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CLINICAL TRIAL REPORT

Vitamin D Status of Preterm Newborns at Approximately 4 Weeks of Age in Shenzhen, China: A Retrospective Observational Cohort Study Conducted Across Two Centers

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Background and Objectives: To examine the correlation between the concentration of vitamin D (VD) in venous blood at approximately 4 weeks of age (±4 weeks of age) and neonatal outcomes in preterm infants (birth weight <1500 g or gestational age <32 weeks) in two neonatal intensive care units (NICUs) located in Shenzhen, China.

Methods and Study Design: Preterm infants were split into two groups based on their VD concentration at ±4 weeks of age: VD insufficiency (VDI) group (≤20 ng/mL) and VD sufficient (VDS) group (>20 ng/mL). Binary logistic regression analysis was used to examine relationships between outcomes and VDI.

Results: Of 230 infants in total, 119 (51.7%) were assigned to the VDI group and 111 to the VDS group (48.3%). No correlation was found between serum VD at ±4 weeks of age and gestational age (p>0.05). The starting point of the two groups for oral VD intake did not differ significantly (p>0.05). At ±4 weeks of age, oral VD dose (P<0.05) was greater in the VDS group. Gestational diabetes mellitus was associated with VDI (OR=1.94, 95% CI 1.01–3.75, p=0.047) after controlling for this risk. Following correction for gestational age and oral VD dosage at ±4 weeks old, VDI was also linked to a significant risk of retinopathy of prematurity (OR=2.00, 95% CI 1.08–3.68, p<0.027).

Conclusion: Preterm newborns (gestational age <32 weeks or birth age <1500 g) in NICUs in Shenzhen, China continue to have significantly high VDI. Higher VDI is associated with gestational diabetes mellitus and retinopathy of prematurity.

Keywords: very preterm birth, very low birth weight infant, vitamin D, 4 weeks of age, outcome

Introduction

Vitamin D insufficiency (VDI) is prevalent in premature babies. In very preterm newborns, the incidence of VDI at birth can reach around 70%, due to early pregnancy termination and lack of a source of VD.[1,2] VD is crucial to calcium homeostasis, bone health, and overall health.[3–6] The most accurate indicator of VD deficiency is 25-hydroxyvitamin D (25-OH-D), which is the predominant and more stable form of VD circulating in the blood.[7] Research has established a link between VD deficit and preterm birth, and VDI also has a negative impact on pregnancy outcomes.[8] Therefore, it is essential to regularly monitor the VD status of preterm newborns and to supplement VD in a timely and acceptable manner. Serum 25-OH-D concentration have been measured approximately 4 weeks after birth in clinical studies conducted both domestically and in other countries to determine the VD status of preterm infants.[9,10] The aim of this study was to retrospectively examine the VD status at about 4 weeks postpartum [gestational age (GA) <32 weeks or birth weight (BW) <1500 g] in preterm newborns, assess its risk factors, and assess its influence on the major problems of preterm children.

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Methods

Participants

This study was an observational cohort, retrospective, two-center investigation. The study included all newborns admitted to the neonatology departments of Peking University Shenzhen Hospital and Shenzhen People's Hospital between January 1, 2020 and December 31, 2022. All newborns with a GA of less than 32 weeks or a BW of less than 1500 g who were hospitalized for more than or equal to 28 days and who survived at 36 weeks' postmenstrual age were included in the research cohort. Exclusion criteria included missing clinical data, congenital anomalies, congenital chromosomal or genetic metabolic illnesses, and failure to test 25-OH-D concentration in venous blood at about 4 weeks of age. Additionally, infants who died during the trial were not included. The hospital's academic ethics committee accepted this study without the need to obtain informed consent {Peking University Shenzhen Hospital Ethics Review (Research) [2019] No. (019-Revision 2)}.

Data Collection

Maternal age, method of conception, pregnancy-induced hypertension (PIH), and gestational diabetes mellitus (GDM) were among the maternal data gathered. Data about newborns, such as sex, BW, GA, delivery method, and multiple births (twins or more), were gathered. Records were kept on the usage of pulmonary surfactant (PS), length of stay, oral VD intake time, oral VD intake dose, and serum 25-OH-D concentration at approximately 4 weeks (±4 weeks) postpartum. A number of conditions potentially lead to poor outcomes in neonates, including periventricular leukomalacia in preterm infants (PVL), neonatal respiratory distress syndrome (NRDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), early onset sepsis (EOS), late onset sepsis (LOS), and bronchopulmonary dysplasia (BPD), and these were all considered in this study.

