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Serum levels of vitamin D in preterm neonates and its association with respiratory distress syndrome

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ABSTRACT

Objectives: Prematurity and related respiratory distress syndrome (RDS) is the major cause of mortality among neonates in India. Although some studies were showing an association between vitamin D and lung maturation, conclusive evidence was not found yet. The objective of this study was to assess the serum vitamin D in preterm neonates and to determine its possible association with RDS.

Material and Methods: A case–control study in which the preterm neonates <37 weeks of age and <2 kg birth weight admitted to neonatal intensive care unit and in postnatal wards in a tertiary care center were included and divided as cases-those with RDS and controls-those without RDS. Two milliliters of whole blood samples were collected from the study population for 25 (OH) D levels.

Results: (1) RDS was predominantly seen in <32 weeks (<30 and 30–31 weeks) when compared with the other two gestational age groups. (2) The mean serum vitamin D levels in cases (RDS) were lower compared to controls (non-RDS) (6.97 ± 3.24 in cases vs. 17.08 ± 4.15 in controls). (3) A significant difference in vitamin D levels was obtained among those on a mechanical ventilator and received surfactant administration compared to those who were not on a mechanical ventilator or administered surfactant ($P = 0.001$ and 0.003). (4) A significant association between vitamin D and adequacy of maternal vitamin D-rich food intake and sunlight exposure was found to be present ($P < 0.001$ and 0.018). (5). Serum levels of vitamin D were found to be lower (3.3 ± 1.6 ng/mL) in cases who died during the hospital stay compared to those who survived (8.4 ± 2.6 ng/mL), ($P < 0.001$).

Conclusion: A significant difference in vitamin D concentration between preterms with respiratory distress syndrome and those without RDS was reflected in our study. And we also noted low serum vitamin D levels associated with poor outcome.

Keywords: Neonates, Preterm, Respiratory distress syndrome, Vitamin D

INTRODUCTION

According to the World Health Organisation estimates each year 15 million babies are born preterm, and this number is on a rising trend. Complications from preterm births are the leading cause of death among children under 5 years of age, responsible for nearly 1 million deaths each year. In India, out of 27 million babies born every year, 3.5 million babies are premature.[1]

Neonatal respiratory distress syndrome (RDS) affects approximately 1% of all live births. The pulmonary system is among the last of the fetal organ systems to become functionally mature. As such, RDS is primarily – although not exclusively – a disease of premature infants with an incidence and severity that is highly dependent on gestational age.[2] The main cause of RDS is the lack of surfactant in the lungs. Vitamin D deficiency is more common among infants and pregnant and lactating mothers worldwide. Recently, in many studies, vitamin D has been shown to assist in lung maturation. The correlation between lung maturation and vitamin D is explained by the mechanism of phospholipid (surfactant) production and secretion on the surface of alveolar type II cells. The newborn infant born to a vitamin D-replete mother is protected from vitamin D deficiency for the first few months of life as 25-OHD crosses the placenta readily and their vitamin D levels approximate two-thirds of the maternal serum concentrations.[3]

This study is thereby undertaken in the interest to know the status of serum vitamin D levels in preterm neonates with RDS and its association.

OBJECTIVES

This study aims to assess serum vitamin D levels in preterm neonates and to determine its possible association with RDS.

MATERIAL AND METHODS

This case–control study was conducted in a neonatal intensive care unit (NICU) in a tertiary care center. All the preterm neonates <37 weeks of age and <2 kg birth weight were included in this study. All those with any detectable gross congenital anomalies or those born from complicated pregnancies, mothers who were on vitamin D supplements, or on any antiepileptic drugs were excluded from this study. A sample size of 100 was calculated by the formula $Z^2 = pq/d^2$ where Z = 1.96, p=prevalence of RDS being 7% in our hospital, d = margin of error 5%, and q = (1−p). Out of which 50 were taken as cases and another 50 as controls. Those neonates fulfilling the inclusion criteria were divided into two groups; those with RDS as cases and those without RDS as controls. Neonates were included in the case group according to the RDS score system – Downe's scoring and oxygen requirement. Neonates in the control group were premature infants <2 kg birth weight admitted to NICU for non-respiratory causes and those in the postnatal wards.

