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ORIGINAL ARTICLE

Lower vitamin D levels are associated with increased risk of early-onset neonatal sepsis in term infants

M Cetinkaya[1], F Cekmez[2], G Buyukkale[1], T Erener-Ercan[1], F Demir[1], T Tunc[2], FN Aydın[3] and G Aydemir[2]

OBJECTIVE: To evaluate the effect of vitamin D levels on early-onset sepsis (EOS) in term infants.
STUDY DESIGN: Fifty term infants with clinical and laboratory findings of EOS (study group) and 50 healthy infants with no signs of clinical/laboratory infection (control group) were enrolled. Blood was drawn at the time of admission during the first 3 postnatal days of life in both groups for measurement of 25-hydroxyvitamin D (25-OHD) levels.
RESULT: Maternal and neonatal 25-OHD levels (22.2/8.6 ng ml^{-1}, respectively) in the study group were significantly lower than those of the control group (36.2/19 ng ml^{-1}, respectively, $P < 0.001$). A positive correlation was detected between maternal and neonatal 25-OHD levels. Severe vitamin D deficiency was significantly more common in the sepsis group.
CONCLUSION: Lower maternal and neonatal 25-OHD levels are associated with EOS. These data suggest that adequate vitamin D supplementation during pregnancy may be helpful to prevent EOS in term neonates.

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INTRODUCTION

Neonatal sepsis is characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life and is an important cause of morbidity and mortality.[1,2] The incidence of neonatal sepsis varies between 1 and 8 neonates per 1000 live births.[3] It is estimated to cause almost 1 million deaths that accounts for more than 25% of neonatal deaths worldwide.[4] Neonatal sepsis may be classified into three groups: early-, late- and very late-onset sepsis.[3]

Early-onset sepsis (EOS) is generally associated with the acquisition of microorganisms from the mother and usually presents with respiratory distress and pneumonia.[1,5] Prematurity, low birth weight, foul smelling and/or meconium-stained liquor, premature rupture of membranes, prolonged labor and perinatal asphyxia constitute the main risk factors for EOS.[1,6]

Vitamin D is a fat-soluble steroid hormone that contributes to the maintenance of normal calcium homeostasis and skeletal mineralization.[7] Vitamin D also has immunomodulatory effects on immune function.[8] It was suggested that it might have a role in the optimal functioning of the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils and macrophages.[8,9] Newborns are more susceptible to infections as both innate and adaptive immune systems are not entirely developed. The relationship between vitamin D deficiency and infections, especially lower respiratory tract infections (RTIs), has been demonstrated in children and newborns.[10–13] Low cord blood 25-hydroxyvitamin D (25-OHD) levels in healthy newborns were found to be associated with an increased risk of developing respiratory syncytial virus infections during infancy.[14] Although some studies reported a link between vitamin D deficiency and critical illness in adults, a direct relationship has not as yet been shown.[9] To the best of our knowledge, no study evaluated the association between EOS and maternal/neonatal vitamin D levels.

The objective of this prospective study was to determine the possible role of maternal and neonatal plasma vitamin D levels on EOS development in term infants. We also aimed to evaluate the possible effect of the severity of vitamin D deficiency on EOS development in the study population.

METHODS

This prospective study was performed in term infants with clinical and laboratory findings of EOS who were >37 weeks of gestational age and were admitted to Neonatal Care Unit of Kanuni Sultan Suleyman Training and Research Hospital between March 2012 and December 2012. During the study period, a total of 394 term infants were hospitalized and enrolled in the study. From these, a total of 76 term infants were diagnosed as having a probability of EOS according to the criteria defined by Gitto *et al.* (Table 1).[15] However, 26 of them were excluded due to the following criteria: infants with maternal risk factors, such as clinical and/or histological chorioamnionitis and premature rupture of membrane, which may be predisposing factors for development of EOS; infants with probable or possible sepsis according to criteria, refusal of parental consent, lack of laboratory data and major congenital abnormalities. The study protocol was approved by the local Ethics Committee. Informed parental consent was obtained for all infants. Figure 1 shows the flow diagram of participants in the study.

