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Effects of Vitamin D deficiency and supplementation on 25(OH)D3 levels and neuropsychobehavioral development in premature infants.

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Keywords: Vitamin D; Neuropsychobehavioral development; Premature infants; Vitamin D; 25(OH)D3; Neurodevelopment; Psychomotor Performance; Infant, Premature.

Abstract. This study systematically examined how vitamin D metabolic imbalance impacts 25(OH)D3 levels and neuropsychological development in premature infants and proposed a personalized supplementation approach. Premature infants were classified as adequate, insufficient, or deficient based on umbilical cord blood 25(OH)D3 levels and then randomly assigned to either a standard-dose group (800 IU/d) or an individualized supplementation group (400-1000 IU/d) with vitamin D. In the vitamin D-deficient group, infants receiving personalized supplementation had significantly higher 25(OH)D3 levels at three and nine months, adjusted for gestational age, than those receiving the fixed dose, indicating that 1000 IU/d is more effective than 800 IU/d for correcting deficiency ($p<0.05$). At nine and 18 months adjusted gestational age, infants in the vitamin D-insufficient and deficient groups scored significantly lower on the Gesell Developmental Scales across categories such as gross motor, fine motor, language, adaptive, and social skills compared to the adequate group ($p<0.05$). Within the deficient group, those receiving personalized supplementation scored higher in all five areas at both nine and 18 months adjusted gestational age compared to those on the fixed dose ($p<0.05$). The study highlights notable differences in umbilical cord blood 25(OH)D3 levels among premature infants, emphasizing that a customized vitamin D supplement protocol is more effective for correcting deficiencies.

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Efectos de la deficiencia de vitamina D y la suplementación sobre los niveles de 25(OH)D3 y el desarrollo neuropsicológico-conductual en bebés prematuros.

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Palabras clave: Vitamina D; 25(OH)D3; Desarrollo Neuropsicológico/Desarrollo Psicomotor; Recién Nacido; Prematuro.

Resumen. Este estudio exploró sistemáticamente el impacto del desequilibrio metabólico de la vitamina D en los niveles de 25(OH)D3 y en el desarrollo neuropsicológico de bebés prematuros, y propuso una estrategia de suplementación individualizada. Los bebés prematuros se categorizaron en grupos adecuados, insuficientes y deficientes según los niveles de 25(OH)D3 en la sangre del cordón umbilical, y luego se asignaron aleatoriamente a un grupo con dosis estándar (800 UI/día) o a otro grupo con suplementación individualizada (400-1000 UI/día) con vitamina D. Entre los bebés prematuros con deficiencia de vitamina D, el grupo de suplementación individualizada presentó niveles significativamente más altos de 25(OH)D3 a los 3 y 9 meses de edad gestacional corregida, en comparación con el grupo de dosis estándar, lo que indica que una dosis de 1000 UI/día fue más efectiva que 800 UI/día para corregir la deficiencia de vitamina D ($p<0,05$). A los 9 y 18 meses de edad gestacional corregida, los bebés prematuros de los grupos con insuficiencia y deficiencia de vitamina D obtuvieron puntuaciones significativamente más bajas en las Escalas de Desarrollo de Gesell para la habilidad motora gruesa, la habilidad motora fina, la competencia lingüística, la capacidad adaptativa y la habilidad personal-social en comparación con el grupo adecuado ($p<0,05$). Dentro del grupo deficiente, el grupo de suplementación individualizada obtuvo puntuaciones más altas en las cinco habilidades a los 9 y 18 meses de edad gestacional corregida en comparación con el grupo de dosis estándar ($p<0,05$). Existen diferencias significativas en los niveles de 25(OH)D3 en la sangre del cordón umbilical entre los bebés prematuros, y un protocolo de suplementación de vitamina D específico para cada individuo es más eficaz para corregir la deficiencia de vitamina D.

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INTRODUCTION

Premature infants, defined as those born before 37 weeks of gestation, encounter various health issues after birth because their organ systems are not fully developed[1]. In recent years, with the continued development of perinatal medicine and significant advances in neonatal intensive care and diagnostic techniques, the treatment of premature infants has been greatly enhanced, resulting in a rising survival rate [2]. Subsequent to their survival, long-term issues such as abnormal neurological development in premature infants have also received increasing attention [3]. The normal development of the nervous system is directly related to the future quality of life of premature infants, including cognition, motor skills, language, and other aspects [4]. Therefore, identifying

factors that affect the neuropsychological and behavioral development of premature infants and implementing effective interventions are of great significance for improving their prognosis.

