Arch Iran Med. January 2022;25(1):32-36

ARCHIVES OF IRANIAN MEDICINE

doi 10.34172/aim.2022.06

http://www.aimjournal.ir

Open Access

Original Article

Association between Vitamin D Insufficiency and Respiratory Problems in Premature Neonates

Nahid Jafari, MD[1]; Naeeme Taslimi Taleghani, MD[2*]; Sayed AliNaghi Kazemi, MD[1]; Shabnam Abouoasef, MD[3]; Nima Motamed MD[4]; Ahmad Jalilvand MD[5]

[1]Department of Pediatrics, Zanjan University of Medical Sciences, Zanjan, Iran
[2]Neonatal Health Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Pediatrics, Zanjan University of Medical Sciences, Zanjan, Iran
[4]Department of Social Medicine, Medical School, Zanjan University of Medical Sciences, Zanjan, Iran
[5]Department of Pathology, Zanjan University of Medical Sciences, Zanjan, Iran

Abstract

Background: Few studies have been performed to investigate the association between vitamin D and respiratory problems in premature neonates.

Methods: In this cohort study, a low serum level of vitamin D was considered as exposure and respiratory problems and associated interventions were considered as outcome. All patients were followed during their hospital stay. All preterm neonates admitted to the neonatal intensive care unit of a general hospital in Iran during one-year period from January 2018 were enrolled in this study. Serum vitamin D level was measured in the first 24 hours of life by liquid chromatography-spectrometry. Then, respiratory complications were compared between neonates with and without vitamin D insufficiency.

Results: Among the 113 preterm newborns, 65 (58%) had a low and 48 (42%) had a normal level of vitamin D who were classified into two groups I and II, respectively. Respiratory distress syndrome (RDS) and requirement for surfactant administration was found in 40 cases (61.5%) in group I and in 20 cases (41.7%) in group II ($P=0.036$). Also, 46 newborns (70.8%) in the first group and 22 (45.8%) in the second group needed non-invasive ventilation (NIV) ($P=0.007$). Multiple logistic regression showed a significant association between vitamin D status and RDS (OR, 95% CI = 2.840 (1.083–7.447), $P=0.034$), need for surfactant (OR, 95% CI = 2.840 (1.083–7.447), $P=0.034$) and need for NIV (OR, 95% CI = 3.929 (1.526–10.113), $P=0.005$).

Conclusion: The incidence of RDS, need for surfactants, and need for NIV in newborns with vitamin D insufficiency were higher than the neonates with normal levels.

Keywords: Neonatal respiratory distress syndrome, Pregnancy, Premature infant, Preterm birth, Vitamin D

Cite this article as: Jafari N, Taslimi Taleghani N, Kazemi SA, Abouoasef S, Motamed N, Jalilvand A. Association between vitamin d insufficiency and respiratory problems in premature neonates. Arch Iran Med. 2022;25(1):32-36. doi: 10.34172/aim.2022.06

Received: October 4, 2020, Accepted: March 3, 2021, ePublished: ePublished: January 1, 2022

Introduction

Vitamin D insufficiency is very common in pregnant mothers, especially in countries where women do not take regular vitamin D supplements.[1,2] In one study, vitamin D deficiency was observed in 64% of premature infants.[3] Vitamin D deficiency is associated with reduced fetal growth, lower respiratory tract infection, type 1 diabetes, multiple sclerosis, colorectal cancer, cardiovascular disease, schizophrenia, and depression.[4,5] Vitamin D also contributes to maturation of the immune system and lung growth.[6] On the other hand, the level of vitamin D in infants at birth depends largely on the level of vitamin D in the mothers. The more the vitamin D deficiency in mothers, the greater the deficiency in their infant.[5] Also, the lower the gestational age of mothers with vitamin D deficiency, the higher the risk of death and multiple defects in their newborns.[6] Premature infants may need respiratory support and admission to the neonatal intensive care unit (NICU) because of respiratory problems. These problems include respiratory distress, tachypnea, grunting, apnea, and cyanosis. Nasal continuous positive airway pressure (NCPAP) is used to prevent these problems. These infants are subjected to mechanical ventilation and surfactant administration if they have no respiration or have respiratory failure. Studies have shown that the more severe the vitamin D deficiency in infants, the greater are the risks of acute respiratory morbidity and bronchopulmonary dysplasia (BPD).[7,8] Also, respiratory distress syndrome (RDS) is more common in infants with severe vitamin D deficiency compared with those with mild vitamin D deficiency.[9,10]