The study group consisted of term neonates who were clinically suspected to have an early infection within the first 3 postnatal days of life. Blood for neonatal and maternal vitamin D levels were obtained from all infants and their mothers at the postpartum period at the time of hospital admission. Although these samples were obtained from all infants with the suspicion of EOS within 72 h of life, only infants with high probable sepsis consisted the study group. The healthy infants who were admitted to our outpatient clinic for routine evaluation at postnatal day 3 with no signs of clinical and laboratory infection and evaluated for hyperbilirubinemia were referred to as the control group. The control group consisted of term infants with the same gestational and postnatal age of the infants who were in the study group. Analyses of 25-OHD levels in control group were

[1]Department of Neonatology, Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey; [2]Gulhane Military Medical Faculty, Department of Neonatology, Istanbul, Turkey and [3]Gulhane Military Medical Faculty, Department of Biochemistry, Istanbul, Turkey. Correspondence: Dr M Cetinkaya, Department of Neonatology, Kanuni Sultan Suleyman Training and Research Hospital, Turgut Ozal Bulvarı No:1, Halkalı/Küçükçekmece/İSTANBUL, Istanbul 16059, Turkey.
E-mail: drmerih@yahoo.com
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Table 1. The sepsis criteria used in the study defined by Gitto *et al*.[15]

Groups	*Criteria*
Highly probable sepsis	At least three sepsis-related clinical signs[a] CRP >1 mg dl^{-1} At least two other altered serum parameters in addition to CRP[b] Blood culture; positive or negative
Probable sepsis	Less than 3 sepsis-related clinical signs[a] CRP >1 mg dl^{-1} At least two other altered serum parameters in addition to CRP Blood culture; negative
Possible sepsis	Less than 3 sepsis-related clinical signs[a] CRP <1 mg dl^{-1} Less than 2 other altered serum parameters Blood culture; negative
No sepsis	No sepsis-related clinical signs[a] CRP <1 mg dl^{-1} No altered serum parameters Blood culture; negative

[a]Sepsis-related clinical signs: temperature instability, apnea, need for supplemented oxygen, need for ventilation, tachycardia/bradycardia, hypotension, feeding intolerance, abdominal distension, necrotizing enterocolitis. [b]Serum parameters other than C-reactive protein (CRP): white blood cell count, absolute neutrophil count, platelet count.

performed from the same blood sample that was used for bilirubin detection at postnatal day 3.

The maternal demographic features including age, educational level, socioeconomic status, presence of disease, mother's head cover status were all recorded. Gestational age, birth weight, sex, mode of delivery, Apgar scores, birth season of all infants were also recorded. Season of birth was classified into three groups during the study period: spring (March, April, May), summer (June, July, August) and fall (September, October, November). Maternal vitamin D supplementation was classified in terms of usage: no usage, insufficient usage (total usage <3 months), regular usage (total usage >3 months).[13] In Turkey, multivitamin supplement including 500 IU vitamin D has been prescribed routinely to all pregnant women. Vitamin D deficiency was staged as severe deficiency (serum 25-OHD <10 ng ml^{-1}), insufficiency (serum 25-OHD between 11 and 32 ng ml)$^{-1}$ and adequate (serum 25-OHD between 32 and 100 ng ml^{-1}).[16]

A septic screen including total leukocyte count, absolute neutrophil count, immature to total neutrophil count, blood smear evaluation and C-reactive protein (CRP) were performed in all neonates with suspected sepsis to corroborate EOS diagnosis. Blood samples for whole blood count, CRP and culture were obtained before initiating antimicrobial therapy. This procedure was repeated at 48 h, 7 days and 10 days. Changes in hematologic parameters were processed according to the Manroe and Rodwell scoring systems.[17,18]

Infants were treated with appropriate antibiotic therapies including ampicillin in combination with gentamicin for the first-line therapy of EOS. Neonates with positive cultures were treated with antibiotics according to the culture antibiogram. The antimicrobial therapy was stopped after clinical and laboratory improvement.

Plasmas of both maternal and neonatal blood samples were separated and stored at − 80 °C. Levels of 25-OHD were determined using Shimadzu LC-20AT model High Performance Liquid Chromatography (HPLC) system (Shimadzu Scientific Instruments, SSI Kyoto, Japan) attached with a ultraviolet detector at Biochemistry Laboratory of Gulhane Military Medical Faculty.

Whole blood count, CRP and cultures were studied immediately. Whole blood count was performed using an automatic counter, Cell Dyn 3700 (Abbott Diagnostics Division, IL, USA). CRP was determined by an immunonephelometric method using BN II device (Dade Behring Marburg GMBH, Marburg, Germany). The detection limit for CRP was 5 mg l^{-1}. Blood cultures were analyzed using fully automatic BACTEC method by BACTEC 9240 device (Becton Dickinson, Heidelberg, Germany).