The demographic details including age sex, birth weight, gestational age, clinical examination findings, Apgar score, resuscitation, oxygen requirement, surfactant administration and dose and outcome were documented. Maternal history including antenatal events, vitamin D supplementation, antiepileptic drug intake, vitamin D-rich diet (dairy, egg yolk and fish), and duration of sunlight exposure were also noted down in the predesigned pro forma. On average, 30 min of sunlight exposure during the day between 10 am and 3 pm was taken as adequate sunlight exposure.[4] Gestational age assessment was done by Ballards scoring.

Ethical clearance was obtained from the Ethical Committee. Informed and written consent was taken from the parents of all the eligible neonates in both cases and controls. Under aseptic precautions, 2 mL of whole blood sample was drawn by venepuncture to estimate serum 25 (OH) D levels using standard sampling tubes and preserved at 0–4° centigrade. Serum 25 (OH) D level was estimated by method of solid phase enzyme-linked immunosorbent assay (ELISA). Vitamin D deficiency is considered as level of 25 (OH) D ≤12 ng/mL, vitamin D insufficiency as level of 25 (OH) D 12–20 ng/mL and normal vitamin D as level of 25 (OH) D ≥20 ng/mL (Indian Academy of Pediatrics [IAP] guidelines on vitamin D and calcium deficiency).[5]

RESULTS

A total of 100 neonates were enrolled in this study who were born in our hospital, including those admitted to NICU and in postnatal wards.

Out of 50 neonates with RDS – 23 (46%) were female and 27 (54%) were male. Among control groups, 21 (41%) were female and 30 (58.8%) were male. Among the cases, 56% were below 32 weeks, whereas, in controls, only 26.6% belongs to this group. Overall, 42.4% of the study subjects were in between 32 and 33 weeks. There were seven cases weighing <1000 g and 27 (54%) between 1000 and 1500 g when compared to 0 and 24 (47%) among controls in those respective groups. There was no statistically significant difference between cases and controls with respect to appropriateness of gestational age, maternal age, parity, antenatal history, mode of delivery, vitamin D intake and adequacy of sunlight exposure. There was a statistically significant difference in vitamin D concentration found between RDS and non-RDS subjects with a mean level of 6.97 ± 3.249 and 17.08 ± 4.156 among the respective groups (<0.001). Mean level of vitamin D among all the study subjects was 12.08 ± 6.296 showing a significant insufficiency of vitamin D among preterm neonates [Table 1 and Figure 1].

Comparison of mean vitamin D concentrations between RDS and non-RDS subjects with respect to different parameters considered in this study is given in the Tables 2 and 3.

Among RDS patients, there was significant difference in vitamin D levels according to gestational age. RDS cases were concentrated mainly in <30 and 30–31 weeks and vitamin D levels were also found to be less in these groups compared to 32–33 and 34–35 weeks (3 ± 1.2, 7.9 ± 3.2, 8.3 ± 2.3 and 9.2 ± 2 ng/mL in each category with–$P < 0.001$). Although these values are lower compared to non-RDS subjects in control group, this is not statistically significant as the number of subjects among different age groups was different in both the groups. A significant difference with $P < 0.001$ was seen in vitamin D levels among different birth weight in those with RDS (3.3 ± 1.8, 6.7 ± 3.2 and 9 ± 2 ng/mL in <1000, 1000–1500 and >1500 g). Similar trend was seen among controls with $P = 0.002$ and here the subjects were in two groups 1000–1500 and 1500 g each having 15.3 ± 2.9 and 18.7 ± 4.5 ng/mL, respectively.

