Prevalence of vitamin A and vitamin D deficiency in hospitalized neonates in Xi'an, China

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Running title: Vitamin A and D deficiency in neonates

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ABSTRACT

Background and Objectives: To investigate the prevalence of vitamin A and vitamin D deficiency and the associated factors in hospitalized neonates in Xi'an, China. **Methods and Study Design:** A total of 524 hospitalized neonates were collected in this study. Serum vitamin A and D concentrations were detected in neonates within two weeks of birth. **Results:** Serum vitamin A and D concentrations of hospitalized neonates were 0.55±0.21 μmol/L and 42.0±20.6 nmol/L, respectively. They were greater in full-term neonates than in preterm neonates, greater in rural neonates than in urban, and greater in single than in twin (all $p<0.001$). The prevalence of vitamin A and D deficiency were 14.9% and 33.0%, the prevalence of marginal vitamin A deficiency was 64.7%, and vitamin D insufficiency was 35.1%. Neonatal serum vitamin A and D concentrations were all positively correlated with birth weight and gestational age. Neonatal serum vitamin D concentration was also positively correlated with maternal serum vitamin D concentration. Additionally, neonatal vitamin A concentration was positively correlated with neonatal serum vitamin D concentration. **Conclusions:** Vitamin A and vitamin D statuses are compromised in hospitalized neonates in Xi'an, especially in premature neonates, low birth weight neonates, twins, and those born in urban areas. Individualized supplementation with vitamin A and vitamin D in neonates should be a clinical consideration.

Key Words: vitamin A, vitamin D, deficiency, neonate, China

INTRODUCTION

Fat-soluble vitamins A, D, E and K play an important role in the growth and development of children. Vitamin A and vitamin D are involved in the metabolism of calcium and phosphorus, normal embryogenesis, immune response, visual functioning, genetic expression, and hematopoiesis.[1] They are related to repeated infections, anemia, slow growth, blindness, rickets, and death.[2] Vitamin A deficiency may lead to an increased risk of bronchopulmonary dysplasia. Low vitamin D concentrations in neonates may be detrimental to fetal brain development, and also had a higher risk of exposure to elevated inflammation at birth.[3,4] In addition, vitamin D deficiency is also associated with autoimmune diseases, malignant tumors, diabetes, cardiovascular diseases, allergic diseases, infectious diseases, and osteoarthritis.[5-7] Vitamin E is an antioxidant protecting cellular structures and functions against harmful effects of free radicals. It also acts as a regulator of signal transduction and gene expression.[8] Vitamin K is crucial to the production of many proteins involved with the coagulation process.

Routine administration of vitamin K shortly after birth will prevent major neonatal morbidity and mortality related to hemorrhage.[9] Therefore, it is vital to ensure adequate concentrations of fat-soluble vitamins for neonates.

The aim of this study was to investigate serum vitamin A and vitamin D concentrations in hospitalized neonates in Xi'an, China. Meanwhile, to compare their concentrations and status with different birth conditions in order to understand the influence factors, and thus provide a reference for individualized supplementation in neonates. It also provides data support for scientific research and clinical work.

MATERIALS AND METHODS

Participants

This is a cross-sectional study. The neonates hospitalized in the neonatology of Xi'an Children's Hospital from January 2018 to December 2019 were included in the study. The neonates who were older than 14 days, had liver metabolism disease, had pregnancy complications, did not live in Xi'an and surrounding areas, and had not obtained informed consent were excluded (Figure 1). This study was executed according to the Helsinki Declaration guidelines and approved by the Medical Ethics Committees of Xi'an Children's Hospital (20190025). All guardians of the neonates provided informed consent.

Data collection

Birth information of neonates including gender, gestational age, birth weight, place of birth, the month of birth, single or twin, and the mother's residential address during pregnancy was collected by questionnaires or from medical records.

Measurements

Fasting venous blood samples were collected from neonates and their mothers in the morning. Serum samples were extracted from blood samples after centrifugation, then stored in a refrigerator, and followed the principles of cold chain sent to Xi'an Hehe Medical Laboratory (Xi'an, China) for vitamin A and D testing.