Measurements

On the day of blood collection, the hospital laboratory used an Access 25(OH) Vitamin D Total test to measure the concentration of serum 25-OH-D (Roche Cobas e601 automatic electrochemiluminescence immunoanalyzer and LIAISON® XL automatic immunochemiluminescence immunoanalyzer). The Access 25(OH) Vitamin D Total assay, which integrates 25-OH-D2 and 25-OH-D3 to determine total 25-OH-D concentrations directly, is a paramagnetic particle chemiluminescent immunoassay that serves as the best analyte for assessing VD status overall.

Standards and Definitions

Serum concentration of less than 20 ng/mL indicated VDI, with serum concentration of more than 20 ng/mL indicating VD adequacy.

The Expert Consensus on Diagnosis and Treatment of Neonatal Sepsis (version 2019)[11] was used for diagnostic standards for EOS and LOS. The Practice of Neonatology (5th Edition)[12] provided the diagnostic standards for RDS, IVH, NEC, retinopathy of prematurity (ROP), and PVL. Various definitions of BPD were used in our study. BPD (2001) was classed as mild, moderate, or severe and was defined as the need for supplemental oxygen for 28 days or longer.[13] BPD (2018) was defined as the need for respiratory support for at least 3 days, according to the revised GA of 36 weeks.[14] To determine the most appropriate diagnostic standards for BPD, Jensen et al carried out a comprehensive multicenter clinical analysis in 2019.[15,16] In our study, only oxygen flow was taken into account for grading BPD (2019), not oxygen concentration. Survival without major morbidity was defined as survival in the absence of any the serious morbidities indicated in the Data collection section.[17]

Statistical Analysis

Medians [M (Q1, Q3)] or percentages were used to express demographic information. Spearman correlation was employed for analysis. We used the chi-square test or the Kruskal–Wallis test in the univariate analysis. After adjusting

for variables in the univariate analysis, we performed a logistic regression analysis to determine the odds ratios (OR) based on the presence of VD. $P<0.05$ was deemed statistically significant. SPSS v.18.0 was used to perform the statistical analyses (SPSS Inc., Chicago, Illinois).

Results

Participant Attributes

A total of 454 in-born with a GA <32 weeks or BW <1500 g were included. Of these, 137 with missing serum 25-OH-D data at ±4 weeks of age and 87 babies who were hospitalized for fewer than 28 days were excluded. This left the data of 230 newborns for analysis (Figure 1).

Vitamin D Concentrations at Approximately 4 Weeks of Age

Figure 2 displays the distribution of serum VD levels in the 230 newborns at ±4 weeks of age. At this age, the mean serum 25-OH-D level was 19.8 (15.9, 23.8) ng/mL (Table 1). Table 1 shows that 119 newborns (51.7%) were in the VDI group and 111 infants (48.3%) were in the vitamin D sufficient (VDS) group. At ±4 weeks of age, there was no correlation between GA and 25-OH-D level (Rs=–0.1, $p=0.131$) (Figure 2).

Relationship Between Risk Factors and VDI

Lower VD levels were associated with a higher probability of GDM ($p=0.018$) and with a lower oral dosage of VD ($p=0.012$) at ±4 weeks of age (Tables 1 and 2). Nevertheless, following multivariable linear regression and correction for the oral intake dose of VD at ±4 weeks of age, only GDM was found to be significant (OR 1.94, 95% CI 1.01–3.75, $p<0.05$) (Table 3).

Relationship Between Significant Morbidity and VDI in Premature Newborns

Following multivariable linear regression, with correction for GA and the oral intake dose of VD at ±4 weeks of age, VDI was also linked to a high risk of ROP (OR=2.00, 95% CI 1.08–3.68, $p<0.05$) (Table 4).

Discussion

This was a retrospective, two-center, observational cohort study exploring VD status ±4 weeks postpartum (BW <1500 g or GA <32 weeks), assessing its risk factors, and assessing its influence on the major complications of preterm infants at Shenzhen People's Hospital and Peking University Shenzhen Hospital in China. According to our research, 51.7% of preterm infants who consistently received the recommended dose of VD after delivery were still

