Lower Vitamin D Level as a Risk Factor for Late Onset Neonatal Sepsis: An Observational Case–Control Study

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Abstract

Objective The aim of the study is to investigate the relation of neonatal and maternal vitamin D and late-onset sepsis (LOS)

Study Design One-hundred twenty term neonates along with their mothers were enrolled in this case–control study. Sixty neonates who were admitted in the neonatal intensive care unit by LOS and had not been previously admitted for last 48 hours and did not receive antibiotics or vitamin D were enrolled as cases (sepsis) group. On the other hand, 60 healthy term neonates were referred as control group. Maternal and neonatal serum 25-OH vitamin D levels were assessed in both the cohorts.

Results Maternal and neonatal 25-OH vitamin D levels in cases (17.2 and 16.1 ng/mL, respectively) were significantly lower than in controls (22.7 and 21 ng/mL, respectively) $p = 0.001$. In the study group, the neonatal 25-OH vitamin D was negatively correlated with C-reactive protein and length of hospital stay ($r = -0.616$ and -0.596, respectively) $p < 0.001$ for both. With a cut-off value of 12.9 ng/mL, the specificity and positive predictive value of neonatal vitamin D were 83.3 and 74.4%, respectively. The odds ratio was 1.088 (95% CI = 1.034–1.144)) for LOS in vitamin D-deficient neonates.

Conclusion Neonates with higher vitamin D level are at lower risk of LOS than those with vitamin D deficiency. Maternal vitamin D correlates with neonatal vitamin D. These data suggest that maternal vitamin supplementation during pregnancy may lower the risk of LOS.

Keywords

- 25-OH vitamin D
- late-onset neonatal sepsis
- neonatal sepsis

Key Points

- Neonatal and maternal vitamin D deficiency increase risk of LOS.
- Neonatal vitamin D correlates with maternal vitamin D.
- Neonatal vitamin D is independent predictor for LOS.

Neonatal sepsis is a clinical syndrome associated with hemodynamic changes and variable clinical manifestations occurring during the first month of life and resulting from the presence of pathogenic microorganisms.[1] Neonatal sepsis is an important cause of substantial neonatal morbidity and mortality worldwide, especially in low and middle-income countries.[2] According to the age of onset, neonatal sepsis can be classified into early-onset sepsis

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(EOS) and late-onset sepsis (LOS). LOS occurs after 72 hours.[3]

Vitamin D is a fat-soluble steroid hormone, mainly responsible for the maintenance of calcium homeostasis in the body as well as the development of a healthy skeleton.[4] Vitamin D deficiency is a common health problem that affects all age groups around the world, especially those in the Middle East.[5] Despite the availability of sunlight in the Middle East, people living in these regions are frequently suffering from vitamin D insufficiency or deficiency, due to presence of many risk factors such as traditional dress, avoidance of sunlight exposure, and multiple dietary factors because of specific cultural beliefs.[5,6] The biological action of 25 OH vitamin D is not limited to calcium-phosphate-bone metabolism, but also extends to influence human immunity in several ways, including its effects on T cell proliferation immunoglobulin class switching, and cytokine release.[7,8] Vitamin D deficiency has been implicated in sepsis in adults[9–11] and children.[12,13] Few recent studies have shown that lower levels of vitamin-D increase risk of early-onset neonatal sepsis in term infants.[14–16] Another importance of neonatal vitamin D status is due to its dependence on maternal vitamin D levels. Maternal vitamin D deficiency has been related to many adverse neonatal outcomes, including sepsis.[17]

In this context, we conducted this study to explore possible relation between vitamin D deficiency and LOS in term infants and to study the correlation between maternal and neonatal vitamin D.

Materials and Methods

This case–control study was designed to evaluate vitamin D deficiency as a possible risk factor for LOS in term neonates. We conducted this study at 25-beds neonatal intensive care unit level 3, Benha University Hospital which is a tertiary-care university hospital, Benha, Egypt, during the period between October 2019 and April 2020. The study was conducted in accordance with ethical principles that had their origin in the Declaration of Helsinki. This study was reviewed and approved by the Institutional Ethical Committee of Faculty of Medicine, Benha University. Written informed consent was obtained from the guardian of the neonate who were included in the study.