Serum vitamin A concentration was measured by high-performance liquid chromatography (HPLC; LC-20A, Shimadzu, Japan) and vitamin D concentration by liquid chromatography-mass spectra (LC-MS; MS8030, Shimadzu, Japan). Liquid-liquid extraction was used and quantification by the internal standard. Thawed serum samples (200 μL), 10 μL of internal standard and 400 μL of ethyl acetate were placed into a centrifuge tube, adequately mixed for

5 minutes. Subsequently, the mixture was centrifuged at 15,000 rpm for 10 minutes. Accurately absorb 390 μL of supernatant and place it in a centrifuge tube, blow dry with nitrogen, then add 200 μL of methanol, mix for 1 minute. The supernatant of 100 μL was accurately absorbed and injected into the HPLC system for detection.

Standards

Vitamin A deficiency was defined as serum vitamin A concentration of <0.35 μmol/L, marginal vitamin A deficiency was defined as serum vitamin A concentration between 0.35~< 0.7 μmol/L, vitamin A sufficiency as serum vitamin A concentration ≥0.7 μmol/L.[10]

Vitamin D deficiency was defined as serum vitamin D concentration of <30 nmol/L, vitamin D insufficiency as serum vitamin D concentration between 30 nmol/L and 50 nmol/L, vitamin D sufficiency as serum vitamin D concentration of >50 nmol/L.[11,12]

Statistical analysis

Statistical analyses were performed using SPSS Statistics 18.0. Results are expressed as number and percentage, mean ± standard deviation (SD) for normally distributed data. Single-sample mean *t*-test, independent-sample *t*-test and analysis of variance (ANOVA) were used to analyze quantitative data, and the chi-square test was used to compare qualitative data. Correlations were assessed using Pearson partial correlations. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Participant characteristics

A total of 524 neonates (320 boys and 204 girls) were included, within the age of 6.92±5.26 days (0-14 days), gestational age of 37.6±3.18 weeks (27-42 weeks), and birth weight of 2879.9±763.8 g (750-4740 g). There were 136 premature neonates and 388 full-term neonates, 438 singletons and 86 twins, 298 neonates born in urban areas and 226 in rural areas.

Concentrations and status of vitamin A and vitamin D

Neonatal serum vitamin A and vitamin D concentrations and status with different birth conditions are shown in Table 1-2. There were statistically significant differences between preterm and full-term neonates, urban and rural neonates, singleton and twin neonates, and different gestational age groups.

Serum vitamin A and D concentrations in neonates born in different months were analyzed, and the trends are shown in Figure 2(A) and Figure 3(A). There were no significant differences in vitamin A concentration between the four seasons, while it was relatively less in the spring (March, April, May). The highest vitamin D concentration was in September (48.1±21.3 nmol/L), and the lowest was in March (31.3±17.1 nmol/L). The changing trend between different seasons was: autumn (September-October-November) (46.4±20.9 nmol/L), summer (June-July-August) (43.2±22.1 nmol/L), winter (December-January-February) (38.6±17.0 nmol/L), and spring (March-April-May) (32.4±17.3 nmol/L).

Correlation analysis of vitamin A and vitamin D

As shown in Figure 2, there were positive correlations between serum vitamin A concentration and birth weight (r=0.186, $p<0.001$), gestational age (r=0.189, $p<0.001$), and serum vitamin D concentration (r=0.437, $p<0.001$). Figure 3 shows that there were positive correlations between neonatal serum vitamin D concentration and neonatal birth weight (r=0.191, $p<0.001$), neonatal gestational age (r=0.193, $p<0.001$), and maternal serum vitamin D concentration (r=0.833, $p<0.001$).

DISCUSSION

In this study, we investigated the prevalence of vitamin A and vitamin D deficiency in hospitalized neonates in Xi'an, Northwest China (34 °N). Serum vitamin A and D concentrations of hospitalized neonates were 0.55±0.21 μmol/L and 42.0±20.6 nmol/L, respectively. The serum vitamin A and D concentrations in neonates were significantly lower than the sufficient low limit. In this study, 14.9% of neonates had vitamin A deficiency, and 64.7% had marginal vitamin A deficiency. Meanwhile, 33.0% of neonates had vitamin D deficiency, and 35.1% had vitamin D insufficiency. In a previous study, the neonatal serum retinal concentrations in two counties in Hebei province were 0.78±0.13 μmol/L, no neonates had vitamin A deficiency, and 28.2% had marginal vitamin A deficiency.[13] The serum vitamin A status in hospitalized neonates in Xi'an was still a major public health nutrition issue.