Data were analyzed using SPSS software (SPSS, version 16.0, Chicago, IL, USA). Descriptive statistics were given as mean ± standard deviation (mean ± s.d.) for continuous data with normal distribution, median and interquartile range (median (IQR)) for continuous data with non-normal distribution and frequencies and percentages for quantitative data. The differences between groups were evaluated using X^2 tests for qualitative data and *t*-test for independent sample for continuous data with normal distribution and Mann–Whitney *U*-test for continuous data with non-normal distribution. Two-way analysis of variance was used to indicate interaction between season and group. Pearson correlation was used to evaluate the relation between maternal and neonatal 25-OHD. Values of $P<0.05$ were considered statistically significant.

RESULTS

The study population included a total of 100 term infants. From these infants, 50 had suspected neonatal sepsis (study group) and 50 did not have any findings of sepsis (control group). Mean gestational age and birth weight of the study population were 38.9 ± 1.0 weeks and 3338 ± 472 g, respectively. A total of 55 infants (55%) were male and 40% of the study population was born via cesarean section. No significant difference was found between two groups in terms of sex, birth weight, gestational age, birth season, mode of delivery and Apgar scores (Table 2). Similarly, no significant difference was detected with respect to maternal demographic features including maternal age and perinatal co-morbidities between the two groups (Table 2). Educational status was significantly lower in the study group. In addition, the number of mothers in the study group who never and/or irregularly used vitamin supplementation was significantly higher than that in the control group ($P<0.05$; Table 2).

All infants in the study group were hospitalized with suspected sepsis due to clinical findings and laboratory findings. As expected, the white blood cell count and CRP levels of the infants in the study group were significantly higher than those in the control group ($P<0.05$; Table 2). There was no difference between the infants in the study and control groups with respect to time of blood drawing for 25-OHD ($P>0.05$). Both maternal and neonatal 25-OHD levels in the study group were significantly lower compared with those in the control group ($P<0.05$; Table 3). Both maternal and neonatal 25-OHD levels were significantly higher in summer (Table 4). Similarly, both maternal and neonatal 25-OHD levels were significantly higher with regular vitamin D supplementation during pregnancy. When the effects of season on maternal and neonatal 25-OHD levels were evaluated, although maternal 25-OHD levels of the study group were lower in all seasons compared with those of the control group, a markedly significant increase was detected in maternal 25-OHD levels in summer in the control group ($P=0.0001$). Although neonatal 25-OHD levels of the study group were lower in all seasons compared with the control group, this was not statistically significant (Table 5). A positive correlation was detected between maternal and neonatal 25-OHD levels for both groups (control group: $r=0.58$, $P=0.001$ and study group: $r=0.29$, $P=0.04$). The majority (84%) of infants in the sepsis group had a mean 25-OHD level <11 ng ml^{-1}, which was statistically significant ($P<0.05$; Table 6).

The association between the presence of vitamin D deficiency and culture-proven EOS was also evaluated. Three infants had positive blood culture for Gram-negative sepsis (2 *Escherichia coli*, 1 *Klebsiella pneumonia*) and 2 for Gram-positive sepsis (1 *Staphylococcus epidermidis*, 1 *Enterococcus faecalis*). None of them had meningitis. There were no significant differences between maternal and neonatal 25-OHD levels of infants with and without culture-proven sepsis (Table 7). As *S. epidermidis* was isolated in two separate sets of blood cultures from two different sites, it was considered as a pathogen rather than a contaminant. None of the infants died during the study period.