Participant

Study Group

The infants along with their mothers were illegible for this study if they were term (37–42 weeks of gestation) neonates, with age less than 28 days of life, and admitted to the neonatal intensive care unit (NICU) by LOS which was defined as the development of signs and symptoms of sepsis after 72 hours of life with positive blood culture or positive sepsis screen.

Neonates who had received antibiotics prior to admission, or who had a history of previous NICU admission for more than 48 hours were excluded from the study. In addition, the neonates who had vitamin D supplementation were excluded. We also excluded the neonate whose parents refused to give written informed consents. A total of 77 neonates were enrolled as LONS cases, but 17 were excluded due to the presence of any exclusion criteria.

Control Group

Full-term healthy neonates with no clinical or laboratory evidence of sepsis who came to our outpatient clinic for routine postnatal evaluation and care along with their mothers were referred as the control group. The infants in the control group were with the same gestational age as the infants who were enrolled in the case group.

Collection of Data

All enrolled patients in study and control group were subjected to detailed history, complete physical examination, and laboratory investigation including complete blood count (CBC), C-reactive protein (CRP), and serum 25-OH vitamin D level. Data were collected from the mothers of these neonates regarding their age, perinatal co-morbidities such as gestational diabetes, hypertension, or thyroid disease and vitamin D supplementation during pregnancy. Serum 25-OH vitamin D of mothers was also tested.

Blood culture, cerebrospinal fluid analysis and culture, urine culture, and chest radiograph, when needed, were done for the study group. Sepsis screen included a total leucocyte count of $<5{,}000/mm^3$ or $>20{,}000/mm^3$,[3,18] an absolute neutrophil count as per *Manroe* chart,[19] immature/total neutrophil (I:T) ratio of ≥ 0.2, an erythrocyte sedimentation rate ESR >15 mm, and CRP ≥ 1 mg/L, sepsis screen was considered positive if two or more of these five parameters were positive.[20] The signs and symptoms of sepsis were considered if there were fever ($\geq 38.0°C$), hypothermia ($\leq 36.5°C$), convulsions, lethargy, inability to feed, vomiting, bulging fontanels, jaundice, umbilical pus infections, and signs of respiratory distress as; tachypnea (≥ 60 breath/min), nasal flaring, chest retraction, and grunting.[21]

Some definitions were used such as clinical sepsis, neonate with symptoms, and signs of sepsis associated with positive sepsis screen only; septicemia, neonate with symptoms, and signs of sepsis with positive sepsis screen and positive blood culture (two positive blood cultures for coagulase-negative staphylococcus were required to consider it positive); pneumonia, chest radiograph showing alveolar opacities assessed by a radiologist.[21] Urinary tract infection (UTI) was defined as a positive urine culture with growth of a known bacterial pathogen at a level of $\geq 50{,}000$ colony-forming units (cfu)/mL,[22] the urine samples were obtained either by urethral catheterization or suprapubic aspiration.

Neonates were treated for neonatal sepsis as per our unit protocol. All neonates were followed up daily until discharge or death to detect the hospital length of stay.

Laboratory Investigation

Three mL venous blood was collected from each subject under complete sterile aseptic condition in a sterile test tube. Serum was obtained by centrifugation of clotted samples at 1,000 g for 15 minutes. All samples were coded and stored at −20°C. ELISA kit was used to detect the serum level of total 25-OH vitamin D by competitive immunoassay technique, utilizing a monoclonal antibody that bind to both 25-OH vitamin D2 and 25-OH vitamin D3 (Cat #: KT815, EDI Epitope Diagnostic, Inc, San Diego, CA). As per the U.S. Endocrine Society classification, the vitamin D levels were classified as deficiency (serum 25-OH vitamin D <20 ng/mL), insufficiency (serum 25-OH vitamin D 21–29 ng/mL), sufficiency (serum 25-OH vitamin D >30 ng/mL).[23] The serum level of CRP was detected using a diagnostic quantitative latex agglutination assay (Cat #: 13 921, Biosystems, Barcelona, Spain) by the turbidimetry method at wavelength 540 nm. Also, CBC was done by full-automated hematology analyzer (Sysmex XN-L series, United States).