In the present study, we aimed to determine the relationship between vitamin D levels and neonatal respiratory complications in our NICU of a general hospital in Iran.

Materials and Methods

We conducted a cohort study in which a low serum level of vitamin D was considered as exposure and the frequency of respiratory diseases, need for non-invasive ventilation (NIV), need for surfactant consumption and need for mechanical ventilation were considered as the

***Corresponding Author:** Naeeme Taslimi Taleghani, MD; Shariati Ave., Neonatal Health Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran 15468-155514, Iran. Tel: +98-21-22922828; Fax: +98-21-22220254; Email: naeemetaslimi@yahoo.com; naeemetaslimi@sbmu.ac.ir

related outcome data. All patients were followed during their hospital stay. We enrolled 113 neonates who were admitted to the NICU in our general hospital during a one-year period in 2018. In the first sampling that was carried out in the first 24 hours of birth, 25 (OH) vitamin D levels were measured by liquid chromatography-mass spectrometry. Depending on the serum level of vitamin D below or above 30 ng/mL, the neonates were divided into two groups with insufficient and/or with normal vitamin D levels.[3,11,12]

Physicians were not aware of the results during the study to prevent bias because the aim of the present study was to determine the association of vitamin D levels and neonatal respiratory complications by the time of discharge from the hospital. Therefore, after being full-fed, the studied infants received vitamin D supplementation as a routine protocol and not as a treatment for vitamin D deficiency. The frequency of respiratory diseases and then the clinical outcomes of infants in each group were compared. Respiratory support for the patients was selected relevant to the latest recommendations by the European consensus for neonatal respiratory support and according to the clinical and paraclinical indices. In the neonates with moderate respiratory distress (presence of retraction, $FIO_2 > 30$), NCPAP was applied with PEEP of 4–6 cmH_2O. The need for PEEP above 6 cmH_2O or FIO_2 over 40% in a neonate on NCPAP to maintain the target SaO2 (arterial oxygen saturation)was considered as NCPAP failure. These cases underwent NIPPV (noninvasive positive pressure ventilation) with PIP of 12–14 cmH_2O, PEEP of 4–6 cmH_2O, respiratory rate of 25–30 bpm and FIO_2 of less than 40%. Patients requiring FIO_2 more than 40% or PIP more than 14 cmH_2O were considered for INSURE (INtubation-SURfactant-Extubation). In case of INSURE failure (requiring FIO_2 above 40% or MAP higher than 7), mechanical ventilation was considered for the patient. The clinical outcomes included degree of neonatal resuscitation in the delivery room, need for and duration of mechanical ventilation, need for NIV, need for surfactant consumption and BPD syndrome, patent ductus arteriosus (PDA), length of intravenous feeding, length of stay in the NICU, and mortality.

Newborns with diabetic and addicted mothers, infants with a congenital anomaly, infants transferred from another hospital, and infants who died before hospital admission were excluded.

