A cohort study of serum 25-hydroxyvitamin D levels and lung disease in preterm infants

Abstract

Objectives To analyze the relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and lung diseases (wet lung, RDS, BPD, pneumothorax) in preterm infants.

Methods Preterm infants (corrected gestational age <37 weeks) hospitalized in the neonatology department of Yan'an University Hospital from January 2023 to December 2023 were selected as the study subjects, and their clinical data and 25-hydroxyvitamin D [25(OH)D] levels in the first 24 h of life were collected (by the random number table method to avoid selection bias) in a retrospective cohort study with the basis of the Serum 25(OH)D level was used to categorize preterm infants into high vitamin D and low vitamin D groups, and to compare the incidence of lung diseases in preterm infants in the 2 groups.

Results A total of 414 preterm infants were selected, and 237 preterm infants were finally included for analysis. The mean serum 25(OH)D level in preterm infants within 24 hours of birth was 16.97 ng/mL. 140 cases in the low-vitamin D group had a serum 25(OH)D level of (11.88± 2.74) ng/mL. 97 cases in the high-vitamin D group had a serum 25(OH)D level of (24.31± 7.52) ng/mL; the rate of births in the fall in the low-vitamin D group was was significantly higher than that of the high-vitamin D group (P<0.05), the utilization rate of lung surface active substance was higher than that of the high-vitamin D group (P<0.05), and the incidence of RDS and BPD was significantly higher than that of the high-vitamin D group (P<0.05). Univariate logistic regression analysis suggested that season of birth, serum 25(OH)D level, 5 min Apgar score and prenatal hormone use were associated with pulmonary complications in preterm infants (*P<0*.05). Multifactorial logistic regression analysis showed that higher serum 25(OH)D levels reduced the risk of pulmonary complications in preterm infants, which was statistically significant (B=-0.056, RR= 0.946, 95% *CI*: 0.910-0.984, P=0.006); higher 5-min Apgar scores had a lower incidence of pulmonary complications in preterm infants, which was statistical significance (B=-0.722, RR= 0.486, 95% *CI*: 0.281~0.840, P=0.010); prenatal use of hormones will reduce the risk of pulmonary complications in preterm infants (B=-0.763, RR= 0.466, 95% *CI*: 0.261~0.833, P=0.010).

Conclusion Low vitamin D levels at birth in preterm infants may increase the incidence of RDS and BPD.

Keywords Vitamin D,Preterm infants, Lung disease, Cohort study

Introduction

Vitamin D is a class of fat-soluble steroid derivatives with a wide range of biological activities. It undergoes 25-hydroxylation in the liver by the mitochondrial form of 25-hydroxylase (CYP27A1) to form 25-hydroxyvitamin D_3 [$25(OH)D_3$](osseodiol), which is the major circulating form of vitamin D_3 , and then is converted in the kidney to active 1,25-dihydroxyvitamin D_3 [1 ,$25(OH) D_{23}$] (osteotriol)i , which is considered a key measure of vitamin D levels in the body because of its relative stability and long half-life.

Its main role is to promote the absorption of calcium and phosphorus from the gastrointestinal tract and to reduce the excretion of calcium and phosphorus from the gastrointestinal tract, which leads to an increase in the concentration of calcium and phosphorus in the blood[ii] . In addition to this, it is also involved in immune regulation, neurotransmission and cell differentiation, and has a

role in promoting cartilage synthesis, chondrocyte development, and bone maturation. In recent years, the effect of vitamin D on neonatal lung disease has received widespread attention. Vitamin D plays a crucial role in embryonic development, cell growth and differentiation (including lung development and fetal lung maturation), and late pregnancy is a critical stage for placental transfer of vitamin D. Vitamin D deficiency during pregnancy increases the risk of preterm labor, which in turn leads to neonatal lung disease.

There are not many clinical studies on the effect of 25(OH)D level on lung disease in preterm infants, so the aim of this study was to analyze the vitamin D deficiency status of preterm infants and to investigate the relationship between 25(OH)D level and lung disease in preterm infants, with a view to providing diagnostic and therapeutic ideas for the prevention and treatment of lung disease in preterm infants.