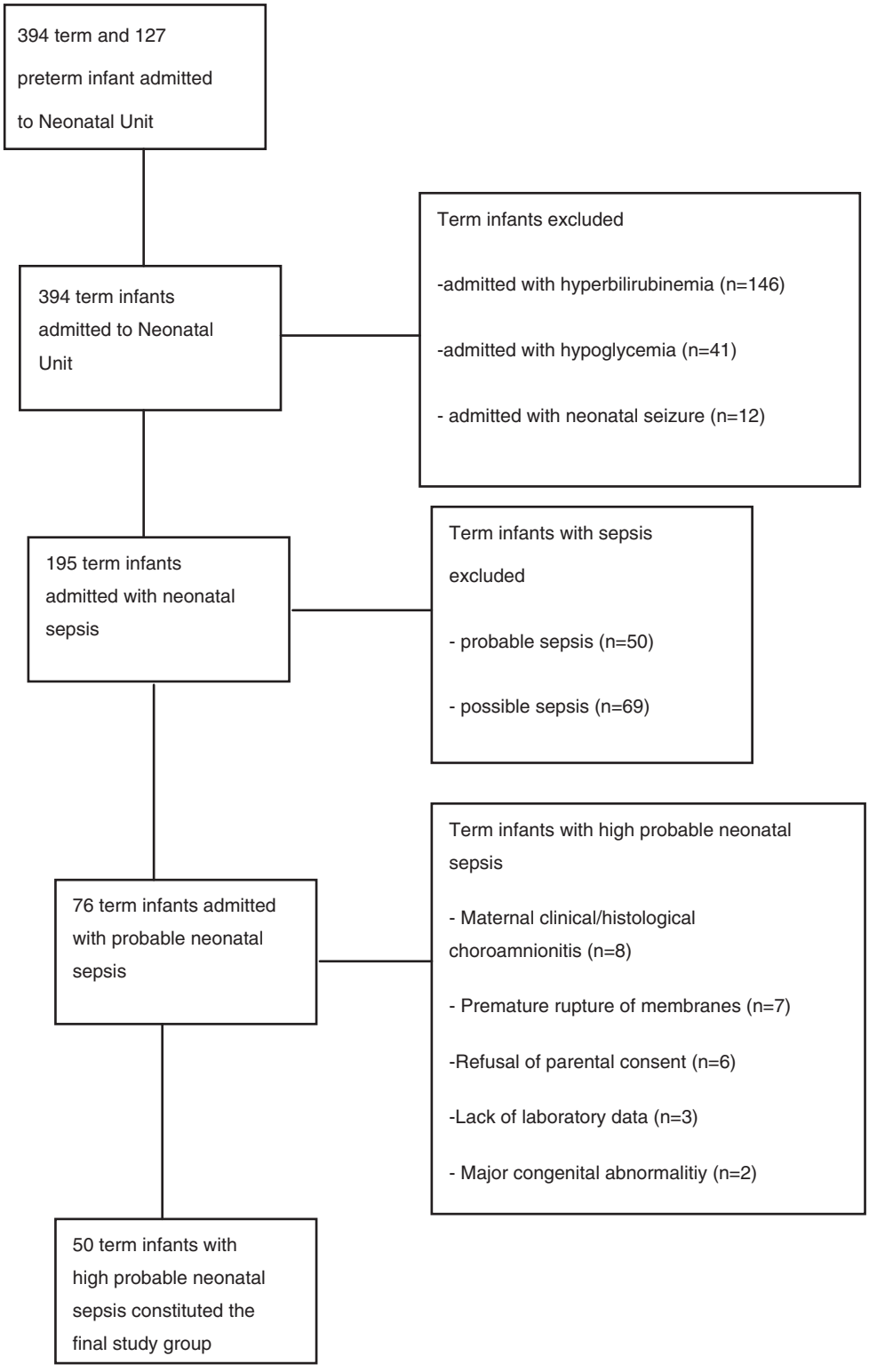

Figure 1. Flow diagram of the study group.

DISCUSSION

This study showed for the first time that maternal and neonatal 25-OHD levels were significantly lower in term infants who were admitted with EOS. Neonatal 25-OHD levels were positively correlated with maternal 25-OHD levels. Levels of 25-OHD were also higher in summer and with regular vitamin supplementation. These data suggest that regular supplementation with vitamin D during pregnancy may be helpful to prevent EOS in term neonates.