Vitamin D, a crucial fat-soluble nutrient, holds a fundamental position in maintaining human health [5]. In recent years, in-depth research on vitamin D and its roles in bone health, immune function, and neurodevelopment has received increasing attention [6, 7]. Especially among premature infants, pediatric research has increasingly focused on vitamin D status and corresponding supplementation strategies [8]. Premature infants often suffer from vitamin D deficiency [9, 10]. On the one hand, premature infants have inadequate vitamin D stores during pregnancy, especially in the late gestational period, when the amount of vitamin D obtained by the fetus from the mother gradually increases; however, premature birth leads to relatively insufficient vitamin D stores [11]. On the other hand, premature infants have a limited capacity to synthesize vitamin D through their skin after birth, and breast milk, typically their primary source of nutrition, provides insufficient vitamin D to meet their rapid growth and developmental demands [12, 13]. Furthermore, premature infants may not receive adequate sunlight exposure during their hospitalization, thereby hindering vitamin D synthesis[14]. Humans obtain vitamin D primarily from two sources: skin synthesis of 7-dehydrocholesterol under UV-B light to form vitamin D3, and dietary intake of vitamin D2 [15]. Both vitamin D forms undergo hepatic hydroxylation to yield 25(OH)D3, which then undergoes renal metabolism to form its biologically active form, 1,25(OH)2D3 [16]. This metabolic pathway requires the collaboration of various organs, with 25(OH)D3 being the main circulating form and the key indicator for evaluating vitamin D levels [17].

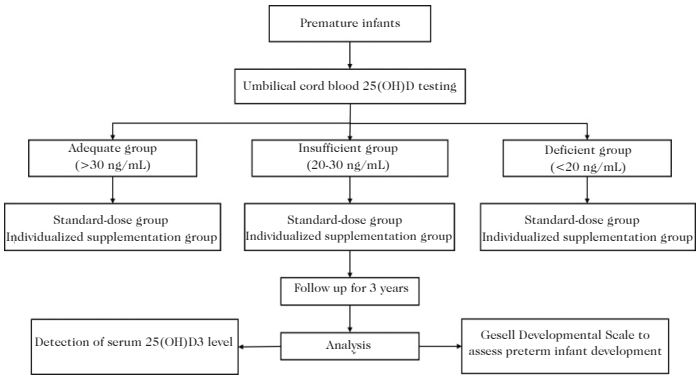
Vitamin D deficiency not only affects the bone development of premature infants but may also have far-reaching impacts on their neuropsychological and behavioral development [18]. Research indicates that insufficient vitamin D levels in premature infants may impair growth and development, including intellectual and motor abilities, at one year of age [19]. Moreover, insufficient vitamin D levels may affect the neurological and behavioral development of preterm infants, particularly if they do not receive adequate supplementation shortly after birth[20]. A study demonstrated a positive association between serum 25(OH)D3 levels in premature infants and neuropsychological developmental quotient scores, which were enhanced by vitamin D supplementation administered both prenatally and postnatally [21]. This suggests that adequate vitamin D supplementation has a positive effect on the neurodevelopment and cognitive function of premature infants. Timely vitamin D supplementation can alleviate vitamin D deficiency and mitigate its adverse effects on neurodevelopment, making it crucial for improving the long-term prognosis of premature infants [22]. Vitamin D influences the morphogenesis and physiological functions of the nervous system through diverse mechanisms, including regulating the expression of neurotrophic factors, influencing neurotransmitter synthesis, and modulating calcium signaling pathways [23]. Vitamin D and its receptor (VDR) are ubiquitously expressed across diverse tissues and cell types in the human body, including neurons and glial cells in the central nervous system, and participate in neuronal proliferation, differentiation, and apoptosis. Vitamin D is essential for neurodevelopment via epigenetic regulation mediated by VDR [24, 25]. 1,25(OH)2D3 upregulates the expression of synaptic proteins such as Synaptophysin and PSD-95, promoting synaptic plasticity. Additionally, vitamin D influences behavioral control and cognitive function by regulating the activity of the dopamine synthesis rate-limiting enzyme (tyrosine hydroxylase) and the glutamate transporter (EAAC-1) [26, 27]. Therefore, examining the impact of vitamin D insufficiency and augmentation on serum 25[OH]D3 concentrations, alongside neuro-

cognitive and behavioral progress in preterm infants, possesses considerable theoretical and practical significance.