Among the cases, significant difference was found with respect to mechanical ventilation, $P < 0.001$ (8.5 ± 2.7 and 4.2

± 2.3 ng/mL in MV and non-MV patients). Cases who had been administered surfactant showed significant low levels of vitamin D (P = 0.003) and further change also noticed based on number of dose administered P < 0.001 (0–9.1 ± 2.3, 1–6.7 ± 3.2, 2–3 ± 1.2 ng/mL).

Among RDS patients, LSCS delivery was seen to be associated with a lower level of vitamin D compared to normal vaginal delivery (5.1 ± 2.4 vs. 8.1 ± 3.3) P < 0.001, but such a significant difference was not observed in case of controls (P = 0.37).

Vitamin D levels in those whose mothers consumed vitamin D rich food during delivery (8.1 ± 3.3) found to be higher than those who were on deficient diet (6.1 ± 2.9) P < 0.001 among cases as well as controls P < 0.001 (20.1 ± 4.8 and 15.9 ± 3.3).

Among cases, adequate sunlight exposure in mothers showed higher vitamin D levels in neonates (8.8 ± 3.5) compared to 6.3 ± 2.9 in those who were not exposed (P = 0.018). Similar results were obtained in those without RDS (P < 0.001).

Outcome expressed in terms of death or survival also showed significant change in serum levels of vitamin D among both cases and controls (P ≤ 0.001) (RDS–8.4 ± 2.6 vs. 3.3 ± 1.6 and non-RDS – 17.2 ± 4.2 vs. 13.2).

Other parameters such as SGA/AGA, Downes score, oxygen requirement, positive pressure ventilation, age at collection of sample, maternal age and parity and associated comorbid conditions showed no statistically significant difference among both cases and controls.

Table 1: Comparison of vitamin D between cases and controls.

	Vitamin D (ng/mL)	
	Mean	**Std. Deviation**
Cases	6.97	3.249
Controls	17.08	4.156
Total	12.08	6.296

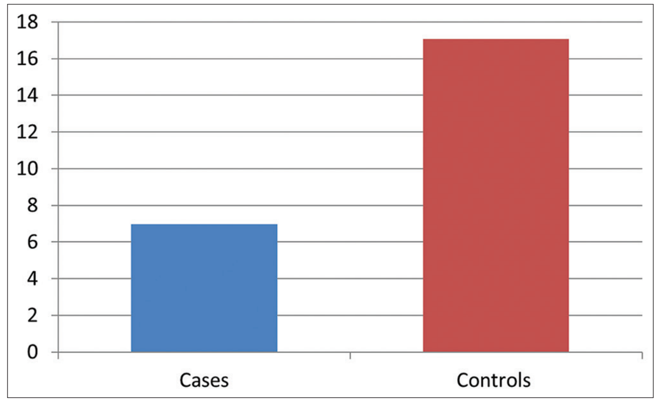

Figure 1: Graph showing comparison of vitamin D between cases and controls.

DISCUSSION

RDS accounts for around 45% of morbidity and mortality profile of neonates admitted to NICU. Prevalence of RDS is high as gestational age decreases. India ranks one among the ten countries with greatest number of preterm birth and thus contributing to risk of RDS as well.[3]

This study showed that the prevalence of vitamin D deficiency in preterm with RDS is more than those preterms with no RDS and also an overall low vitamin D concentration among preterm neonates.

Although there are not many modifiable factors for RDS, vitamin D can be hypothesised as one such modifiable factor from the different studies which showed lower serum levels of vitamin D with decreasing gestational age and also its association with RDS and BPD. Some research suggested the role of active form of vitamin D in lung maturation through alveolar type 2 cells as well as fibroblasts.

This study is a comparative study which included 100 preterm neonates <37 weeks of gestation and <2000 g birth weight. Most of the study population were seen in the age group 30–31 and 32–33 weeks. RDS was seen more concentrated in the gestational age groups of <30 and 30–31 weeks compared to 32–33 and 34–35 weeks. This is also the fact in accordance with other studies and literature which shows high prevalence of RDS as gestational age decreases.

