± 31 nmol/L (range 8–176 nmol/L). As expected, strong seasonal variation was observed in 25(OH) D concentrations in mothers and their babies (Figure 2). The average cord blood 25(OH)D concentration was significantly higher in the September (74 ± 33 nmol/L) and June (60 ± 30 nmol/L) groups compared with the December (53 ± 27 nmol/L) and March (37 ± 23 nmol/L) groups ($p < 0.001$). Cord blood 25(OH)D concentrations correlated strongly with maternal levels (September: $r = 0.8$, $p < 0.001$;

Table 1. Maternal and neonatal characteristics by season of birth (summer, fall, winter, and spring for September, December, March, and June births, respectively).

	Sep 2013		Dec 2013		Mar 2014		Jun 2014		
Maternal	n = 100	%	n = 100	%	n = 100	%	n = 100	%	p-value
Age, years (mean ± SD)	29 ± 4		29 ± 5		30 ± 5		30 ± 5		0.33
Gravidity									0.70
1	52	52	52	52	51	51	39	39	
2	30	30	34	34	31	31	35	35	
>2	18	18	14	14	18	18	26	26	
Cesarean section	9	9	4	4	13	13	11	11	0.15
GDM									0.44
On diet	13	13	6	6	5	5	7	7	
On insulin	5	5	4	4	5	5	6	6	
Hypertension	8	8	8	8	5	5	5	5	0.13
VitD suppl.	36	36	36	36	44	44	37	37	0.65
Neonatal	n = 101	%	n = 100	%	n = 101	%	n = 100	%	
Male sex	44	44	52	52	47	47	51	51	0.52
Birth weight, g (mean ± SD)	3340 ± 500		3370 ± 470		3300 ± 540		3290 ± 440		0.61
GA, weeks (mean ± SD)	39 ± 1		39 ± 1		39 ± 2		39 ± 1		0.16
BW for GA									0.93
AGA	83	82	84	84	83	82	86	86	
SGA	9	9	7	7	11	11	9	9	
LGA	9	9	9	9	7	7	5	5	
Preterm birth	1	1	8	8	7	7	6	6	0.13
Hyperbilirubinemia	19	19	19	19	15	15	16	16	0.72
Infections	7	7	5	5	6	6	11	11	0.42
Minor anomaly	9	9	7	7	9	9	8	8	0.98

Significance of maternal age, birth weight, and gestational age was assessed by ANOVA; significance of all other variables was assessed by chi-square test.

GDM, gestational diabetes mellitus; vitD suppl., vitamin D supplementation; BW, birth weight; GA, gestational age; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age.

December: $r = 0.7$, $p < 0.001$; March: $r = 0.8$, $p < 0.001$; June: $r = 0.9$, $p < 0.001$). The average 25(OH)D concentration in cord blood was significantly higher than that in the corresponding maternal blood at delivery ($p < 0.001$); on average, serum cord blood 25(OH)D concentration was 128% of maternal 25(OH)D concentration. Crude linear regression showed that a 1-nmol/L increase in maternal concentration increased cord blood 25(OH)D concentration by 1.2 nmol/L (95% CI 1.2–1.3, $p < 0.001$).

Only 52% of newborns and 34% of their mothers were classified as having "sufficient" 25(OH)D (>50 nmol/L). Optimal 25(OH)D concentration (>75 nmol/L) was observed in 25% of newborns and only 10% of their mothers. Baseline characteristics of the study population by 25(OH)D cut points (deficiency/insufficiency/sufficiency) in accordance with season are presented in Table 2.

The neonates did not significantly differ in basic characteristics (sex, weight, length, head circumference, gestational age) or health status (incidence of low birth weight, jaundice, perinatal infections, anomalies, bone fractures, and hip dysplasia). None of these categories or any other