At present, there is no universally agreed standard for the dose and schedule of vitamin D supplements for premature babies, with variations in recommendations among countries and organizations [28, 29]. Generally speaking, the range of vitamin D supplementation for premature infants is 400-1000 IU/day, and the specific dosage needs to be adjusted according to factors such as gestational age, birth weight, and feeding mode [30]. Numerous studies have explored the effects of vitamin D supplementation on 25(OH)D3 levels in premature infants, revealing that adequate supplementation can significantly elevate serum 25(OH)D3 levels; nonetheless, it is crucial to recognize that the connection between dosage and 25(OH)D3 levels is non-linear, and excessively high doses may pose a risk of vitamin D excess or toxicity [31, 32]. Secondly, the duration of supplementation also affects the outcome, with studies showing that long-term supplementation maintains stable 25(OH)D3 levels better than short-term supplementation[33]. In addition, factors such as gestational age, birth weight, and liver and kidney function status in premature infants also affect the metabolism and utilization efficiency of vitamin D [34]. One of the research hotspots is the comparison of the effects of different supplementation regimens. Drawing on the aforementioned research background and evidence, this study aims to determine the optimal dose and schedule for administering vitamin D supplements to premature infants, while comprehensively assessing the potential long-term effects of such supplementation on their 25(OH)D3 levels and neuropsychobehavioral development.

Patients and Methods

This is a clinical study conducted in the neonatal unit at our hospital's Children's Medical Center. The designed operational procedure is shown below.



Clinical data

A total of 175 premature infants admitted between January 2020 and December 2021 who underwent umbilical cord blood 25(OH)D3 testing within 24 hours after birth were selected as study subjects. Inclusion criteria included: gestational age less than 37 weeks; no severe complications; stable vital signs; mothers without severe pregnancy-related complications; and participants free from conditions or medications that could affect calcium and vitamin D metabolism. Exclusion criteria included: twin or multiple pregnancies; congenital malformations affecting normal body structure and function; genetic metabolic diseases; brain hypoplasia with obvious neurological abnormalities; and mothers with hypertension, diabetes, metabolic diseases, or other conditions during pregnancy that could negatively impact the fetus.

Grouping and intervention

All premature infants underwent umbilical cord blood 25(OH)D3 testing within 24 hours of birth and were classified into three groups: adequate (>30 ng/mL), insufficient (20-30 ng/mL), and deficient (<20 ng/mL). Each group was further divided into a standard vitamin D dosage group or an individualized supplementation group. All premature infants received vitamin D3 supplementation starting on the first day after birth. The standard-dose group received a routine supplementation of 800 IU/day, while the individualized group received 400, 800, or 1000

IU/day for three months, depending on their 25(OH)D3 levels (adequate, insufficient, or deficient, respectively). After three months, the dose was increased to 400 IU/day for all infants and maintained at this level until age 3 years. Follow-up visits occurred in the outpatient clinic over three years, and cases lost to follow-up were excluded. Ultimately, 175 infants completed the follow-up: 51 in the adequate group (25 in the standard dosage group and 26 in the individualized group), 54 in the insufficient group (26 in the standard dosage group and 28 in the individualized group), and 70 in the deficient group (35 in each group). All premature infants received oral vitamin D3 drops in capsule form [400 IU/capsule, Sinopharm Xingsha Pharmaceutical (Xiamen) Co., Ltd.].

Observation indicators

(1) Serum 25(OH)D3 levels served as a crucial indicator for assessing vitamin D nutritional status. Regular monitoring of serum 25(OH)D3 levels at 24 hours after birth, at 3 months, at 9 months' corrected gestational age (CGA), and at 18 months' CGA can provide insights into the dynamic changes in vitamin D status in premature infants and evaluate the effectiveness of vitamin D supplementation.