Methods

Participants

Inclusion criteria: 1. Preterm infants who were hospitalized in the neonatology department of the Affiliated Hospital of Yan'an University from January 2023 to December 2023 and met the enrollment criteria were selected.2. Corrected gestational age <37 weeks.3. Within 24 h of birth.4. Vitamin D test was performed on blood collected intravenously prior to vitamin D supplementation.5.Vitamin D was not included in the study;Exclusion criteria: 1. Neonates/pregnant mothers with hypothyroidism and or hepatic or renal disease. 2. Mothers taking medication during pregnancy that affects vitamin D metabolism. 3. Incomplete clinical data. 4.The study was approved by the hospital ethics committee.

Data collection:

Clinical data of the children were obtained through the hospital electronic case management system records, including gestational age, birth mass, gender, mode of delivery, 1,5 min Apgar score, season of birth, in vitro fertilization, history of intrauterine distress, and history of meconium aspiration; maternal data, including mother's age, multiple pregnancies, primiparous women, prenatal use of hormones, preterm premature rupture of membranes, contaminated amniotic fluid, placental Abnormalities, umbilical cord abnormalities (umbilical cord around the neck, umbilical cord kinking, umbilical cord twisting), pregnancy complications (including gestational hypertension, gestational diabetes mellitus); hospitalization, including endotracheal intubation, use of pulmonary surfactant (PS), length of hospitalization; respiratory complications, including neonatal respiratory distress syndrome (NRDS); and maternal history of fecal aspiration. Respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), wet lung, pneumothorax.

25(OH)D test

2ml of venous blood was taken from the children, and the supernatant was centrifuged and processed, and the serum 25(OH)D level was detected using electrochemiluminescence immunoassay with the instrument and kit provided by Roche (Cobas), and the operation method was carried out by the specialists in the Department of Laboratory Medicine.

Definition of vitamin D level

serum 25 (OH)D <20 ng/mL (50 nmol/L) is considered vitamin D deficiency, 20-30 ng/mL (50-75 nmol/L) is considered insufficient, and >30 ng/mL (75 nmol/L) is considered adequate. Preterm infants were categorized into high-vitamin D and low-vitamin D groups according to the mean serum 25 (OH)D level within 24 hours of birth.

Definition of neonatal lung disease

its diagnostic criteria refer to the fifth edition of Practical Neonatology.

statistical analysis

Data were analyzed using the software SPSS 25.0, and count data were expressed as percentages, and comparisons between two groups were made using the χ^2 test. Measurement information that conformed to normal distribution was expressed as mean ± standard deviation, and independent samples t-test was used for comparison between two groups. Measures that were not normally distributed were expressed as median (interquartile spacing), and comparisons between groups were made using the rank sum test. The relationship between 25(OH)D levels and complications in preterm infants was analyzed using univariate and multivariate logistic regression. Differences were considered statistically significant when $P < 0.05$.

Results

General conditions of premature infants

A total of 237 eligible preterm infants with a mean gestational age of (34.10±1.20) weeks (28-36 weeks) were included in this study, including 140 males and 97 females, with a male-to-female ratio of approximately 1.4:1. The mean serum 25(OH)D level was (16.97.1±8.06) ng/mL (5.22-57.92 ng/mL). There were 175 cases (73.84%) with vitamin D deficiency, 39 cases (16.46%) with vitamin D insufficiency and 23 cases (9.70%) with vitamin D sufficiency. In the hypovitaminosis D group: [25(OH)D level <16.97 ng/mL, 140 cases], 81 (57.9%) males and 59 (42.1%) females; gestational age at delivery was 34 (33-35) weeks. Mean birth weight was 2308.07±448.37 g; mean serum 25 (OH)D level was (11.88±2.74) ng/mL; in the hypervitaminosis D group [25(OH)D level ≥16.97 ng/mL, 97 cases], 59 (60.8%) males and 38 (39.2%) females; gestational age at delivery was 34 (33-35) weeks. Mean birth weight was 2312.49±455.11 g; mean serum 25(OH)D level was (24.31±7.52) ng/mL.