Although the incidence of EOS was reported to decrease in recent years due to the advances in both obstetrical and neonatal

Table 2. The maternal and demographic features of the study and control groups

Neonatal demographic features	*Study group*, n = *50*	*Control group*, n = *50*	P-*value*
Gestational age, mean ± s.d.	39.3 ± 0.8	38.1 ± 1.0	> 0.05
Birth weight (g), mean ± s.d.	3454 ± 460	3223 ± 460	> 0.05
Gender (male), *n* (%)	26 (52)	29 (58)	> 0.05
Cesarean section, *n* (%)	20 (40)	28 (56)	> 0.05
Apgar minute,[1] median (interquartile range, IQR)	8 (3)	7 (2)	> 0.05
Apgar minute,[5] median (IQR)	8 (2)	8 (2)	> 0.05
C-reactive protein (mg l^{-1}), mean ± s.d.	33.9 ± 5.5	3.0 ± 0.2	< 0.001
White blood cell (mm^{-3}), mean ± s.d.	17 300 ± 1300	12 000 ± 700	< 0.001
Platelet count (mm^{-3}), mean ± s.d.	209 000 ± 17 000	300 000 ± 17 000	< 0.001
Birth season, n (%)			
Spring (March to May)	12 (24)	10 (20)	
Summer (June to August)	23 (46)	24 (48)	> 0.05
Fall (September to November)	15 (30)	16 (32)	
Maternal demographic features			
Maternal age, mean ± s.d.	26.8 ± 6.6	28.4 ± 5.2	> 0.05
Perinatal co-morbidity, n (%)			
None	46 (92)	48 (96)	
Gestational diabetes	2 (4)	1(2)	> 0.05
Thyroid disease	2 (4)	1 (2)	
Maternal sun-protective clothing, *n* (%)	27 (54)	12 (24)	0.03
Maternal education status, n (%)			
No education	4 (8)	3 (6)	
Less than high school graduation	38 (76)	22 (44)	> 0.05
High school graduation	7 (14)	17 (34)	
University graduation	1 (2)	8 (16)	
Vitamin D supplementation during pregnancy, n (%)			
No usage	12 (24)	3 (6)	
Irregular usage	33 (66)	16 (32)	0.001
Regular usage	5 (10)	31 (64)	

Table 3. The comparison of maternal and neonatal 25-hydroxyvitamin D (25-OHD) levels between two groups

	Study group, n = *50*	*Control group*, n = *50*	P-*value*
Maternal 25-OHD (ng ml^{-1}), mean ± s.d.	22.2 ± 6.8	36.2 ± 1.8	< 0.001
Neonatal 25-OHD (ng ml^{-1}), mean ± s.d.	8.6 ± 3.1	19.0 ± 4.8	< 0.001

Table 4. Comparison of maternal and neonatal 25-hydroxyvitamin D (25-OHD) levels in terms of season at birth

	Spring, n = *22*	*Summer*, n = *47*	*Fall*, n = *31*	P-*value*
Maternal 25-OHD (ng ml^{-1}), mean ± s.d.	24.4 ± 7.5	37 ± 12.8	20.9 ± 6.4	0.0001,[a] 0.07,[b] 0.0001[c]
Neonatal 25-OHD (ng ml^{-1}), mean ± s.d.	12.7 ± 5.0	16.2 ± 6.9	10.9 ± 5.7	0.03,[a] 0.24,[b] 0.0001[c]

[a]Comparison of Spring with Summer. [b]Comparison of Spring with Fall. [c]Comparison of Summer with Fall.

Table 5. Comparison of maternal and neonatal 25-hydroxyvitamin D (25-OHD) levels in terms of season and group at birth

Group	*Spring*	*Summer*	*Fall*	*P-interaction (season by group)*
Maternal 25-OHD (ng ml^{-1}), mean ± s.d.				
Study	20.7 ± 5.8	25.6 ± 7.5	18.4 ± 3.8	0.0001
Control	29.0 ± 7.0	47.9 ± 4.8	23.3 ± 7.5	
Neonatal 25-OHD (ng ml^{-1}), mean ± s.d.				
Study	8.5 ± 1.0	10.6 ± 3.2	5.8 ± 1.5	0.534
Control	17.8 ± 2.0	21.7 ± 4.9	15.7 ± 3.6	

Table 6. Comparison of neonatal 25-hydroxyvitamin D (25-OHD) levels in terms of vitamin D deficiency in both groups

Neonatal 25-OHD level	*Study group*	*Control group*	P-*value*
< 11 ng ml^{-1}	42 (84)	1 (2)	0.00001
11–32 ng ml^{-1}	8 (16)	49 (98)	

care, 2 to 3% of term infants still die due to EOS.[5,19] Maternal factors including intrapartum fever, chorioamnionitis, premature rupture of membrane and Group B Streptococcus colonization have been reported as main risk factors for EOS in term

Table 7. The comparison of maternal and neonatal 25-hydroxyvitamin D (25-OHD) levels of the sepsis group in terms of culture positivity

	Culture-proven sepsis group, n = *5*	*Culture-negative sepsis group*, n = *45*	P-*value*
Maternal 25-OHD (ng ml^{-1}), mean ± s.d.	27.1 ± 8.7	21.7 ± 6.5	0.09
Neonatal 25-OHD (ng ml^{-1}), mean ± s.d.	10.1 ± 1.8	8.4 ± 3.2	0.25

neonates.[1,6,19] However, despite significant improvement in neonatal EOS risk assessment and prevention, there is still a burden in neonatal EOS in all gestational ages.