This study showed comparatively low levels of vitamin D than other similar studies in infants with RDS.

In a study by Hasan Boskabadi *et al.* in the year 2018 among 160 preterm infants weighing less than 2 kg and born at less than 34 weeks, the mean vitamin D level in the cases and controls was 11.69 ± 8.8 and 17.9 ± 12.5 ng/dl respectively and they observed it to be higher among those infants with no respiratory distress.[6] Another study by Yang yang *et al.* in the year 2017 included 106 preterm neonates between 30 -34 weeks of gestation divided into two groups with vitamin D levels of 29.48 ± 13.06 mmol/l among those with RDS and 40.47 ± 20.52 mmol/l among non RDS.[7] In the year 2019 Ian Kim *et al*. in a study observed the association between vitamin D level at birth and respiratory morbidities in very low birth weight infants and concluded vitamin D deficiency as a risk factor for RDS and BPD. The mean vitamin D concentration was 13.4 ± 9.3 ng/ml and 79.8% of preterm in this study had vitamin D deficiency at birth and low vitamin D status was associated with respiratory morbidity.[8] Atasven F *et al* in an observational cohort study among 152 infants between gestational age of 29 to 35 weeks in the year 2013 showed the prevalence of RDS as 28% in those with vitamin D levels less than 25 mmol/l and 14% among those with >25mmol/l.9 [Table 4].

In our study, serum levels of vitamin D were analysed by solid phase ELISA in 100 neonates. Almost 100% (deficient–92% and insufficient–8%) had low vitamin levels among RDS and 78%

Table 2: Comparison of vitamin D levels between various factors among cases.

Cases	Vitamin D (ng/mL)		*P*-value
	Mean	SD	
Gestational age category			
<30 weeks	3.0	1.2	**<0.001**
30–31 weeks	7.9	3.2	
32–33 weeks	8.3	2.3	
34–35 weeks	9.2	2.0	
Appropriate for age			
Appropriate for gestational age	6.9	3.5	0.799
Small for gestational age	7.2	2.7	
Birth weight category			
<1 kg	3.3	1.8	**<0.001**
1–1.5 kg	6.7	3.2	
1.5–2 kg	9.0	2.0	
Downes score			
Mild	7.4	1.8	0.084
Moderate	7.4	3.5	
Severe	4.6	2.5	
Oxygen requirement			
Yes	7.0	3.2	----
Continuous positive airway pressure			
No	7.0	1.5	0.995
Yes	7.0	3.5	
Mechanical ventilator			
No	8.5	2.7	**<0.001**
Yes	4.2	2.3	
Surfactant administered			
No	9.1	2.3	**0.003**
Yes	6.2	3.2	
Dose			
0	9.1	2.3	**<0.001**
1	6.7	3.2	
2	3.0	1.2	
Mode of delivery			
Normal vaginal delivery	8.1	3.2	**<0.001**
Cesarean section	5.1	2.4	
Vitamin D rich food			
No	6.1	2.9	**0.026**
Yes	8.1	3.3	
Duration of sunlight exposure			
<30 min/day	6.3	2.9	**0.018**
>30 min/day	8.8	3.5	
Associated comorbidities			
No	8.1	3.2	0.076
Yes	7.1	2.4	
Outcome			
Discharged	8.4	2.6	**<0.001**
Death	3.3	1.6	

Bold values: *P*<0.05 is statistically significant.

(5.9% deficient and 72.5% insufficient) among non-RDS and overall there was 89% having low vitamin D levels. Among those with low levels, 48.5% had deficient levels as per IAP guidelines and 40.6% had insufficient levels and 10.9% had normal vitamin D levels. About 48% prevalence of vitamin D deficiency was seen in all preterm neonates with a statistically significant difference among RDS and non-RDS groups. Hence, our study did find an association between vitamin D levels and RDS.

Table 3: Comparison of vitamin D levels between various factors among controls.