Comparison of general clinical data of children between the two groups

The birth rate in the low-vitamin D group was significantly higher than that in the high-vitamin D group in the fall, and the difference was statistically significant (P<0.05); the differences between the two groups in gestational age, birth mass, sex, mode of delivery, 1,5-minute Apgar scores, in vitro fertilization, intrauterine distress, and meconium aspiration were not statistically significant (P>0.05). See Table 1.

Table 1 Comparison of general clinical data of children between the two groups

Characteristics	Low vitamin D group (n=140)	High vitamin D group (n=97)	*p* value
Gestational age (weeks)	34 (33-35)	34 (33-35)	0.411
Body mass at birth (g)	2308.07±448.37	2312.49±455.11	0.941
Gender			
male	81 (57.9%)	59 (60.8%)	0.648
women	59 (42.1%)	38 (39.2%)	
Delivery			
vaginal delivery	29 (20.7%)	20 (20.6%)	0.986
Cesarean section	111 (79.3%)	77 (79.4%)	
Apgar score			
1 min	10 (9-10)	10 (10-10)	0.975

5min	10 (10-10)	10 (10-10)	0.111
season of birth			
Spring (March-May)	36 (25.7%)	39 (40.2%)	0.000
Summer (June-September)	37 (26.4%)	32 (33.0%)	
Autumn (October-November)	38 (27.1%)	5 (5.2%)	
Winter (December, January-February of the same year)	29 (20.7%)	21 (21.6%)	
Invitro fertilization			
Negative	131 (93.6%)	91 (93.8%)	0.94
Positive	9 (6.4%)	6 (6.2%)	
Intrauterine distress			
Negative	123 (87.9%)	79 (81.4%)	0.171
Positive	17 (12.1%)	18 (18.6%)	
Fecal Aspiration			
Negative	123 (87.9%)	89 (91.8%)	0.337
Positive	17 (12.1%)	8 (8.2%)	

Comparison of general clinical data of pregnant mothers between the two groups

There was no statistically significant difference between the 2 groups when comparing the incidence of mother's age, multiple pregnancies, primiparity, prenatal use of hormones, premature rupture of membranes, contaminated amniotic fluid, placental abnormalities, umbilical cord wrapping around the neck, kinking, torsion, and maternal complications during pregnancy (diabetes mellitus, hypertension) (P all > 0.05). See Table 2.

Table 2 Comparison of general clinical data of pregnant mothers between the two groups

Characteristics	Low vitamin D group (n=140)	High vitamin D group (n=97)	p value
Mother's age (years)	31.24 (28.25-34)	31.24 (29.5-33.5)	0.786
Multiple pregnancies			
Negative	111 (79.3%)	13 (75.3%)	0.464
Positive	29 (20.7%)	24 (24.7%)	
primiparous woman			
Negative	77 (55.0%)	45 (46.4%)	0.192
Positive	63 (45.0%)	52 (53.6%)	
Prenatal hormone use			
Negative	107 (76.4%)	69 (71.1%)	0.359
Positive	33 (23.6%)	28 (28.9%)	
Premature rupture of membranes			
Negative	98 (70.0%)	68 (70.1%)	0.986
Positive	42 (30.0%)	29 (29.9%)	
Amniotic fluid contamination			
Negative	133 (95.0%)	94 (96.9%)	0.697
Positive	7 (5.0%)	3 (3.1%)	
Placental anomaly			

Negative	129 (92.1%)	89 (91.8%)	0.913
Positive	11 (7.9%)	8 (8.2%)	
Umbilical cord bypass			
Negative	104 (74.3%)	72 (74.2%)	0.992
Positive	36 (25.7%)	25 (25.8%)	
Knotting of the umbilical cord			
Negative	140 (100.0%)	96 (99.0%)	0.853
Positive	0 (0.0%)	1 (1.0%)	
Umbilical cord torsion			
Negative	134 (95.7%)	89 (91.8%)	0.203
Positive	6 (4.3%)	8 (8.2%)	
Maternal diabetes mellitus			
Negative	123 (87.9%)	76 (78.4%)	0.050
Positive	17 (12.1%)	21 (21.6%)	
Maternal hypertension during pregnancy			
Negative	90 (64.3%)	64 (35.7%)	0.788
Positive	50 (66.0%)	33 (34.0%)	