Statistical Methods

Data management and statistical analysis were done using SPSS versus 25. (IBM, Armonk, NY). Numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Comparisons between both groups were done using independent *t*-test or Mann-Whitney U test for normally and non-normally distributed numerical data, respectively. Categorical data was compared using the Chi-square test. Receiver operating characteristic (ROC) analysis was done for neonatal vitamin D in the diagnosis of late-onset neonatal sepsis. Area under curve (AUC) with 95% confidence interval, best cutoff point, and diagnostic indices were calculated. Multivariate logistic regression analysis was done for predictors of late-onset neonatal sepsis. Odds ratio with 95% confidence intervals were calculated. All P values were two sided. *p*-Values less than 0.05 were considered significant.

Results

The study group included 60 neonates, who had been diagnosed with LOS and their mothers. On the other hand, 60 healthy neonates without sepsis, along with their mothers, were enrolled as controls. The basic demographic data and laboratory investigations for the two cohorts were detailed in ►Table 1. The mothers and infants of both groups had nearly the same demographic characteristics. As expected, the WBC and CRP levels of neonates in the study group were significantly higher than those of the control group ($p = 0.001$ and <0.001), respectively. Neonatal 25-OH vitamin D levels were significantly lower in sepsis (case) group (16.1 ± 7.9 ng/mL) than in control group (21 ± 8.4 ng/mL) ($p = 0.001$). Similarly, maternal 25-OH vitamin D levels were also significantly lower in case group (17.2 ± 8.4 ng/mL) than in the control group (22.7 ± 9.4 ng/mL) ($p = 0.001$) (►Table 1).

Regarding the vitamin D status, the rates of vitamin D deficiency were slightly higher in neonates and mothers of the study group than those of the control group. Only 10 and 20% of neonates in study and control group, respectively, had sufficient vitamin D level (►Table 2).

A strong positive correlation was detected between neonatal and maternal 25-OH vitamin D levels for both cohorts (case: $r = 0.942$, $p < 0.001$ and control: $r = 0.892$, $p < 0.001$). In sepsis group, the neonatal 25-OH vitamin D showed significant negative correlation with CRP ($r = -0.616$ and $p < 0.001$).

Fourteen patients in study group had positive blood culture. The vitamin D levels in culture positive cases and culture negative cases were 16.3 ± 9.3 ng/mL and 15.9 ± 7.5 ng/mL, respectively; the difference, however, was not found to be statistically significant ($p = 0.9$).

All infants in the study group were hospitalized, pneumonia was the most common diagnosis (43.3%) followed by clinical sepsis (23.3%), septicemia (13.3%), UTI (11.7%), and meningitis (8.3%). The mean length of hospital stay for the recruited patients was 12 ± 5 days. A significant negative correlation was detected between neonatal vitamin D level and length of hospital stay ($r = -0.596$ and *p*-value <0.001) (►Fig. 1). Fifty-eight out of the 60 sepsis cases were discharged and only two cases died. One of the dead neonates had culture positive sepsis with pneumonia and the other one had meningitis; both had very low 25-OH vitamin D levels: 5.1 and 7.9 ng/mL, respectively.

ROC analysis was done for neonatal vitamin D in diagnosing LOS. It showed a significant AUC of 0.664 with a 95% confidence interval ranged from 0.568 to 0.761. The best cutoff point was ≤12.9 ng/mL, at which sensitivity, specificity, positive predictive value, and negative predictive value were 48.3 and 83.3%, 74.4, and 61.7%, respectively (►Fig. 2).

Logistic regression analysis was done for the prediction of late onset neonatal sepsis. Neonatal vitamin D was a significant predictor for late-onset neonatal sepsis (OR = 1.088 and 95% CI = 1.034–1.144), *p*-value = 0.001. This means for one - ng/mL decrease in neonatal vit D, the risk of LOS increases by 9% approximately, controlling for all other parameters included in the model (►Table 3).