(2) The Gesell Developmental Scales were used to evaluate the developmental status of premature infants. This scale covers adaptive ability, gross motor skills, fine motor skills, language ability, and personal-social skills, offering a comprehensive view of the children's intellectual development. Assessments with the Gesell Developmental Scales were performed at 9 months CGA and 18 months CGA. A pediatric nurse trained to administer the scales conducted these assessments at each time point. The scale includes adaptive ability, gross motor skills, fine motor skills, linguistic ability, and personal-social ability, fully reflecting children's intellectual growth. For children aged 0-3, the scale contains 514 items, all completed within 60 minutes. Results are expressed as a Developmental Quotient (DQ). DQ is calculated as Measured Developmental Age divided by Chronological Age, multiplied by 100. A DQ of 130 or higher indicates superior development; 110 to 129, good development; 80 to 109, average development; 70 to 79, borderline low development; and below 70, indicates intellectual developmental delay.

Statistical analysis

Statistical analysis was done with SPSS 25.0. Normally distributed data were reported as mean ± SD and analyzed using a t-test (for two groups) or ANOVA with Bonferroni correction (for multiple groups). Categorical data were presented as the number of individuals and the composition ratio (%), and the chi-square test was employed for analysis. A p-value < 0.05 was considered statistically significant.

RESULTS

Comparison of Baseline characteristics

Baseline demographic features showed no significant differences among the adequate, insufficient, and deficient groups ($p > 0.05$), ensuring comparability of subsequent intervention effects (Table 1).

Comparison of 25(OH)D3 levels among the three groups of infants at 24 hours after birth, 3 months after birth, 9 months CGA, and 18 months CGA

At 24 hours after birth, 3 months after birth, and 9 months CGA, the 25(OH)D3 levels in both the vitamin D insufficient group and the deficient group were lower than those in the adequate group ($p<0.05$). At 18 months CGA, there were no statistically significant differences in 25(OH)D3 levels among the three groups of infants ($p>0.05$ (Table 2).

Table 1. Comparison of baseline characteristics.

Variables	Adequate group (n=51)	Insufficient group (n=54)	Deficient group (n=70)	F/χ^2	p
Gender (n, %)					
male	23 (45.10)	25 (46.30)	33 (47.14)	0.050	0.975
female	28 (54.90)	29 (53.70)	37 (52.86)		
Mode of delivery (n, %)					
spontaneous labor	25 (49.02)	26 (48.15)	31 (44.29)	0.318	0.853
cesarean section	26 (50.98)	28 (51.85)	39 (55.71)		
Gestational age (weeks)	35.33±0.74	35.43±0.63	35.40±0.71	0.248	0.781
Birth weight (g)	2462.82±211.96	2489.46±212.43	2459.87±205.66	0.344	0.709
Mother age (years)	28.96±5.38	28.76±4.59	28.94±5.33	0.026	0.974
1 min Apgar score (scores)	8.33±0.62	8.30±0.71	8.30±0.73	0.046	0.955
5 min Apgar score (scores)	9.04±0.34	9.11±0.32	9.04±0.27	0.971	0.381

Baseline characteristics are presented as mean ± SD or n (%). Between-group differences were assessed using one-way ANOVA for continuous variables and the χ^2 test for categorical variables.

Table 2. Comparison of 25(OH)D3 levels at different time points in the 3 groups.

Groups	n	24 h after birth	3 months after birth	9 months CGA	18 months CGA
Adequate group	51	35.74±4.27	34.95±4.38	35.82±3.88	35.18±4.83
Insufficient group	54	24.15±2.14[a]	29.48±3.44[a]	31.07±4.38[a]	34.53±4.61
Deficient group	70	13.18±2.31[ab]	23.54±4.24[ab]	29.93±5.00[a]	34.65±4.10
F		853.143	118.449	26.8893	0.327
p		0.000	0.000	0.000	0.722

Data are presented as mean ± SD in ng/mL. Between-group comparisons at each time point were performed using one-way ANOVA, followed by Bonferroni post hoc tests. [a]$p<0.05$ vs. Adequate group; [b]$p<0.05$ vs. Insufficient group. CGA: corrected gestational age.

Comparison of 25(OH)D3 levels between the standard dosage group and the individualized supplementation group within the deficient group

Within the deficient group, there were no statistically significant differences in 25(OH)D3 levels between the standard-dose and individualized-supplementation groups at 24 hours after birth ($p>0.05$). However, at 3 months after birth, 9 months CGA, and 18 months CGA, the 25(OH)D3 levels in the individualized supplementation group were significantly higher than those in the standard dose group ($p<0.05$) (Table 3).