With descriptive statistics, the mean and standard deviation of continuous quantitative data and percentages of qualitative and nominal data were reported in tables and graphs. The chi-square test was used to determine the association between nominal data, including vitamin D deficiency and respiratory system diseases. We applied the independent t test to compare the normal continuous data between the two groups and the Mann-Whitney test to compare the non-normal data. Logistic regression was used to eliminate the effects of other confounding variables. Thus, we conducted multiple logistic regression on related outcomes which showed a significant association with vitamin D status in chi-square tests. In multiple logistic regression, we considered vitamin D status as potential predictor; gestational age, sex, need for total parenteral nutrition (TPN), PDA and BPD as confounding variables; and RDS, need for NIV and also need for surfactant as outcomes, separately. The associated analyses were performed using the SPSS software version 21 (SPSS Statistics Inc., Chicago). For all analyses, the significance level was set at 0.05.

Results

Of the 113 included preterm infants, 65 newborns (58%) had vitamin D insufficiency (group I) and, 48 newborns (42%) had a normal level of vitamin D (group II). Of the total neonates included in the study, 23% were male and 77% female (Table 1). In the first group (vitamin D insufficiency group), 20% were male, and 80% were female. In the normal vitamin D group, 27% of the neonates were male and 73% were female ($P = 0.377$). The mean birth weight of newborns was 1544.15 g in group I and 1456.35 g in group II ($P > 0.05$). RDS in the vitamin D insufficiency group was significantly higher than the group with normal vitamin D ($P = 0.036$) (Table 2).

Neonates in the vitamin D insufficiency group needed more oxygen supplement and mechanical ventilation compared with the normal group ($P = 0.390$ and $P = 0.549$, respectively). The number of infants who needed NIV in the vitamin D insufficient group was significantly higher compared with the normal group ($P = 0.007$) (Table 2). The infants' need for surfactant in the vitamin D insufficient group was significantly higher compared with the normal group ($P = 0.036$) (Table 2). There were no significant differences in days of needing oxygen, NIV, and mechanical ventilation between the groups (Table 2).

The number of neonates with PDA ($P = 0.817$), BPD ($P = 0.453$), retinopathy of prematurity (ROP) ($P = 0.273$), and intraventricular hemorrhage (IVH) ($P = 0.377$) was not significantly different between the groups (Table 3). Also, the need for TPN ($P = 0.263$) in the two groups was not significantly different. The mean length of hospital stay was also not significantly different between the two groups (group one 23.40 days with standard deviation (SD) 14.14 days and group two, 23.25 days with SD 14.34 days, $P = 0.956$). In the insufficient and normal vitamin D groups, mortality was 5 (7.7%) and 4 (8.3%) cases, respectively ($P = 0.901$).

Multiple logistic regression was performed on the related outcomes which showed a significant association with vitamin D status. As a result, three multiple logistic regressions were conducted in which vitamin D status was considered as the potential predictor; gestational age, sex, need for TPN, PDA and BPD were considered as potential confounding variables; and RDS, need for NIV and also need for surfactant were outcomes, separately. The results showed that the chance of vitamin D insufficiency was 2.840, 2.840 and 3.929 times higher in neonates with RDS,

Table 1. Demographic and Basic Clinical Data of the Study Groups

Variables		Vitamin D Insufficiency Group n (%)	Normal Level of Vitamin D Group n (%)	Total Samples n (%)	*P* Value*
Gender	Male	13 (20)	13 (27)	26 (23)	0.377
	Female	52 (80)	35 (73)	87 (77)	
Gestational age (wk)	<28	3 (4.6)	4 (8.3)	7 (6.2)	0.773
	28–31	35 (53.8)	22 (45.8)	57 (50.5)	
	32–34	19 (29.2)	16 (33.3)	35 (31)	
	35–37	8 (12.3)	6 (12.5)	14 (12.4)	
Need for TPN	Yes	27 (41.5)	15 (31.2)	42 (37.2)	0.263
	No	38 (58.5)	33 (68.8)	71 (62.8)	
PDA	Yes	19 (29.2)	15 (31.2)	34 (30.1)	0.817
	No	46 (70.8)	33 (68.8)	79 (69.9)	
IVH	Yes	13 (20)	13 (27)	26 (23)	0.377
	No	52 (80)	35 (73)	87 (77)	
BPD	Yes	10 (15.4)	10 (20.8)	20 (17.7)	0.453
	No	55 (84.6)	38 (79.2)	93 (82.3)	
ROP	Yes	21 (23.3)	11 (29.2)	32 (28.3)	0.273
	No	44 (67.7)	37 (77.1)	81 (71.7)	
Total		65 (100)	48 (100)	113 (100)	

n, Number; TPN, total parenteral nutrition; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.
*Chi-square test was used.