Comparison of treatment of children between the two groups

The use rate of lung surfactant in the low-vitamin D group was higher than that in the high-vitamin D group, and the difference was statistically significant (P<0.05); the differences in hospitalization time and tracheal intubation rate were not statistically significant when comparing between the 2 groups (both P>0.05). See Table 3.

Table 3 Comparison of treatment of children between the two groups

Characteristics	Low vitamin D group (n=140)	High vitamin D group (n=97)	*p* value
Length of hospitalization (day)	10 (8-14)	9 (7-13)	0.595
Endotracheal intubation	3 (2.1%)	3 (3.1%)	0.97
Lung surfactant use	24 (17.1%)	7 (7.2%)	0.026

Comparison of pulmonary complications in children between the two groups

The incidence of RDS and BPD in the low-vitamin D group was significantly higher than that in the high-vitamin D group, and the differences were all statistically significant (P<0.05). The differences in the incidence of wet lung and pneumothorax between the 2 groups were not statistically significant (P>0.05). See Table 4.

Table 4 Comparison of pulmonary complications in children between the two groups (%)

Characteristics	Low vitamin D group (n=140)	High vitamin D group (n=97)	*p* value
wet lung	25 (17.9)	17 (17.5)	0.948

BPD	18 (12.9)	4 (4.1)	0.023
RDS	47 (33.6)	17 (17.5)	0.006
pneumothorax	5 (3.6)	3 (3.1)	1.000

Univariate and multivariate logistic regression analysis of serum 25(OH)D level and lung complications in preterm infants

The alternative indicators to be included in the multifactorial logistic regression analysis of serum 25(OH)D level and pulmonary complications in preterm infants were: season of birth (with reference to winter), serum 25(OH)D level (continuous variable), multiple births (with reference to singleton), 5 min Apgar score (continuous variable), history of prenatal use of hormones, and history of diabetes mellitus during maternal pregnancy. Univariate logistic regression analysis suggested that season of birth, serum 25(OH)D level, 5 min Apgar score, and prenatal hormone use were associated with pulmonary complications in preterm infants (P<0.05). Multifactorial logistic regression analysis showed that higher serum 25(OH)D levels reduced the risk of pulmonary complications in preterm infants, which was statistically significant (B=-0.056, RR= 0.946, 95% *CI*: 0.910-0.984, P=0.006); the higher the 5-min Apgar score was, the lower the incidence of pulmonary complications in preterm infants, which was statistical significance (B=-0.722, RR= 0.486, 95% *CI*: 0.281~0.840, P=0.010); prenatal use of hormones would reduce the risk of pulmonary complications in preterm infants (B=-0.763, RR= 0.466, 95% *CI*: 0.261~0.833, P=0.010). See Table 5.

Table 5 Univariate and multivariate logistic regression analysis of hypovitaminosis D and pulmonary complications in preterm infants

Characteristics	one-way regression analysis			multifactor regression analysis		
	B	RR (95% *CI*)	*p* value	B	RR (95% *CI*)	*p* value
season of birth	-0.744	0.475 (0.226-0.997)	0.049	-0.781	0.458 (0.208-1.005)	0.052
Serum 25(OH)D level	-0.047	0.954 (0.921-0.989)	0.010	-0.056	0.946 (0.910-0.984)	0.006
multiple births	-0.122	0.885 (0.507-1.547)	0.669	-	-	-
5min Apgar Rating	-0.618	0.539 (0.316-0.920)	0.024	-0.722	0.486 (0. 281-0.840)	0.010
Prenatal use of hormones	-0.711	0.491 (0.284-0.851)	0.011	-0.763	0.466 (0.261-0.833)	0.010
Maternal diabetes during pregnancy	0.358	1.430 (0.713-2.868)	0.313	-	-	-

The multifactor regression model test was tested by Hosmer-Lemeshow goodness of fit test, P=0.782,suggesting that the regression model was good good fit.