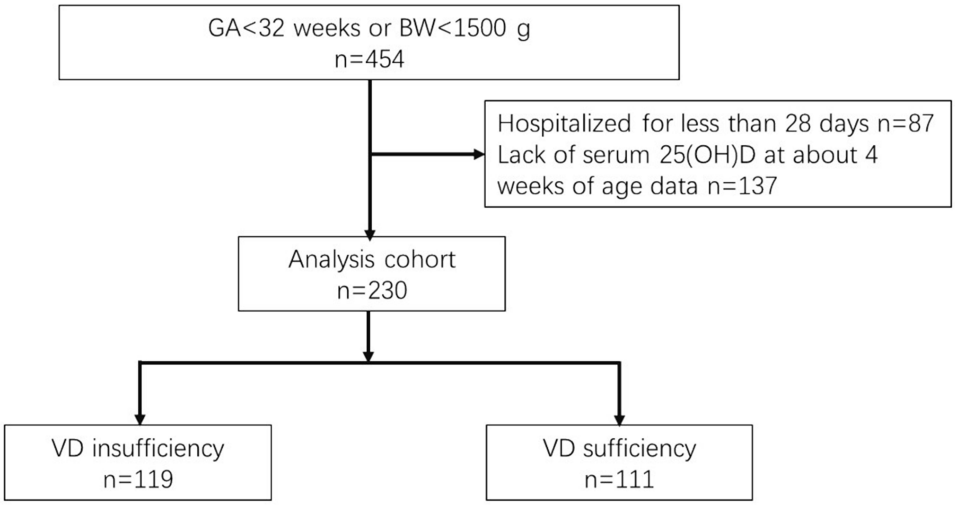

Figure 1 Flow chart for the population under study.

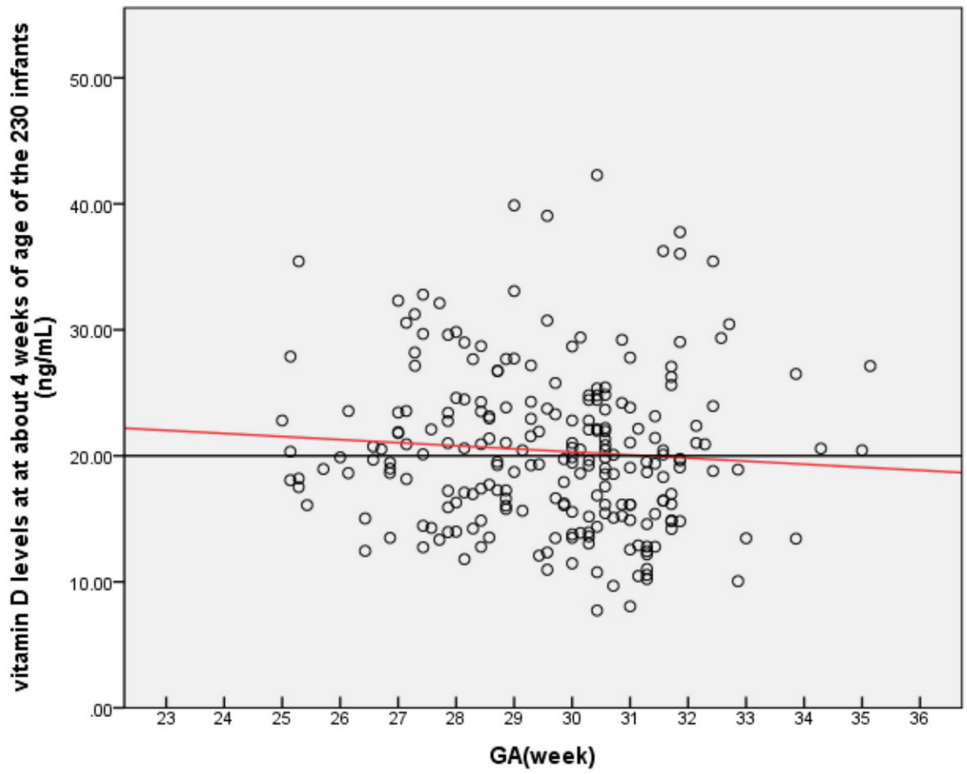

Figure 2 The scatter plot displays the distribution of serum 25-OH-D levels in 230 newborns at approximately 4 weeks of age based on gestational age. The 25-OH-D level is shown as a solid line at 20 ng/mL. Coefficient of correlation: Rs=–0.1; p>0.05.