In recent years, emerging evidence supports the immunomodulatory effects of vitamin D on immune function.[8] Vitamin D was reported to have a complex effect on immune functions as it enhanced innate immunity while it also downregulated the acquired immune response. The mechanical barrier of the skin and other epithelial surfaces constitute the first barrier to infections and activated vitamin D has an important role in maintaining the integrity of epithelial cells by encoding the proteins needed for several tight junctions.[8,20] Vitamin D has an effect on induction of antimicrobial peptides like cathelicidin (LL37), beta-2 and beta-3 defensins, explaining the antibiotic action of vitamin D.[21,22] Vitamin D also affects T helper (Th) cells 1 and 2. Th2 differentiation is directly induced by vitamin D, whereas it inhibits activation and differentiation of Th1 cells.[8] Vitamin D has anti-inflammatory actions on neutrophils. In a study in which human monocytes stimulated with lipopolysaccharide and treated with 1,25-OHD showed dose-dependent decrease in TLR2 and TLR4 synthesis with an increase in CD14.[23] Vitamin D has a role in superoxide generation in monocytes by presumably increasing and prolonging the oxidative stress of monocytes.[24] It also prevents excessive production of inflammatory cytokines and facilitates neutrophil motility and phagocytosis.[25]

In addition to systemic inflammatory response modulation, vitamin D also has effects on the local control of pathogens. Vitamin D was reported to inhibit the growth of and/or killed strains of *Staphylococcus aureus, S. pyogenes, K. pneumoniae*, and *E. coli*.[25] Vitamin D also prevents direct invasion of pathogenic bacteria by enhancing the clearance of these invading organisms at sites such as respiratory tract.[25] In addition, Chinn *et al.* [26] reported that higher vitamin D levels in pregnant women were associated with a lower rate of Group B Streptococci vaginal carriage. As all cells have a specific vitamin D receptor, vitamin D acts as an immune system modulator by boosting innate immunity, the activity of monocytes and macrophages in addition to activation of B and T cells.

Although basic science and translational research data report promising beneficial effects of vitamin D on immune functions, there are limited clinical studies that evaluated its role in sepsis, especially in adults. Previous studies reported conflicting data on the role of vitamin D in the prevention and control of infections, especially those in the respiratory tract.[9] However, studies performed in neonates and infants supported the preventive role of vitamin D against respiratory tract infections. In a recent, large and long-term follow-up study, low cord blood levels of 25-OHD were found to be associated with a higher risk of RTI by the age of 3 months and a higher cumulative risk of wheezing in early childhood.[26] The cord blood vitamin D deficiency was also reported to increase the risk of respiratory syncytial virus infections during infancy.[14] In another study, subclinical vitamin D deficiency in newborns was associated with frequent development of acute RTIs.[13]

Although the role of vitamin D on development of RTIs has been evaluated in both children and adults, its role in both development and prevention of neonatal sepsis has not been investigated comprehensively. Although vitamin D had a positive modulating effect on sepsis-induced coagulation disturbances in the cecal ligation model, it was not beneficial in lipopolysaccharide-induced sepsis model.[27] In two studies investigating the prevalence of vitamin D deficiency in critically ill children admitted to the pediatric intensive care unit, a high rate of vitamin D deficiency was present among critically ill children and was associated with greater severity of critical illness.[28,29] In a multicenter observational study including 2399 adult patients, 25-OHD deficiency was associated with blood culture positivity and increased mortality.[30] However, to the best of our knowledge, no study investigated the association between neonatal sepsis and maternal/neonatal 25-OHD levels in both term and preterm infants. It was hypothesized in only two 'letters to the editor' that maternal and neonatal vitamin D supplementation in neonates might reduce sepsis risk in neonates, but data regarding the association of neonatal sepsis with blood levels of maternal and neonatal 25-OHD lacked in these publications.[31,32]