Discussion

The fetus itself cannot produce vitamin D. Maternal 25(OH)D crosses the placental barrier and serves as the main source of vitamin D in the fetus. Preterm infants are at high risk of vitamin D

deficiency due to maternal vitamin D deficiency[iii] , which leads to insufficient storage of vitamin D in the newborn, premature birth that disrupts the normal accumulation of calcium and phosphorus in the uterus, insufficient dietary supplementation of vitamin D, and impaired intestinal absorption. Several studies have reported that the prevalence of vitamin D deficiency in children ranges from 30% to 76%, including in the Middle East, Europe, Asia, and Africa [iv] . The prevalence of vitamin D deficiency is 64% in the United States and 83% in India. In the present study, 175 (73.84%) preterm infants were vitamin D deficient, 39 (16.46%) were vitamin D insufficient, and 23 (9.70%) were vitamin D adequate, which is in general agreement with the global prevalence of vitamin D deficiency.

Cuneyt Karagol [v] Retrospective analysis of vitamin D levels in 3,368 healthy children aged 0-18 years found that winter or spring and living north of the 40th parallel were risk factors for vitamin D deficiency. Kaibai et al.[vi] retrospectively analyzed 1,528,685 serum 25-hydroxyvitamin D (25(OH)D) results from the laboratory of the Goldfield Diagnostic Center, with samples drawn from individuals aged 0-119 years from January 2017 to December 2019 in 30 provinces in China, and there was a significant seasonal variation in serum 25(OH)D concentrations over a 3-year period, with higher median concentrations in summer (25.3 ng/mL (IQR 19.3-31.9 ng/mL)) in summer and lower (18.5 ng/mL (IQR)) 12.3-26.6 ng/mL)) in winter. A cross-sectional study[vii] showed a significant correlation between season and hypovitaminosis (winter-spring P= 0.007). Liu Ruiping [viii] et al. tested vitamin D in neonates born in different months and showed that it was highest in September (19.08±8.83 ng/mL) and lowest in January (12.87±5.80 ng/mL) throughout the year, suggesting that neonatal vitamin D levels varied according to the season of birth, with the highest in summer and the lowest in winter. The results of this study showed that the birth rate of the low-vitamin D group was significantly higher than that of the high-vitamin D group in the fall, and the difference was statistically significant ($P<0.05$), which slightly deviated from the results of the above studies, and may be related to the reduction of the time spent outdoors during pregnancy and the use of relevant sunscreens by pregnant mothers in order to avoid strong exposure to ultraviolet rays and overprotection, as well as to sample bias.

With the improvement of social living standards, the incidence of GDM has been a high trend, vitamin D affects glucose metabolism by the following mechanisms: (1) 1,25(OH)2D binds to the vitamin D receptor (VDR) on β-cells to regulate the intra- and extracellular calcium levels and promote the pancreatic β-cells to secrete insulin; (2) inhibition of parathyroid hormone secretion and regulation of the extracellular calcium level increase insulin mediated intracellular physiological processes and increase tissue sensitivity to insulin; (3) 1,25(OH)2D has immunomodulatory properties when bound to the VDR on immune cells; and (4) Vitamin D deficiency status is often indicative of a lack of outdoor activity, and lack of outdoor activity is a risk factor for insulin resistance and GDM. A meta-analysis found that , 1682 patients with GDM, of whom 837 received vitamin D supplementation.Vitamin D supplementation in patients with GDM increased serum 25(OH)D levels (SMD = 4.07, 95% CI: (2.73, 5.41)), and in addition, vitamin D supplementation reduced the risk of preterm labor (OR = 0.37, 95% CI: (0.22, 0.62)), suggesting that appropriate vitamin D supplementation may reduce adverse neonatal outcomes. This is consistent with the results of the present study, suggesting that appropriate vitamin D supplementation during or before pregnancy may be beneficial. However, well-designed randomized controlled trials are needed to validate the correlation between hypovitaminosis D status and GDM, and to determine the appropriate supplemental dose of vitamin D in different trimesters

as well as the target concentration of serum 25(OH)D.