Table 2. Frequency Distribution of Study Groups Based on the Presentation with Respiratory Distress Syndrome, Need to for Non-invasive Ventilation, and Need to for Surfactant

Variables		Vitamin D Insufficiency Group n (%)	Normal Level of Vitamin D Group n (%)	Total Samples n (%)	*P* Value*
RDS	With RSD	40 (61.5)	20 (41.7)	60 (53.1)	0.036
	Without RSD	25 (38.5)	58.3 (53)	53 (46.9)	
Need for NIV	With NIV	46 (70.8)	22 (45.8)	60 (53.1)	0.007
	Without NIV	19 (29.2)	26 (54.2)	53 (46.9)	
Need for surfactant	Yes	40 (61.5)	20 (41.7)	60 (53.1)	0.036
	No	25 (38.5)	28 (58.3)	53 (46.9)	
Need for mechanical ventilation	Yes	21 (32.3)	13 (27.1)	34 (30.1)	0.549
	No	44 (67.7)	35 (72.9)	79 (69.9)	
Total		65 (100)	48 (100)	113 (100)	

n, Number; RSD, respiratory distress syndrome; NIV, non-invasive ventilation.
*Chi-square test was used.

Table 3. Number of Days Required for Respiratory Support in the Study Groups

Variables	Vitamin D Insufficiency Group			Normal Level of Vitamin D Group			*P* Value*
	N	M	SD	N	M	SD	
Need for O_2 (days)	64	14.45	13.55	48	11.77	11.4	0.293
Need for NIV (days)	46	8.11	7.98	22	7.45	7.74	0.640
Need for mechanical ventilation (days)	21	9.81	8.18	13	8.38	8.17	0.337

N, Number; M, Mean; SD, Standard deviation; NIV, Non-invasive ventilation; TPN, Total parenteral nutrition.
*Mann-Whitney test was applied.

needing surfactant and needing NIV, respectively (Table 4).

Discussion

In the current study, we examined the relationship between vitamin D levels and the incidence of RDS. In our study, 58% of the included preterm infants had vitamin D insufficiency. Our results showed a significant inverse relationship between the serum level of vitamin D and

Table 4. Results of Multiple Logistic Regression on Vitamin D Deficiency as Predictor

Outcome	Wald	OR (95% CI)	*P* value
RDS	4.503	2.840 (1.083–7.447)	0.034
need for surfactant	4.503	2.840 (1.083–7.447)	0.034
need for NIV	8.044	3.929 (1.526–10.113)	0.005

RSD, Respiratory distress syndrome; NIV, Non-invasive ventilation; OR, Odds ratio; CI, confidence interval.

the incidence of RSD in preterm infants (Table 2). In a study by Onwuneme and colleagues in Ireland, however, 64% of preterm infants had vitamin D deficiency but there was no significant relationship between the serum levels of vitamin D and the incidence of RSD. It seems that the small sample size of their study led to the conclusions, which might not be accurate enough.[3] However, a recent study in Iran reported that vitamin D levels in infants were significantly associated with RSD; and also there was a direct relationship between the vitamin D levels of the mothers with that of the neonates.[13] In a study performed by Fort et al, infants with vitamin D deficiency were at higher risk of acute respiratory morbidity and BPD.[7] Another study by Burris et al showed that RSD was higher in infants with severe vitamin D deficiency than neonates with mild vitamin D deficiency.[9] Çetinkaya and colleagues showed that in 31% of neonates (less than 32 weeks) with BPD, 25 (OH) D was significantly lower in neonates and mothers compared with neonates without this problem. The serum level of 25 (OH) D was less than 10 ng/mL in neonates with BPD. They reported that the maternal and neonatal vitamin D levels can be a prominent predictor for BPD.[14] These reports are consistent with our study results.