Discussion

The immune functions of vitamin D have been recently studied.[24] The presence of vitamin D in adequate concentration was found to play an important role in genetic expression of antimicrobial peptides, especially cathelicidin in human monocyte, neutrophil, and other cell lines.[25] Interleukin-37 (IL-37), the activated form of cathelicidin, was found to be active against various pathogens, including the main pathogens implicated in LOS such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli*.[26]

Table 1 Demographic, clinical, and laboratory characteristics

			Cases ($n=60$)	Controls ($n=60$)	*p*-Value
Maternal age (years)	Mean ± SD		28.7 ± 5.3	28.4 ± 5.5	0.737
Comorbidity	*n* (%)		9 (15.0)	8 (13.3)	0.793
Vitamin D supplementation	Regular	*n* (%)	13 (21.7)	12 (20.0)	0.972
	Irregular	*n* (%)	16 (26.7)	16 (26.7)	
	No	*n* (%)	31 (51.7)	32 (53.3)	
Maternal BMI	Mean ± SD		25.9 ± 3.1	25.9 ± 3.1	0.953
Birth season	Fall	*n* (%)	11 (18.3)	13 (21.7)	0.974
	Spring	*n* (%)	12 (20.0)	12 (20.0)	
	Summer	*n* (%)	16 (26.7)	15 (25.0)	
	Winter	*n* (%)	21 (35.0)	20 (33.3)	
Mode of delivery	CS	*n* (%)	25 (41.7)	29 (48.3)	0.463
	NVD	*n* (%)	35 (58.3)	31 (51.7)	
Gestational age (weeks)	Mean ± SD		38.7 ± 0.9	38.7 ± 0.9	0.804
Gender	Males	*n* (%)	27 (45.0)	23 (38.3)	0.459
	Females	*n* (%)	33 (55.0)	37 (61.7)	
Weight (g)	Mean ± SD		3,625 ± 380	3,629 ± 380	0.958
Length (cm)	Mean ± SD		48.5 ± 1	48.5 ± 1	0.791
Head circumference (cm)	Mean ± SD		35.9 ± 1.2	36.3 ± 1.1	0.119
Age (days)	Mean ± SD		8.86 ± 2.88	8.48 ± 2.41	0.431
Feeding	Breast	*n* (%)	35 (58.3)	32 (53.3)	0.581
	Mixed	*n* (%)	25 (41.7)	28 (46.7)	
Platelets ($\times 10^9$/L)	Mean ± SD		206 ± 96	223 ± 70	0.26
WBCs ($\times 10^9$/L)	Mean ± SD		12.8 ± 4.2	10.6 ± 3	0.001
CRP (mg/L)	Median (range)		19 (0–144)	3 (0–5)	<0.001
Calcium (mg/dL)	Mean ± SD		9.2 ± 0.8	9.3 ± 0.9	0.407
Maternal vit D (ng/mL)	Mean ± SD		17.2 ± 8.4	22.7 ± 9.4	0.001
Neonatal vit D (ng/mL)	Mean ± SD		16.1 ± 7.9	21 ± 8.4	0.001

Abbreviations: BMI, body mass index; CRP, C-reactive protein.
Note: The Independent *t*-test was used for numerical data, and only CRP was compared using Mann-Whitney U-test. Categorical data were compared using the Chi-square test.

Table 2 Maternal and neonatal vitamin D status

		Cases ($n=60$)	Controls ($n=60$)	*p*-Value
Neonatal vitamin D status				
Deficient	*n* (%)	35 (58.3)	31 (51.7)	0.308
Insufficient	*n* (%)	19 (31.7)	17 (28.3)	
Sufficient	*n* (%)	6 (10.0)	12 (20.0)	
Maternal vitamin D status				
Deficient	*n* (%)	39 (65.0)	34 (56.7)	0.619
Insufficient	*n* (%)	13 (21.7)	15 (25.0)	
Sufficient	*n* (%)	8 (13.3)	11 (18.3)	

Note: Chi-square test was used.

From this context, in this study, we hypothesized that vitamin D, which has a well-documented impact on the immune system, may play a role in the pathogenesis of LOS.