Although 25-OHD can be synthesized by the fetal kidney, neonatal vitamin D levels are primarily dependent on and correlated with the maternal vitamin D status at delivery until the infant starts to receive vitamin D from other sources.[33] In accordance, our results showed a correlation between maternal and neonatal 25-OHD levels as the latter was significantly lower in infants born to mothers with lower 25-OHD levels. In a previous study, 25-OHD levels were found to be higher in healthy infants compared with those who had acute lower respiratory infection.[13] Similarly, neonates who had no infection had significantly higher 25-OHD levels compared with those who had EOS in our study. As a result, it can be suggested that EOS may be associated with maternal and neonatal vitamin D deficiency and therefore, it may be reasonable to recommend vitamin D supplementation to all pregnant women for prevention of EOS in their infants.

Maternal skin pigmentation, use of sun-protective clothing and seasonality were all reported as main risk factors for both maternal and neonatal vitamin D deficiency.[33] In good accord, the number of mothers who preferred sun-protective clothing was significantly higher in the study group. In addition, the infants who were born in summer had significantly higher 25-OHD levels compared with those who were born in other seasons. These data show the importance of adequate epidermal vitamin D synthesis following exposure to sunlight. Vitamin D deficiency is common in pregnancy and its prevalence ranges from 18 to 84% depending on the country and local clothing customs.[34] In recent years, studies from different parts of Turkey reported severe vitamin D deficiency (25-OHD levels < 10 ng ml^{-1}) in 46 to 80% of pregnant women and nursing mothers.[18] In a study from the same region of Turkey, low maternal 25-OHD levels were found to be associated with low educational level, insufficient intake of vitamin D and covered dressing habits.[35]

Vitamin D deficiency was classified into three groups: severe deficiency (25-OHD level < 10 ng ml^{-1}), insufficiency (11 to 32 ng ml^{-1}) and adequacy (32 to 100 ng ml^{-1}).[18] Severe vitamin D deficiency was associated with increased risk of lower RTIs in infants.[13] Similarly, the number of infants with a 25-OHD level < 10 ng ml^{-1} was significantly higher in the sepsis group compared with the control group in our study. Therefore, our results show that the severity of vitamin D deficiency increased the risk of EOS in these infants. These data suggest the importance of adequate vitamin D supplementation during pregnancy.

As stated above, vitamin D status of the newborn at birth is primarily dependent on the vitamin D status of the mother during pregnancy. New data support to improve nutritional maternal vitamin D status for improving birth outcomes. Therefore, it is important to establish optimal amount of vitamin D intake to maintain adequate levels for prevention of maternal and neonatal vitamin D deficiency and subsequent adverse health effects. Current vitamin D intake recommendations during pregnancy range from 400 to 600 IU per day to 1500 to 2000 IU per day according to the Institute of Medicine report and Endocrine Society report, respectively.[36–38] Recently, two new randomized controlled studies showed that a daily intake of higher (4000 IU per day) vitamin D resulted with higher circulating 25-OHD levels in pregnant women compared with low doses (200 IU per day and 2000 IU per day).[39,40] Therefore, it was suggested that higher vitamin D supplementation might be required for prevention of hypovitaminosis D and achievement of normal circulating 25-OHD levels (40 to 60 ng ml^{-1}) during pregnancy, which would also decrease the incidence of co-morbidities of pregnancy.[41,42] A more recent study showed that lower maternal 25-OHD levels were associated with increased risk of dental caries in infants.[43] All these data suggest the role of appropriate vitamin D supplementation that leads to higher maternal 25-OHD levels during pregnancy which would subsequently have beneficial effects in prevention of both maternal and neonatal morbidities.

In conclusion, this is the first study that reports significantly lower maternal and neonatal 25-OHD levels in term infants with EOS compared with those who did not have sepsis. Neonatal 25-OHD levels were well correlated with maternal levels. The 25-OHD levels were found to be associated with seasonality, regular intake of vitamin D, socioeconomic status and dress preference of the mother. For elucidation of the exact mechanism and preventive role of vitamin D on EOS, future experimental and clinical studies are warranted. After confirmation of these data by other studies, regular vitamin D supplementation may be a routine recommendation for all pregnant women to prevent EOS in their offsprings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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