VD deficient at the age of 4 weeks. The results of other studies have varied, owing to inconsistent detection techniques and VDI cut-off values; however, the prevalence of VD deficiency has been found to be more than half of infants, reaching as high as 80%.[18–20]

Table 1 Traits of Premature Babies and Levels of Vitamin D at Approximately 4 Weeks of Life

	VDI (n=119)	VDS (n=111)	Z/X^2	*p*
VD levels (ng/mL)[a]	16.08(13.49,18.56)	23.84(21.80,27.88)	−0.054	0.957
Maternal age, M(Q1, Q3) years	31.00(28.00,34.00)	31.00(28.00,34.00)	−0.233	0.817
IVF baby, n(%)	28(23.5)	36(32.4)	2.267	0.143
Cesarean delivery, n(%)	102(85.7)	83(74.8)	4.367	0.046*
PIH, n(%)	40(33.6)	23(20.7)	4.800	0.038*
GDM, n(%)	19(16.0)	33(29.7)	6.218	0.018*
Singleton, n(%)	41(34.5)	41(36.9)	0.154	0.783
Sex (male), n(%)	71(59.7)	53(47.7)	3.282	0.070
GA, M(Q1, Q3) weeks	30.14(28.43,31.14)	29.57(28.00,30.86)	−0.970	0.333
BW, M(Q1, Q3) g	1200(950, 1520)	1210(1000,1430)	−0.054	0.958
Season of delivery				
Winter, n(%)	32(26.9)	23(20.7)	3.327	0.349
Spring, n(%)	27(22.7)	36(32.4)	3.327	0.349
Summer, n(%)	34(28.6)	32(28.8)	3.327	0.349
Fall, n(%)	26(21.8)	20(18.0)	3.327	0.349
Oral VD intake time (d)	8.00(7.00,10.00)	8.00(7.00,10.00)	−1.155	0.249
Oral VD intake dose (IU)[b]	900(500, 900)	900(500, 900)	−2.517	0.012*

Notes: [a]VD levels at ±4 weeks postpartum; [b]oral VD intake dose at ±4 weeks postpartum. *$p<0.05$.
Abbreviations: BW, birth weight; GA, gestational age; GDM, gestational diabetes mellitus; IVF, in vitro fertilization; M, median; PIH, pregnancy-induced hypertension; VD, vitamin D; VDI, vitamin D insufficiency; VDS, vitamin D sufficiency.

Table 2 Risk Variables and VD Levels at ±4 Weeks of Age Analyzed Using Univariate Binary Regression

	B	Wals	*p*	OR	95% CI
Usage of PS	−0.254	0.651	0.420	0.775	0.418–1.438
Oral VD intake time	−0.010	0.094	0.759	0.990	0.929–1.055
Oral VD intake dose [a]	0.002	6.372	0.012*	1.002	1.000–1.003
Length of stay	−0.002	0.073	0.786	0.998	0.984–1.012
NRDS	0.234	0.354	0.552	1.263	0.585–2.726
NEC	−0.368	0.226	0.635	0.692	0.151–3.163
EOS	0.049	0.018	0.892	1.051	0.515–2.142
IVH	1.196	0.274	0.601	1.216	0.584–2.530
PVL	−1.484	1.737	0.187	0.227	0.025–2.060
ROP	−0.196	1.985	0.159	0.822	0.672–1.079
BPD(2001)	−0.334	1.509	0.219	0.716	0.420–1.220
BPD(2018)	−0.415	1.560	0.212	0.660	0.344–1.266
BPD(2019)	−0.464	1.978	0.160	0.629	0.329–1.201
Survival without major morbidity	−0.202	0.349	0.555	0.817	0.418–1.597

Notes: [a]oral VD intake dose at ±4 weeks postpartum. *p<0.05.
Abbreviations: BPD, Bronchopulmonary dysplasia; EOS, early onset sepsis; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRDS, neonatal respiratory distress syndrome; PS, pulmonary surfactant; PVL, periventricular leukomalacia in preterm infants; ROP, retinopathy of prematurity; VD, vitamin D.

Table 3 Multivariate Binary Regression Analysis of Risk Variables and VD Levels After Controlling for Oral VD Intake Dose at ±4 Weeks of Age

	B	Wals	*P*	OR	95% CI
Cesarean delivery	0.402	1.193	0.275	1.495	0.726–3.079
PIH	−0.513	2.510	0.113	0.599	0.317–1.129
GDM	0.665	3.948	0.047*	1.944	1.009–3.747
Constant	−1.414	4.424	0.035	0.243	

Note: *p<0.05.