Few recent studies have shown the association of 25-OH vitamin D deficiency with neonatal EOS.[14–16] Çetinkaya et al had showed that maternal and neonatal vitamin D levels were significantly lower in term infants who were admitted with EOS ($p < 0.001$).[14] A previous study in Turkey, included a total of 83 (40 cases and 43 controls) full-term neonates which showed that cord blood vitamin D levels were significantly lower in neonates with EOS compared with controls ($p = 0.038$).[15] Yang et al, from China, also showed that low serum level of 25-OH vitamin D is associated with EOS in full-term neonates.[16] These results are consistent with the results of our study. However, there is lack of studies that

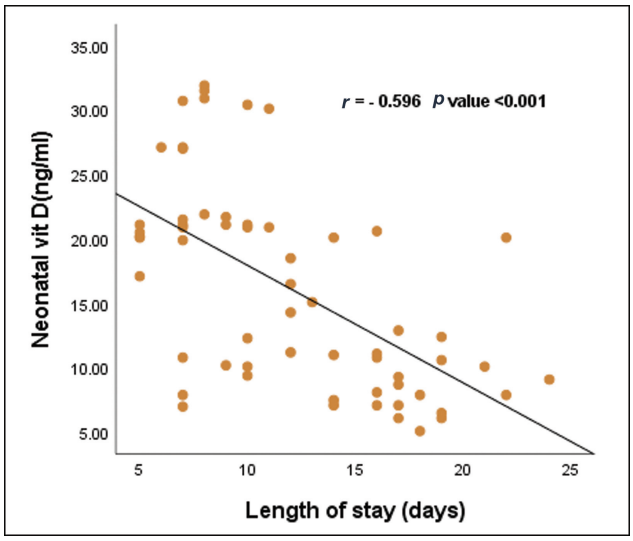

Fig. 1 Correlation between neonatal 25-OH vitamin D and hospital length of stay.

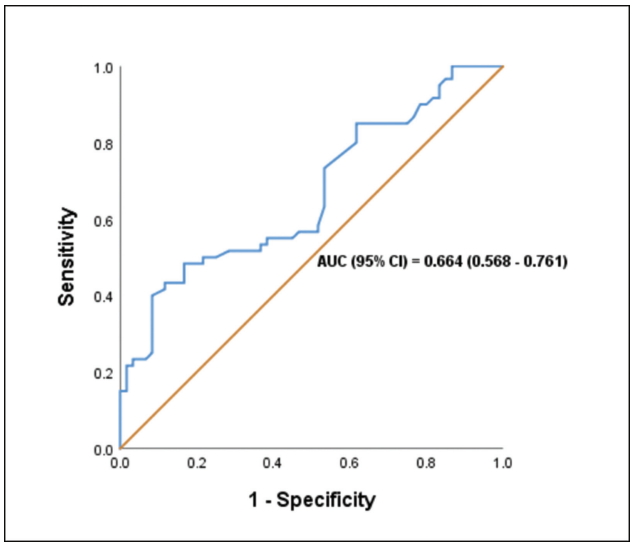

Fig. 2 ROC curve of validity of neonatal vitamin D in prediction of LOS. LOS, length of stay.

Table 3 Multivariate logistic regression analysis for the prediction of late onset neonatal sepsis

	B	SE	Wald	OR (95% CI)	*p*-Value
Maternal age (years)	0.028	0.038	0.569	1.029 (0.956–1.108)	0.451
Maternal Vit D supplementation	0.094	0.39	0.058	1.099 (0.511–2.361)	0.809
Comorbidity	0.707	0.63	1.259	2.027 (0.59–6.966)	0.262
Cesarean delivery	−0.71	0.438	2.626	0.491 (0.208–1.160)	0.105
Exclusive breast feeding	0.095	0.4	0.057	1.1 (0.502–2.409)	0.812
Neonatal vit D(ng/mL)	0.085	0.025	11.018	1.088 (1.034–1.144)	0.001