There is currently no agreement in the cut-off point for sufficient vitamin A concentration for newborns. According to the screening criteria for vitamin A deficiency set by the National Health Commission of the People's Republic of China, serum retinol concentration <0.35

μmol/L was defined as vitamin A deficiency, and 0.35~<0.70 μmol/L as marginal vitamin A deficiency for children under six years old.[10]

Neonates typically have low serum vitamin A concentrations and low liver stores at birth. During the third trimester of pregnancy, the fetus starts to accumulate vitamin A and stores it in the liver, but the transfer from mother to child is limited. Usually, neonates are born with approximately half the vitamin A concentrations compared with their mothers.[14] Besides, neonates have marginal reserves of vitamin A in their liver. Preterm neonates often have low vitamin A concentrations due to the limit of hepatic vitamin A reserves. Colostrum contains a high amount of vitamin A, which can improve neonatal vitamin A concentrations.[15] And neonates depend on breast milk as a source of vitamin A during the first few months of life. If the mother has adequate dietary intake or adequate hepatic vitamin A reserves, as well as sufficient milk production and adequate vitamin A concentrations, the newborn's hepatic vitamin A stock may increase during breastfeeding.[16]

Vitamin A supplementation during the neonatal period is another source of vitamin A. It has been suggested to have an impact by increasing body stores in early infancy. A previous study showed that neonatal vitamin A supplementation reduced infant mortality in South Asia.[17] However, the WHO does not currently recommend neonatal vitamin A supplementation as a public health intervention to reduce infant morbidity and mortality.[18] At present, there are three suggestions to ensure neonatal vitamin A status, including improving maternal nutritional status through more frequent intake of vitamin A-containing foods, promoting proper feeding for infants and young children, and reducing the burden of nutrient-depleting infections.[18]

In this study, preterm neonates, twins, and neonates born in urban areas had lower vitamin D concentrations and higher deficiency rates than full-term neonates, singletons, and neonates born in rural areas. There are three sources of vitamin D, sun exposure, dietary intake, and vitamin D supplementation. Dietary intake of vitamin D is in very few foods, such as marine fish, cod liver oil, egg yolks, milk. People living in the mainland of China rarely consume marine fish. The main derivation of vitamin D in their bodies is exposure to sunlight. Conversion of subcutaneous 7-dehydrocholesterol to vitamin D by ultraviolet rays with wavelengths of 290-315 nm. However, changes in modern lifestyles and various conditions have reduced skin exposure to sunlight. China is a vast country with large differences between the north and the south, with the Qinling Mountains and the Huai River as the dividing line. The lighting time and UV intensity are less in the north than in the south. Xi'an is located in the north and has a long winter. Therefore, people who live in the Xi'an area have less vitamin D by sun exposure. In addition, air pollution and high-rise buildings also affect sun exposure for people living in urban areas. Besides, pregnant women are less likely to outside in winter. Therefore, neonates born in urban areas and winter had lower vitamin D concentrations.

Neonatal serum vitamin D concentration was positively correlated with maternal serum vitamin D concentration, birth gestational age, and birth weight. In the third trimester, the only way for the fetus to obtain vitamin D is maternal-fetal transport. Therefore, the younger the gestational age at birth, the lower the vitamin D concentration of neonates. Vitamin D deficiency in pregnant women may result in vitamin D deficiency in fetuses and neonates. It may increase the risk of premature, small for gestational age and low birth weight neonates, and that neonates were at high risk of fetal dysplasia, rickets, and infant eczema.[19,20] Previous studies have shown that dark skin, race, obesity, educational background, season, a habit of smoking or drinking, vitamin D supplementation dose of <15 μg/d of mothers will affect the vitamin D concentrations both in mothers and their neonates.[21,22]

Vitamin D supplementation is the most significant factor in determining vitamin D status in the third trimester of pregnancy.[23] Vitamin D supplementation with doses of 2000 IU/d or lower during pregnancy may reduce the risk of fetal or neonatal mortality.[24] Vitamin D supplementation during pregnancy had positive effects on fetal cell mass and function, skeletal mineralization, and metabolism. It can reduce the incidence of neonatal respiratory distress syndrome, bronchopulmonary dysplasia, and metabolic bone disease, improve the immune function of premature infants, and avoid the occurrence of multiple metabolic diseases in adulthood.[25] Besides, it was associated with an increase in birth weight and length.[26,27] Therefore, adequate vitamin D supplementation during pregnancy may prevent vitamin D deficiency and adverse clinical outcomes in neonates. Currently, vitamin D supplements of 800–1000 IU/d are recommended for pregnant women in the third trimester of pregnancy in China. If available, they should monitor serum vitamin D concentrations and take vitamin D supplements to maintain normal concentrations if there was a significant deficiency.[28]