The effects of vitamin D deficiency on neonates, especially in preterm infants, are worrisome and can lead to a variety of health problems in preterm infants, including neonatal respiratory disorders, which have become a hot research topic in recent years. In this study, we showed that the rate of lung surfactant utilization was higher in the low-vitamin D group than in the high-vitamin D group, and we considered that vitamin D deficiency affects lung maturation and is related to PS synthesis and secretion. The reasons are as follows[ix] , Vitamin D plays a key role in the development of lung function and synthesis of type II alveolar epithelial cells in fetuses and newborns. The active metabolite of vitamin D, 1,25(OH) D_{23} , inhibits the proliferation of airway smooth muscle cells, which leads to increased responsiveness to acetylmethacholine, increased airway resistance, and altered airway structure. It was found[x] that vitamin D inhibited the fibrogenic effects of transforming growth factor-β1 in rat lung fibroblasts and epithelial cells. In addition, a physiologically relevant BALB/C mouse model of vitamin D deficiency also showed associated defects in lung function[xi] .

Yoo Jinie Kimxii found that vitamin D deficiency or low vitamin D levels within 24 hours of birth were associated with the development of RDS, suggesting that testing or maintaining adequate neonatal vitamin D levels may reduce the risk of RDS. A study showed that the use of vitamin D as an adjunctive therapy in cases of RDS significantly reduced disease severity, complication rates, and length of hospitalization.Haiyan Gexiii et al, randomized 112 preterm infants into two groups, a control group and a vitamin D supplementation (VD) group.The VD group received vitamin D (800 IU/day) within 48 hours of birth for 28 consecutive days, and it was It was found that the incidence of BPD was reduced in the VD group compared to the control group, and the reduced serum 25(OH)D_3 was significantly elevated by vitamin D supplementation, demonstrating that early vitamin D supplementation significantly reduces the incidence of BPD in preterm infants. Lung surface-active substances are produced by alveolar type II epithelial cells, which have vitamin D receptor and renal tubular 1α-hydroxylase protein expression[xiv] . Therefore, alveolar type II epithelial cells may be target cells for vitamin D bioregulation, so vitamin D deficiency leads to insufficient alveolar surface-active substances, thus affecting the development of lung structure and function[xv] . The present study showed that the incidence of RDS and BPD was significantly higher in the low-vitamin D group than in the high-vitamin D group, suggesting that low vitamin D levels increase the incidence of RDS and BPD, which is in agreement with the results of other studies.

In this study, serum 25(OH)D level, 5 min Apgar score, and prenatal hormone use were found to be independent risk factors for pulmonary complications in preterm infants by multifactorial logistic regression analysis. With higher serum 25(OH)D levels, the incidence of pulmonary complications in preterm infants decreased, and there was an association between vitamin D levels and RDS and BPD, which was consistent with the results of the above studies. In asphyxiated children, hypoxia can lead to damage in multiple tissues and organs throughout the body, especially acute lung injury, which can reduce the production of epithelial cells of alveolar type II, leading to reduced expression of PS. Prenatal use of hormones may promote fetal lung maturation, thereby reducing the incidence of postnatal neonatal pulmonary complications.

Conclusion

Vitamin D deficiency is prevalent in preterm infants, and the lower the serum 25(OH)D level, the higher the incidence of pulmonary complications in preterm infants, and early vitamin D

supplementation may be beneficial in avoiding the occurrence of pulmonary complications in preterm infants. The present study has the disadvantage of not being able to perform maternal serum 25(OH)D levels during pregnancy to analyze the relationship between maternal vitamin D levels and pulmonary complications in preterm infants, which needs to be further explored in the future.

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1. Pulmonary surfactant（PS）
2. Respiratory distress syndrome（RDS）
3. Neonatal respiratory distress syndrome (NRDS)
4. Bronchopulmonary dysplasia (BPD)