Abbreviations: B, regression coefficient; CI, 95% confidence interval; OR, odds ratio 95%; SE, standard error.
Note: Comorbidity: gestational diabetes, hypertension, or thyroid disease

have discussed the role of vitamin-D in LOS.[27] Dhandai et al found that neonates with vitamin-D deficiency are at greater risk of LOS than those with sufficient vitamin-D levels. In their study, vitamin D levels were significantly lower in cases (15.4 ng/mL) than controls (21.4 ng/mL) ($p = 0.001$).[27] Their results are corroborative with our results. In the same context, Agrawal et al observed that neonates with lower vitamin D levels were at higher risk of LOS; the cases had significantly lower vitamin D levels than controls (12.28 and 14.88 ng/mL), respectively.[28]

In current study, a strong positive correlation was detected between neonatal and maternal 25-OH vitamin D levels, which means the dependency of neonatal vitamin D status on the maternal vitamin D levels, this agreed with a study from northern India that reported hypovitaminosis D in 95.7% of cord blood samples which were associated with a very high prevalence of maternal vitamin D deficiency (84%).[29] Similarly, Çetinkaya et al had shown the same correlation.[14]

Our study revealed no difference between the two cohorts in the season of birth. This was in contrast with previous studies[14,30] which showed that the incidence of sepsis was high during the winter months as circulating vitamin D is mainly derived from synthesis in the skin under the influence of sunlight; this difference may be due to the fact that most women in our society always wear clothing that covers their entire body, such as the burqa, due to religious beliefs or societal customs, which prevents them from taking the benefit of the sunlight, which play an important role in vitamin D synthesis.

Our study demonstrated a significant negative correlation between vitamin D level and CRP in study group, which was in agreement with a previous study by Liefaard et al who showed that CRP is inversely proportionate to vitamin D level.[31] Similarly, Behera et al found the same correlation.[30]

In the present study there was a significant strong negative correlation between neonatal vitamin D and length of hospital stay in the sepsis group ($r = -0.596$ and p-value <0.001); to our knowledge, the previous studies did not discuss this association, so further studies with larger sample sizes are needed to clearly evaluate such finding. However, a previous study noted an association between neonatal

vitamin D deficiency and sepsis severity and mortality,[32] which might support our observation.

Our study revealed that only 10% of cases and 20% of controls had sufficient level of vitamin D, this agreed with a previous study by Dhandai et al who demonstrated that 8.3% of cases and 13.3% of controls had sufficient level of vitamin D.[27] Also, Agrawal et al showed that 86.28 and 74% of cases and controls respectively, had vitamin D deficiency.[28] This draws attention to the prevalence of vitamin D deficiency among population.

ROC analysis of our study had documented that best cutoff point of neonatal vitamin D in prediction of LOS was 12.9 ng/mL; it was 15.8 ng/mL in a previous study by Behera et al[30] but their study included all cases of sepsis whether EOS or LOS.

In the present study we assessed the association between LOS occurrence and some demographic factors. Based on the multivariate logistic regression analysis for the prediction of late onset sepsis, neonatal vitamin D was a significant predictor for late-onset neonatal sepsis. Similarly, Cizmeci et al found cord-blood 25(OH)D level was predictor for EOS.[15] Another study about the effect of maternal vitamin D on EOS was that they found the first minute APGAR score to be an independent risk factor for EOS; in their study they did not discuss neonatal vitamin D.[33]

Our study had some limitations; Due to financial constraints, the sample size was small, so some outcome parameters such as need for mechanical ventilator, need for inotropes, survival, or oxygen support could not be evaluated; larger sample-sized studies would be needed to evaluate these parameters. As sepsis may affect vitamin D level, so it would be helpful to measure vitamin D after recovery. Data about the duration of sun exposure were not collected which was also a limitation of our study. On the other hand, one of the strengths of this study was the estimation of both neonatal and maternal vitamin D and the correlation between them gave some information about the importance of vitamin D supplementation during pregnancy.

Conclusion

Our data suggested that the prevalence of vitamin D deficiency in mothers and their neonates is very high. Neonatal vitamin D was a significant predictor for late-onset neonatal sepsis. Although a negative correlation was found between neonatal vitamin D and hospital length of stay in sepsis cases, studies with larger sample size are needed to conclusively demonstrate this correlation.

Prior Publication

None.

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None.

Conflict of Interest

None declared.

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