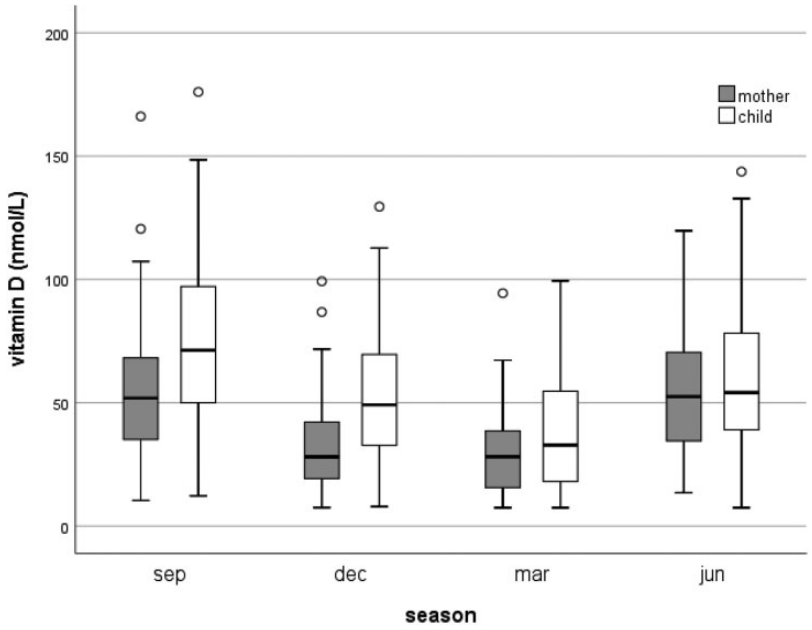

Figure 2. Box and whisker plots of vitamin D concentrations in mother–newborn blood sets in accordance with season (September, December, March, and June). The line and the box represent the medians and interquartile ranges, respectively; the whiskers indicate the range of values; and circles indicate outliers.

Table 2. Distribution of vitamin D concentrations in maternal and cord blood by season [n (%)].

	Sep 2013 n = 101 (%)		Dec 2013 n = 100 (%)		Mar 2014 n = 101 (%)		Jun 2014 n = 100 (%)	
Vitamin D	Mother	Child	Mother	Child	Mother	Child	Mother	Child
<25 nmol/L (severely deficient)	10 (10)	6 (6)	42 (42)	18 (18)	43 (42)	39 (39)	9 (9)	11 (11)
25–50 nmol/L (deficient)	38 (38)	20 (20)	40 (40)	33 (33)	47 (47)	33 (33)	35 (35)	32 (32)
50–75 nmol/L (insufficient)	38 (38)	28 (28)	16 (16)	27 (27)	10 (10)	23 (23)	35 (35)	30 (30)
>75 nmol/L (optimal)	15 (15)	47 (47)	2 (2)	22 (22)	1 (1)	6 (6)	21 (21)	27 (27)

neonatal morbidity were associated with 25(OH)D concentrations except preterm birth ($p < 0.001$) and neonatal respiratory distress syndrome (RDS) ($p = 0.02$). Maternal age was not associated with 25 (OH)D concentration.

The association between cord blood 25 (OH)D concentration and neonatal outcomes, including risk of hospitalization during the first year of life is presented in forest plots as crude odds ratio (calculated with reference to 25(OH)D >50 nmol/L). A significant association was observed between cord blood 25(OH)D <25 nmol/L and preterm birth, neonatal RDS, and risk for hospitalization during the first year of life because of ARI and GAE (Figure 3). In all, 13% of infants had one or more episodes of hospitalization during the first year of life (7% of all infants were hospitalized for ARI, 4% for GAE, 1.7% for allergic etiology, and 0.8% for other reasons).