In our study, there was no significant difference between the two groups in terms of patients' sex. Similar to our results, there has not been an association between neonatal sex and vitamin D levels in various studies such as those done by Fort et al,[7] Burris et al,[9] and Kazemi et al.[4] Vitamin D levels were not significantly different based on gestational age and neonatal birth weight in our study. Also, in the study by Onwuneme and colleagues,[3] no relationship was found between vitamin D levels and gestational age. Another study performed by Belderbos found no association between gestational age and vitamin D levels. It has been suggested that at different levels of vitamin D, there is no significant difference in the need for oxygen administration.[15] The study by Fort and colleagues found no relationship between vitamin D levels and the need for supportive oxygen.[7] However, Onwuneme et al reported that high levels of vitamin D could reduce the need for supplemental oxygen.[3] We also could not find any association between vitamin D levels and the need for supportive oxygen in our study. Consistent with our study, Onwuneme et al concluded that no significant relationship existed between vitamin D levels and the need for mechanical ventilation.[3] In our study, the need for NIV was significantly higher among infants with vitamin D insufficiency. Based on our reviews, no other study has been conducted on this topic; therefore, it is not possible to compare the results.

Our study found that patients with vitamin D insufficiency needed significantly more surfactant. In studies by Onwuneme et al and Fort et al, it was reported that low levels of vitamin D were not associated with the amount of surfactant used.[3,7] The results of our study show that there was no significant relationship between PDA, ROP, IVH, and BPD with vitamin D levels. In the study by Onwuneme et al, there was not a significant difference between various levels of vitamin D and the mentioned neonatal outcomes.[3]

The results of our study show no significant relationship between vitamin D levels and neonatal need for TPN. There are no similar studies to compare these results to. The only study performed by Fort et al found no significant association between TPN and vitamin D levels.[7]

In our study, there was not any significant relationship between vitamin D levels and the length of neonatal hospitalization and neonatal mortality. Consistent with our study, Onwuneme et al[3] and Fort et al[7] reported no relationship between vitamin D levels and length of hospitalization and neonatal mortality rates.

One of the interesting points of the present study is the assessment of the need for non-invasive respiratory support among neonates with insufficient vitamin D levels as initial respiratory support, which was not mentioned in other studies. A probable limitation of our study is that greater sample sizes may be needed to evaluate many clinical outcomes.

In conclusion, in this study, 58% of preterm infants had vitamin D insufficiency. Based on our results, RSD, the need for NIV, and also the need for surfactant administration in preterm infants with vitamin D insufficiency are significantly increased. Therefore, vitamin D deficiency should be considered in neonates who need respiratory support. Also, it is likely that vitamin D deficiency during pregnancy needs to be considered seriously and treated to prevent its consequence on infants. However, it is necessary to confirm this conclusion by future studies that simultaneously check the vitamin D levels of mothers and infants. It is also suggested that future studies should investigate the effect of treating vitamin D deficiency on the improvement of neonatal respiratory complications.

Authors' Contribution

NJ: Conceptualization, and investigation. NTT: Writing original draft, and visualization. ANK: Supervision. SA: Data curation, and resources. NM: Formal analysis. AJ: Investigation.

Conflict of Interest Disclosures

The authors have no conflict of interest with the subject matter of this manuscript.

Ethical Statement

This study was approved by the ethics committee of Zanjan University of Medical Sciences, Zanjan, Iran and informed consent was obtained from all parents.