Comparison of Gesell Developmental Scales scores among the three groups of infants at 9 months CGA and 18 months CGA

At both the 9- and 18-month CGAs, significant differences were observed in scores across the five abilities among the three infant groups ($p<0.05$). Pairwise comparisons revealed that the scores for the five abilities in both the insufficient and deficient groups were lower than those in the adequate group ($p<0.05$). Nonetheless, the scores of the five abilities did not show significant statistical differences when comparing the insufficient and deficient groups ($p>0.05$) (Tables 4 and 5).

Table 3. Comparison of 25(OH)D3 levels between the standard dosage group and the individualized supplementation group within the deficient group.

Groups	*n*	24 h after birth	3 months after birth	9 months CGA	18 months CGA
Standard dose group	35	13.15±2.46	21.34±3.55	27.29±4.18	32.82±3.81
Individualized supplementation group	35	13.22±2.18	25.74±3.73	32.56±4.37	36.47±3.55
t		0.126	5.049	5.146	4.152
p		0.900	0.000	0.000	0.000

Data are presented as mean ± SD in ng/mL. Between-group differences were evaluated using two-sample t-tests for independent samples. CGA: corrected gestational age.

Table 4. Comparison of Gesell Developmental Scales scores among the three groups of infants at 9 months CGA.

Groups	*n*	gross motor ability	fine motor ability	linguistic competence	adaptive capacity	personal-social ability
Adequate group	51	96.31±8.61	97.45±9.36	96.49±7.79	97.22±10.24	96.22±9.88
Insufficient group	54	88.63±6.22[a]	88.78±8.51[a]	90.46±7.35[a]	91.56±8.21[a]	90.11±10.19[a]
Deficient group	70	87.57±5.65[a]	87.34±9.62[a]	89.70±9.23[a]	90.50±9.57[a]	88.64±9.60[a]
F		16.216	19.494	11.165	8.224	9.258
p		0.000	0.000	0.000	0.000	0.000

Data are presented as mean ± SD. Between-group comparisons at each time point were performed using one-way ANOVA, followed by Bonferroni post hoc tests. [a]$p<0.05$ vs. Adequate group. CGA: corrected gestational age.

Table 5. Comparison of Gesell Developmental Scales scores among the three groups of infants at 18 months of CGA.

Groups	*n*	gross motor ability	fine motor ability	linguistic competence	adaptive capacity	personal-social ability
Adequate group	51	96.45±9.16	97.78±10.22	97.65±7.84	97.98±10.21	97.35±10.21
Insufficient group	54	92.61±7.98[a]	91.35±8.77[a]	92.33±8.64[a]	93.44±8.16[a]	92.65±8.54[a]
Deficient group	70	90.06±7.92[a]	89.67±8.64[a]	90.71±7.97[a]	92.84±7.33[a]	91.90±7.33[a]
F		8.721	12.223	11.164	6.012	6.503
p		0.000	0.000	0.000	0.003	0.002

Data are presented as mean ± SD. Between-group comparisons at each time point were performed using one-way ANOVA, followed by Bonferroni post hoc tests. [a]$p<0.05$ vs. Adequate group. CGA: corrected gestational age.

Comparison of Gesell Developmental Scales scores between the standard dosage group and the individualized supplementation group within the deficient group at 9 months CGA and 18 months CGA

Within the deficient group, at both 9-month and 18-month CGA, infants in the individualized supplementation group scored higher on gross motor ability, fine motor ability, linguistic competence, adaptive capacity, and personal-social ability than those in the standard dosage group ($p<0.05$). See Tables 6 and 7.

Table 6. Comparison of Gesell Developmental Scales scores between the standard dosage group and the individualized supplementation group within the deficient group at 9 months CGA.

Groups	*n*	gross motor ability	fine motor ability	linguistic competence	adaptive capacity	personal-social ability
Standard dosage group	35	85.20±9.57	84.37±9.66	86.97±8.01	87.31±9.77	85.29±9.51
Individualized supplementation group	35	91.29±8.53	90.31±8.74	92.43±9.66	93.69±8.35	92.00±8.57
F		2.809	2.698	2.573	2.933	3.103
p		0.007	0.009	0.012	0.005	0.003

Note: Data are presented as mean ± SD. Between-group differences were evaluated using two-sample t-tests for independent samples. CGA: corrected gestational age.