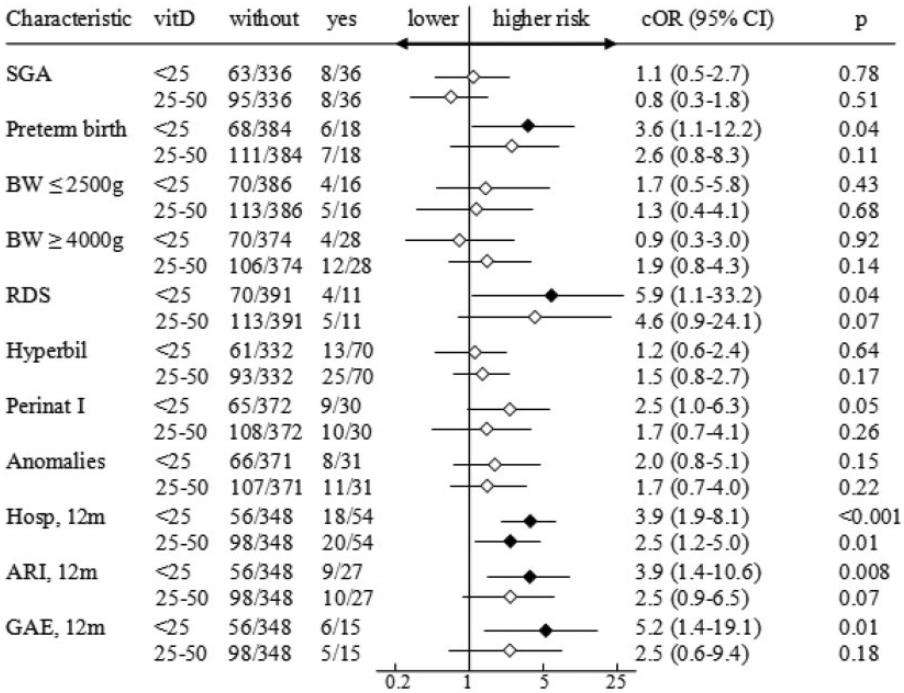

Figure 3. Forest plot of association between cord blood 25(OH)D concentration (in nmol/L) and neonatal outcomes and risk of hospitalization during the first 12 months of life.
SGA, small for gestational age; BW, birth weight; RDS, neonatal respiratory distress syndrome; Hyperbil, hyperbilirubinemia; Perinat I, perinatal infection; Hosp, 12m, hospitalization during the first 12 months of life; ARI, acute respiratory infection; GAE, gastroenterocolitis; vitD, vitamin D (nmol/L); cOR, crude odds ratio (calculated in reference to vitamin D > 50 nmol/L); 95% CI, 95% confidence interval.

Discussion

In our prospective cohort, we found that 48% of newborn infants and 66% of their mothers at the time of delivery were classified as having "deficient" 25(OH)D (<50 nmol/L) in our study. Severe 25(OH)D deficiency (<25 nmol/L) was observed in 18% of newborns and 26% of their mothers. A high prevalence of vitamin D deficiency, especially among vitamin D-unsupplemented pregnant women at delivery in Slovenia, and a marked seasonal effect, was reported recently.[22] Several studies worldwide have evaluated vitamin D status in cord blood[9–12] and have shown a high prevalence of vitamin D deficiency among newborns, ranging from 28% in Poland to over 80% in Germany and Thailand.[5,26–29]

Maternal and cord blood 25(OH)D values correlated strongly in our study. We observed a marked seasonal effect on both maternal and cord blood 25(OH)D levels. On average, cord 25(OH)D values were approximately 25% higher than maternal values, which is consistent with other studies.[27,28] The most similar results were reported recently by Wierzejska et al.,[26] who reported cord values 40% higher than maternal values. However, reverse significant correlations (i.e., lower cord blood values than maternal values) have also been reported,[5,9,11,30] as well as maternal 25(OH)D levels equal to cord levels.[29]

We further evaluated the potential effect of cord blood 25(OH)D deficiency on neonatal outcomes. We found no relationship between any of the investigated neonatal anthropometric parameters at birth and cord 25(OH)D levels. Agarwal found, in a critical review, a positive correlation between maternal 25(OH)D levels and neonatal birth weight (BW).[2] Studies on the association of cord blood 25(OH)D level and BW are sparse. Wierzejska et al.[26] reported no relationship between cord 25 (OH)D levels and neonatal anthropometric measurements, whereas Morgan et al.[31] found an association between BW and 25 (OH)D levels <50 nmol/L. Higher cord blood levels of 25(OH)D were found in neonates of vitamin D-supplemented women, and the neonates had higher BW, head circumference, and increased length compared with those of unsupplemented mothers.[4,32] Interestingly, Lykkedegn et al. demonstrated a U-shaped association between BW and cord blood 25(OH)D concentration in their univariate analysis. After controlling for maternal body mass index at birth and other confounders, no inverse associations persisted and the significant association with BW persisted above the median.[5] Our study similarly showed the lowest risk for SGA newborns when the cord blood level of 25(OH)D was 25 to 50 nmol/L, but increased odds of SGA at <25 nmol/L and 50 to 75 nmol/L relative to >75 nmol/L; however, these results did not reach statistical significance.