Table 4 Results of Multivariate Binary Regression Analysis Performed to Determine Primary Complications and VD Levels After Adjusting for GA and Oral Dosage of VD at ±4 Weeks of Age

	B	Wals	*p*	OR	95% CI
NRDS	0.416	0.890	0.346	1.515	0.639–3.593
NEC	−0.209	0.065	0.798	0.812	0.164–4.017
EOS	−0.232	0.272	0.602	0.793	0.332–1.895
IVH	0.362	0.600	0.439	1.437	0.574–3.595
PVL	−1.778	2.237	0.135	0.169	0.016–1.737
ROP	0.691	4.874	0.027*	1.995	1.081–3.684
BPD(2001)	0.520	1.860	0.173	1.682	0.797–3.550
Constant	1.309	0.163	0.686	3.704	

Note: *p<0.05.

According to our univariate analysis, there was a higher intake of VD in the VDS group at ±4 weeks of age, which was also consistent with clinical practice and related to the dose dependence of VD. The oral intake dose of VD at 4 weeks of age was also closely related to the level of VD at 4 weeks of age (p<0.05). We discovered no correlation between GA and VD content in venous blood at ±4 weeks of age (Figure 2).This could be connected to the lengthier

intravenous feeding of multivitamins in preterm children with lower GAs, as well as the increased oral VD consumption in infants with an increase in alkaline phosphatase concentration 2 weeks after delivery.[21–23] Furthermore, the univariate analysis indicated a strong correlation between VDI and PIH (P<0.05). However, the multivariable analysis revealed that the association between the two variables was not statistically significant (P>0.05), potentially attributable to the presence of multiple confounding factors.

The multivariate analysis revealed a relationship between VDI and GDM after correcting for the oral intake dose of VD at ±4 weeks of age. Many studies have demonstrated that low levels of VD during pregnancy can result in low levels of VD in premature infants after they are born.[24–26] According to Milan et al,[27] GDM patients had lower serum VD levels and serum VD was negatively correlated with their fasting blood glucose levels. Additionally, higher expression of genes linked to VD resistance was seen in GDM patients, and this expression was inversely correlated with serum VD levels. Ali Khan et al[28] discovered that pregnant women with GDM had low serum VD levels, which may be directly linked to the functional genetic variation of the VD receptor gene. Owing to the retrospective nature of our research, data on the status and degree of VD supplementation during pregnancy could not be gathered. Therefore, to better understand VDI in premature infants in Shenzhen, we are developing a prospective large-sample multicenter cohort study.

After controlling for the interaction of gestational age at birth and total vitamin D dose, multivariable regression revealed a strong correlation between VDI and risk for ROP. This finding aligns with prior studies. Kabataş et al[29] determined that there is an inverse correlation between 25-OH-D levels and risk of ROP development and treatment requirement. Low vitamin D levels might have a role in the aetiopathogenesis of ROP in premature infants. Boskabadi et al[30] found that Low serum levels of vitamin D in premature infants and their mothers were associated with incidence of ROP. The higher the stage of ROP, the greater was the severity of vitamin D deficiency. As vitamin D directly affects the vascular endothelial stability, its deficiency will most likely affect the incidence of ROP in premature infants who are at risk of vitamin D deficiency. The inflammatory and angiogenic effects of vitamin D deficiency can cause early damage to the retinal blood vessels. Greater risk for ROP in VDI infants, could be related to the antioxidant effects and improved micronutrient and mineral absorption.[31] The incidence of additional unfavorable outcomes, including as RDS, NEC, EOS, IVH, PVL, and BPD (2001, 2018, 2019), did not differ statistically significantly between the two groups (Tables 1 and 4). There was no correlation between these outcomes and VD levels. This aligns with the findings of earlier research.[32] Additionally, research has demonstrated a strong correlation between preterm outcomes and low VD levels.[33,34] However, the results of studies vary greatly from one another, which may be directly related to research techniques, sample size, and GA in the studies.

Our study had some limitations. First, it was a two-center, retrospective study. Second, the sample size was small due to the large number of cases for which venous blood 25-OH-D concentration was not recorded at ±4 weeks after birth. Many clinical data cannot be collected prospectively. Our next research project will be to conduct a prospective multicenter homogenization study to assess VD status in preterm infants in Shenzhen and determine the effects of VD supplementation in preterm infants of different gestational ages.

Conclusion

In neonatal intensive care units in Shenzhen, China, preterm newborns (BW <1500 g or GA <32 weeks) still have a very high rate of VDI. An increased risk of VDI was associated with GDM and ROP.

Data Sharing Statement

The corresponding author may obtain any data from the study upon reasonable request, guoyanping1223@163.com (Yanping Guo).

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Disclosure

The authors have no conflicts of interest to declare in this work.

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