Table 7. Comparison of Gesell Developmental Scales scores between the standard dosage group and the individualized supplementation group within the deficient group at 18 months CGA.

Groups	*n*	gross motor ability	fine motor ability	linguistic competence	adaptive capacity	personal-social ability
Standard dosage group	35	86.43±7.18	86.49±8.03	86.77±7.53	88.91±6.29	87.57±5.65
Individualized supplementation group	35	93.69±6.98	92.86±8.14	94.66±6.34	96.77±6.15	96.23±6.21
F		4.288	3.297	4.738	5.284	6.100
p		0.000	0.002	0.000	0.000	0.000

Data are presented as mean ± SD. Between-group differences were evaluated using two-sample t-tests for independent samples. CGA: corrected gestational age.

DISCUSSION

Vitamin D plays numerous physiological roles in the human body, including maintaining bone health, modulating the immune system, influencing cell differentiation, and contributing to neurodevelopment, among other functions [35]. Vitamin D can affect the development of the normal fetal brain by regulating the expression of neurotrophic factors, modulating cytokines activity, synthesizing neurotransmitters, modulating intracellular calcium signaling, and controlling the activity of genes and proteins responsible for neuronal differentiation and metabolic processes [36]. During the final stage of pregnancy, the fetus's need for vitamin D increases significantly to support rapid bone growth and calcification [37]. The mother transfers vitamin D to the fetus through the placenta, helping the fetus establish sufficient vitamin D stores to meet early postnatal growth demands [38]. Premature infants, due to their shorter gestational age at birth, have relatively inadequate vitamin D stores, and their rapid growth and development further increase their need for vitamin D [39]. Additionally, premature infants have thinner skin and less subcutaneous fat, which decreases their ability to synthesize vitamin D, making them more vulnerable to deficiency [40]. In our study, we examined 25(OH)D3 levels in the umbilical cord blood of preterm infants, revealing a high rate of vitamin D deficiency in this population.

The results of this research indicate that preterm infants with insufficient vitamin D had significantly lower 25(OH)D3 concentrations at 24 hours, 3 months, and 9 months CGA than those with normal vita-

min D levels. This suggests that variations in umbilical cord blood vitamin D levels at birth significantly influence 25(OH)D3 levels in premature infants during the early postnatal period. Despite postnatal vitamin D3 supplementation, premature infants in the deficient group did not achieve 25(OH) D3 levels comparable to those in the adequate group within a relatively short timeframe. This may relate to the physiological characteristics of premature infants, whose livers and kidneys are not fully developed, limiting their ability to metabolize and convert vitamin D, resulting in a slower increase in 25(OH)D3 levels after supplementation in the deficient group [41]. It may also be affected by the dosage of supplementation and individual differences. Although a standard vitamin D3 supplement was given, absorption and utilization efficiency vary among individuals, making it difficult for premature infants in the deficient group to quickly correct their deficiency [42]. By 18 months CGA, there were no statistically significant differences in 25(OH)D3 levels among the three infant groups. This indicates that, after a period of supplementation, premature infants in the deficient group had sufficient time to increase their levels, gradually closing the gap with the adequate group and eventually reaching comparable levels at 18 months CGA. This improvement may be due to the gradual maturation of liver and kidney function as infants grow, enhancing their ability to metabolize vitamin D, thereby allowing better utilization of supplemental vitamin D3 and a subsequent rise in 25(OH)D3 levels [43]. It may also be related to the cumulative effect of the dose and duration of supplementation. After a longer period, premature infants in the deficient group gradually compensated for their intrauterine vitamin D deficiency, resulting in 25(OH)D3 levels comparable to those in the other groups. At 3, 9, and 18 months of CGA, the group receiving individualized supplementation exhibited significantly higher 25(OH)D3 levels than the standard-dosage group. In the early postnatal period, infants with vitamin D deficiency should undergo closer monitoring of 25(OH)D3 levels and dosage and route of supplementation adjusted to individual circumstances to promote a rapid increase in 25 (OH) D3 levels. By approximately 18 months CGA, monitoring frequency can be adjusted, as vitamin D levels among the groups have converged. Additionally, these findings support the development of more scientifically grounded and rational vitamin D supplementation protocols for premature infants, such as stratifying infants by umbilical cord blood vitamin D levels and applying targeted strategies at different stages to ensure adequate vitamin D for healthy growth.