Moreover, our results suggested that cord blood 25(OH)D <25 nmol/L was associated with an almost four-fold increase in risk of preterm birth and almost six-fold increase in risk of neonatal RDS relative to cord blood 25(OH)D >50 nmol/L. Vitamin D freely crosses the placenta during pregnancy, and neonatal levels at birth depend entirely on maternal levels.[33] Transplacental transfer occurs mainly in the third trimester; therefore, preterm infants are at increased risk of vitamin D deficiency.[34] In contrast to our findings, Hossain et al.[35] found the opposite effect, where higher cord vitamin D status was significantly associated with shorter gestational periods, and Morgan et al.,[31] in their case–control study, found no association between cord 25(OH)D level and preterm birth. Wagner et al.[36] reported that maternal vitamin D status closest to delivery was most significantly associated with preterm birth, but they did not compare preterm birth with cord blood 25(OH)D levels. Similarly, all premature babies from our study were born near term (34 to 36 weeks of gestation) and had significantly lower cord blood 25(OH)D levels than term newborns. However, a recent meta-analysis showed no significant effect of vitamin D supplementation during pregnancy on the prevention of preterm deliveries.[37] Although the effect of vitamin D on immune function and inflammatory response could reduce the risk of preterm birth, many other factors may play a role and have not yet been clearly defined.

There is a paucity of data assessing the association between cord vitamin D status at birth and incidence of neonatal RDS. Animal and human studies have verified the importance of vitamin D in lung development and maturation, achieved lung volume, and surfactant synthesis.[38,39]

In addition to anthropometric parameters of the newborns, we did not find correlations between cord 25(OH)D levels and the occurrence of any other neonatal morbidity. However, these findings might be due to the small number of cases and low incidence in our cross-sectional study.

Our findings indicate that vitamin D deficiency at birth is associated with increased risk of hospitalization during the first year of life. Significant associations were observed between cord blood levels of 25(OH)D <25 nmol/L and increased risk of hospitalization because of ARI

(four-fold increase) and GAE (five-fold increase). Our results are in accordance with the increasing number of studies that support the protective effect of vitamin D on ARI in infants, based on the immunomodulatory effect of vitamin D.[2,16,17] Prospective studies that related vitamin D status in cord blood to subsequent risk of ARI are sparse. Belderbos et al.[40] reported a six-fold increase in respiratory syncytial virus (RSV)-associated ARI in deficient newborns during the first year of life compared with our almost four-fold increase in those infants with cord blood 25(OH)D <25 nmol/L. In 27 cases with ARI in our study, only 70% had confirmed RSV infections. Luczynska et al.[17] found a three-fold increase in risk of ARI in infants born in fall with deficiency cord levels 25(OH)D <25 nmol/L, particularly in infants born to mothers without allergy. Allergy status at mothers was not explored in our study. We did not find a comparative study to our findings of very high risk for GAE during the first year in infants with cord vitamin D deficiency. Hospitalizations for allergic etiology were only 1.7% of cases in our cohort and therefore they were not included in risk calculations.

Our study has several limitations. We included consecutive women admitted for delivery and their newborns with the aim of obtaining a homogeneous sample in accordance with season of delivery. This meant that the number of different neonatal complications was too small to detect correlations between complications and cord 25(OH)D levels, except for preterm birth and RDS. A further important limitation of the study was the cross-sectional approach and the lack of a control group. A general limitation of studies on vitamin D metabolites exists because of method-related differences in measuring 25(OH)D. Even with the same method of collection and analysis of cord blood and maternal blood, results from different studies have shown different and even opposite relationships between maternal and neonatal concentrations of 25(OH)D. The time window between collecting the maternal and cord blood samples might be important. A better explanation of these contrasting outcomes and a further evaluation of the relationship between maternal and cord blood values are necessary.

The main strengths of our study were its prospective design, the use of outcomes diagnosed by a physician, and a large enough sample size to allow analysis of cord vitamin D status by season. Slovenian infants routinely receive vitamin D supplementation in the first year of life (400 IU/day) and probably have higher 25 (OH)D levels compared with later in life. This might attenuate the association between cord blood vitamin D level and risk of hospitalization during the first year of life.

In summary, cord blood hypovitaminosis D classified by 25(OH)D levels <50 nmol/L was present in 48% of newborn infants overall, with significant seasonal variation. Our findings provide further evidence for the association between cord vitamin D deficiency and risk of preterm birth and neonatal RDS, as well as higher risk of hospitalization during the first year of life due to ARI and GAE. Further investigation of the relationship between cord vitamin D status and the risk of adverse neonatal outcomes is required, and optimal cut-offs for these outcomes should be elucidated.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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