Controls	Vitamin D (ng/mL)		*P*-value
	Mean	SD	
Gestational age category			
30–31 weeks	15.1	3.6	**<0.001**
32–33 weeks	15.9	2.9	
34–35 weeks	20.8	4.3	
Appropriate for age			
AGA	17.4	3.9	0.069
SGA	19.5	4.5	
Birth weight category			
1–1.5 kg	15.3	2.9	**0.002**
1.5–2 kg	18.7	4.5	
Downes score			
Mild	17.1	4.2	--
Oxygen requirement			
No	17.7	4.2	0.056
Yes	15.2	3.6	
CPAP			
No	17.1	4.2	---
Mechanical ventilator			
No	17.1	4.2	---
Surfactant administered			
No	17.1	4.2	---
DOSE			
0	17.1	4.2	---
Mode of delivery			
NVD	17.5	4.7	0.371
LSCS	16.3	2.8	
Vitamin D rich food			
No	15.9	3.3	**<0.001**
Yes	20.1	4.8	
Duration of sunlight exposure			
<30 min/day	15.2	2.9	**<0.001**
>30 min/day	20.2	4.1	
Associated comorbidities			
No	17.8	4.6	0.115
Yes	15.9	3.0	
Outcome			
Discharged	17.2	4.2	**<0.001**
Death	13.2	.	

Bold values: *P*<0.05 is statistically significant.

Other determinants of vitamin D status in infants, as observed in this study with significant difference ($P < 0.05$), were gestational age, birth weight, maternal supplementation of vitamin D rich food during pregnancy and adequate sunlight exposure, all of which showed a higher value of serum vitamin D concentration.

Table 4: Comparison of mean serum vitamin D levels in RDS with other studies.

Studies	Present study (*n*=100)	Boskabadi *et al.*[6] 2018 (*n*=160)	Yang *et al.*[7] 2017 (*n*=106)	Kim *et al.*[8] 2019 (*n*=188)
Mean serum Vitamin D level	6.97±3.249 ng/mL	11.69±8.6 ng/mL	29.48±13.06 mmol/L	13.4±9.3 ng/mL

RDS: Respiratory distress syndrome

Vitamin D levels were found to be low in those cases receiving surfactant (among which those who received two doses had still lower value) and those on mechanical ventilator. Vitamin D levels were lower in subjects who died during the hospital stay than those who survived, further adding to its association with severity.

There was no significant association between vitamin D levels and other parameters such as SGA/AGA category, APGAR scores, maternal age, parity, antenatal events, other associated conditions and mode of delivery. A similar study by Ataseven *et al.*, in the year 2013, compared vitamin D levels among gestational age, sex, birth weight, APGAR scores, maternal steroid use and type of delivery antenatal problems and found no significant difference.[9] In the year 2017, Yang *et al.*, in a similar study, compared vitamin D levels among different parameters such as maternal age, birth weight, sex, age, APGAR, mechanical ventilation and outcome (death/survival) and found a statistically significant association with gestational age, birth weight, mechanical ventilation and outcome.[7]

At demonstration of critical, biological role that vitamin D plays in human lung maturation and its association between gestational age and RDS in some literature, further clinical studies are recommended to strengthen this associatiion.

CONCLUSION

We recommend in addition to daily allowance, vitamin d supplementation for those women with history of previous preterm delivery or those with risk factors for vitamin d deficiency. Also providing vitamin d rich food especially to pregnant women with vitamin d fortification can have a beneficial effect so as to improve the placental transfer of vitamin d and enhance fetal maturation thus preventing RDS and its associated mortality. This is a cost effective means of preventing RDS since the available treatment options for RDS include surfactant administration and positive pressure or mechanical ventilation which are expensive and unavailable in resource poor settings.

Limitations

Sample size is not large enough to make a generalized conclusion. this study did not take into account maternal vitamin d levels which could prove the association of it, if any with infant vitamin d levels.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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