Conclusion

Vitamin A and vitamin D statuses are compromised in hospitalized neonates in Xi'an, China, especially in premature neonates, low birth weight neonates, twins, and those born in urban areas. Individualized supplementation with vitamin A and vitamin D in neonates should be a clinical consideration.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Vitamin A concentrations and status in 524 hospitalized neonates

Variables	n	Vitamin A concentration (μmol/L)	*p*	Status of vitamin A, n (%)			*p*
				Deficiency	MVAD	Sufficiency	
All neonates	524	0.55±0.21	<0.001	78 (14.9)	339 (64.7)	107 (20.4)	
Normal limit		0.70					
Sex			0.416				0.931
Boys	320	0.55±0.21		47 (14.7)	206 (64.4)	67 (20.9)	
Girls	204	0.54±0.21		31 (15.2)	133 (65.2)	40 (19.6)	
Preterm/Full-term			<0.001				<0.001
Preterm	136	0.49±0.20		43 (31.6)	71 (52.2)	22 (16.2)	
Full-term	388	0.57±0.21		35 (9.02)	268 (69.1)	85 (21.9)	
Region of birth			<0.001				<0.001
Urban	298	0.52±0.18		50 (16.8)	205 (68.8)	43 (14.4)	
Rural	226	0.58±0.23		28 (12.4)	134 (59.3)	64 (28.3)	
Fetal number			<0.001				<0.001
Singleton	438	0.58±0.21		41 (9.36)	293 (66.9)	104 (23.7)	
Twins	86	0.40±0.13		37 (43.0)	46 (53.5)	3 (3.49)	
Gestational age			<0.001				<0.001
27-32 weeks	53	0.46±0.19		20 (37.7)	28 (52.8)	5 (9.43)	
33-36 weeks	83	0.51±0.21		23 (27.7)	43 (51.8)	17 (20.5)	
37-42 weeks	388	0.57±0.21		35 (9.02)	268 (69.1)	85 (21.9)	

MVAD: marginal vitamin A deficiency

Table 2. Serum vitamin D concentrations and status in 524 hospitalized neonates

Variables	n	Vitamin A concentration (μmol/L)	*p*	Status of vitamin A, n (%)			*p*
				Deficiency	MVAD	Sufficiency	
All neonates	524	42.0±20.6	<0.001	173 (33.0)	184 (35.1)	167 (31.9)	
Normal limit	-	50.0					
Sex			0.161				0.373
Boys	320	41.0±20.5		113 (35.3)	108 (33.8)	99 (30.9)	
Girls	204	43.6±20.8		60 (29.4)	76 (37.3)	68 (33.3)	
Preterm/Full-term			<0.001				0.001
Preterm	136	36.1±19.2		63 (46.3)	40 (29.4)	33 (24.3)	
Full-term	388	44.1±20.7		110 (28.4)	144 (37.1)	134 (34.5)	
Region of birth			<0.001				<0.001
Urban	298	37.0±18.5		128 (43.0)	106 (35.6)	64 (21.5)	
Rural	226	48.7±21.4		45 (19.9)	78 (34.5)	103 (45.6)	
Fetal number			<0.001				<0.001
Singleton	438	44.6±20.4		121 (27.6)	164 (37.4)	153 (34.9)	
Twins	86	28.8±16.3		52 (60.5)	20 (23.3)	14 (16.3)	
Gestational age			<0.001				0.002
27-32 weeks	53	33.4±15.2		27 (50.9)	17 (32.1)	9 (17.0)	
33-36 weeks	83	37.9±21.2		36 (43.4)	23 (27.7)	24 (28.9)	
37-42 weeks	388	44.1±20.7		110 (28.4)	144 (37.1)	134 (34.5)	