This study investigates how vitamin D deficiency affects the neuropsychological and behavioral development of preterm infants. At 9 and 18 months CGA, preterm infants with insufficient or deficient vitamin D levels scored significantly lower on the Gesell Developmental Scales in areas such as gross motor, fine motor, language, adaptive behavior, and personal-social skills compared to those with adequate vitamin D levels. These findings indicate that vitamin D deficiency may adversely affect the neuropsychological and behavioral development of preterm infants. Vitamin D plays several roles in the nervous system, including supporting neuronal development and differentiation and regulating the production and release of neurotransmitters [44, 45]. A deficiency of vitamin D may slow nervous system development, impairing cognitive functions, motor coordination, and social skills in premature infants [46, 47]. Moreover, within the deficiency group, at both 9 and 18 months CGA, infants receiving individualized vitamin D supplementation scored higher across all five skill areas than those given a standard dose. This suggests that an individualized vitamin D supplementation approach not only more effectively corrects deficiency but also enhances the neuropsychological and behavioral development of preterm infants. Such tailored supplementa-

tion more effectively addresses the specific needs of premature infants for vitamin D, thereby maintaining healthy serum levels and supporting nervous system development. Adequate vitamin D levels are crucial for the proper development and function of nerve cells, the formation and connectivity of neural synapses, and overall neuropsychological and behavioral health in preemies. Additionally, personalized supplementation may also modulate immune function, lower infection rates, and indirectly support nervous system development [48]. These findings underscore the importance of customized vitamin D supplementation strategies in the care of preterm infants.

The results of this study carry important implications for clinical practice. Firstly, it reminds healthcare professionals to routinely test umbilical cord blood 25(OH)D3 levels in premature infants at birth to promptly identify those with vitamin D deficiency. Secondly, a personalized approach to vitamin D supplementation offers an efficient way to address vitamin D deficiency in premature infants and cater to their unique requirements. In clinical settings, healthcare providers can develop customized vitamin D supplementation plans for premature infants based on individual circumstances to enhance overall health and well-being.

Limitations of the Study

Although this study provides valuable insights, it is important to acknowledge its limitations. First, the relatively small sample size may introduce bias into the results. Second, the observation period of the study is relatively short, extending only to 18 months CGA, and the long-term effects on the neuropsychological and behavioral development of premature infants remain unclear. Future research should increase the sample size and conduct multicenter, large-sample studies to enhance the reliability and generalizability of the findings. Additionally, extending the observation period to follow premature infants into school age or even adulthood would allow for a more comprehensive assessment of the long-term impact of vitamin D deficiency and supplementation on their neuropsychological and behavioral development. Further research could also explore the specific molecular mechanisms by which vitamin D influences neuropsychological and behavioral development in premature infants, providing a theoretical foundation for developing more targeted treatment strategies. Moreover, combining other nutrients and treatment approaches could help evaluate their overall effect on the growth and development of premature babies, offering more comprehensive support for their healthy development.

This study systematically examined how vitamin D metabolic imbalance affects 25(OH)D3 levels and neuropsychological and behavioral development in premature infants, while proposing an individualized supplementation strategy. The results show significant differences in umbilical cord blood 25(OH)D3 levels among premature babies, and that a tailored vitamin D supplement plan is more effective at correcting deficiency. This personalized approach not only resolves vitamin D deficiency in premature infants but also positively influences their neuropsychological and behavioral growth.

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Consent to publish

The manuscript has neither been previously published nor is under consideration by any other journal. The authors have all approved the content of the paper.

Consent to Participate

We obtained a signed informed consent form from each participant's representative.

Ethic Approval

This study was approved by the Ethics Committee of the Binzhou People's Hospital.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contribution

XG: Edited and refined the manuscript with a focus on critical intellectual contributions. YC, FX, YL: Participated in collecting, assessing, and interpreting the data. Made significant contributions to date interpretation and manuscript preparation. XG, YS: Provided substantial intellectual input during the drafting and revision of the manuscript.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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