Acknowledgements
We sincerely thank Zanjan University of Medical Sciences, Zanjan, Iran, as well as the Center for the Development of Clinical Research in Ayatollah Mousavi Hospital and all the patients participating in this study.

References
1. Wheeler BJ, Taylor BJ, de Lange M, Harper MJ, Jones S, Mekhail A, et al. A longitudinal study of 25-hydroxy vitamin D and parathyroid hormone status throughout pregnancy and exclusive lactation in New Zealand mothers and their infants at 45° S. Nutrients. 2018;10(1):86. doi: 10.3390/nu10010086.
2. Kovacs CS, Ward LM. Disorders of calcium, phosphorus, and bone metabolism during fetal and neonatal development. In: Kovacs CS, Deal CL, eds. Maternal-Fetal and Neonatal Endocrinology. Academic Press; 2020. p. 755-82. doi: 10.1016/b978-0-12-814823-5.00045-3.
3. Onwuneme C, Martin F, McCarthy R, Carroll A, Segurado R, Murphy J, et al. The association of vitamin D status with acute respiratory morbidity in preterm infants. J Pediatr. 2015;166(5):1175-80.e1. doi: 10.1016/j.jpeds.2015.01.055.
4. Kazemi A, Sharifi F, Jafari N, Mousavinasab N. High prevalence of vitamin D deficiency among pregnant women and their newborns in an Iranian population. J Womens Health (Larchmt). 2009;18(6):835-9. doi: 10.1089/jwh.2008.0954.
5. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. Am J Clin Nutr. 2005;81(5):1060-4. doi: 10.1093/ajcn/81.5.1060.
6. MacDorman MF, Martin JA, Mathews TJ, Hoyert DL, Ventura SJ. Explaining the 2001-2002 infant mortality increase in the United States: data from the linked birth/infant death data set. Int J Health Serv. 2005;35(3):415-42. doi: 10.2190/tj2n-dadv-1ep5-5c7f.
7. Fort P, Salas AA, Nicola T, Craig CM, Carlo WA, Ambalavanan N. A comparison of 3 vitamin D dosing regimens in extremely preterm infants: a randomized controlled trial. J Pediatr. 2016;174:132-8.e1. doi: 10.1016/j.jpeds.2016.03.028.
8. Jobe AH. Vitamin D for extremely preterm infants. J Pediatr. 2016;174:3. doi: 10.1016/j.jpeds.2016.05.052.
9. Burris HH, Van Marter LJ, McElrath TF, Tabatabai P, Litonjua AA, Weiss ST, et al. Vitamin D status among preterm and full-term infants at birth. Pediatr Res. 2014;75(1-1):75-80. doi: 10.1038/pr.2013.174.
10. Ataseven F, Aygün C, Okuyucu A, Bedir A, Kücük Y, Kücüködük S. Is vitamin D deficiency a risk factor for respiratory distress syndrome? Int J Vitam Nutr Res. 2013;83(4):232-7. doi: 10.1024/0300-9831/a000165.
11. Aloia JF. The 2011 report on dietary reference intake for vitamin D: where do we go from here? J Clin Endocrinol Metab. 2011;96(10):2987-96. doi: 10.1210/jc.2011-0090.
12. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53-8. doi: 10.1210/jc.2010-2704.
13. Boskabadi H, Mamoori G, Khatami SF, Faramarzi R. Serum level of vitamin D in preterm infants and its association with premature-related respiratory complications: a case-control study. Electron Physician. 2018;10(1):6208-14. doi: 10.19082/6208.
14. Çetinkaya M, Çekmez F, Erener-Ercan T, Buyukkale G, Demirhan A, Aydemir G, et al. Maternal/neonatal vitamin D deficiency: a risk factor for bronchopulmonary dysplasia in preterms? J Perinatol. 2015;35(10):813-7. doi: 10.1038/jp.2015.88.
15. Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics. 2011;127(6):e1513-20. doi: 10.1542/peds.2010-3054.