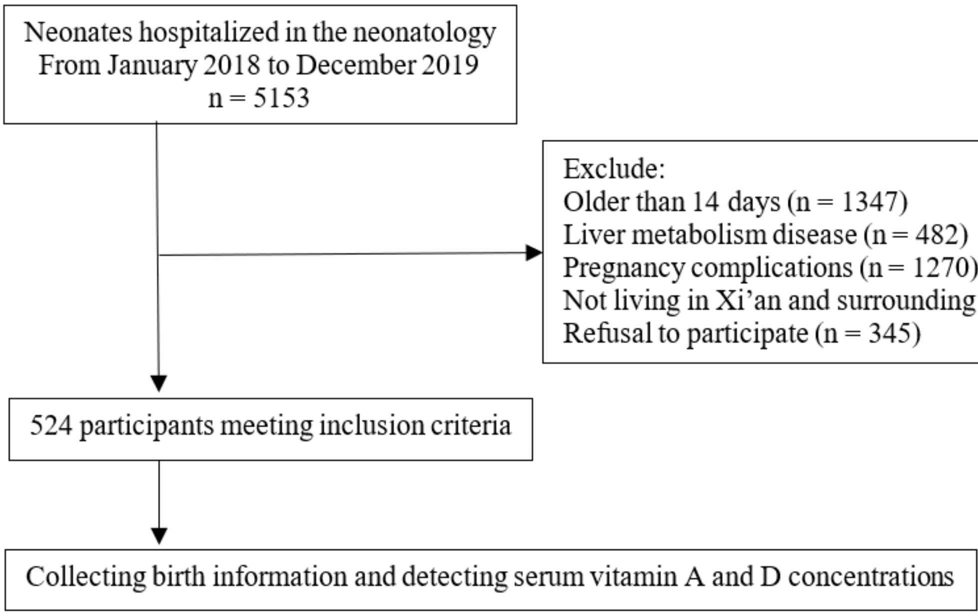

Figure 1. Diagram of study participants.

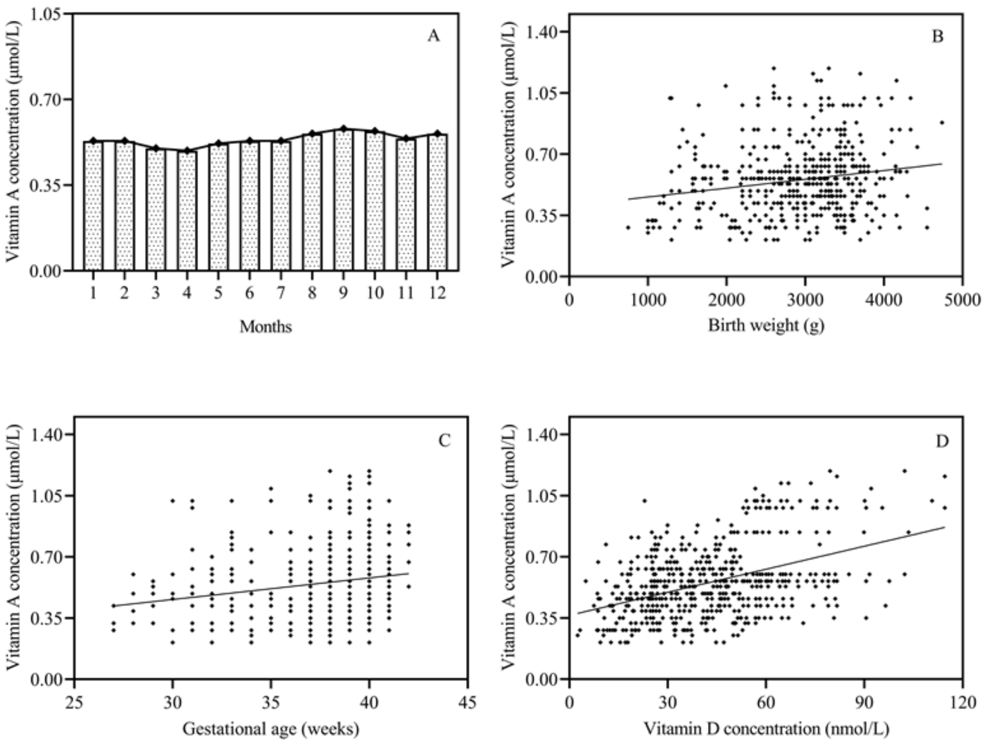

Figure 2. Correlation of neonatal vitamin A concentration with birth weight, gestational age and serum vitamin D concentration. (A) Trends in neonatal vitamin A concentration in different months. (B) Correlation between birth weight and vitamin A concentration (r=0.186, p<0.001). (C) Correlation between gestational age at birth and vitamin A concentration (r=0.189, p<0.001). (D) Correlation between serum vitamin D concentration and vitamin A concentration (r=0.437, p<0.001).

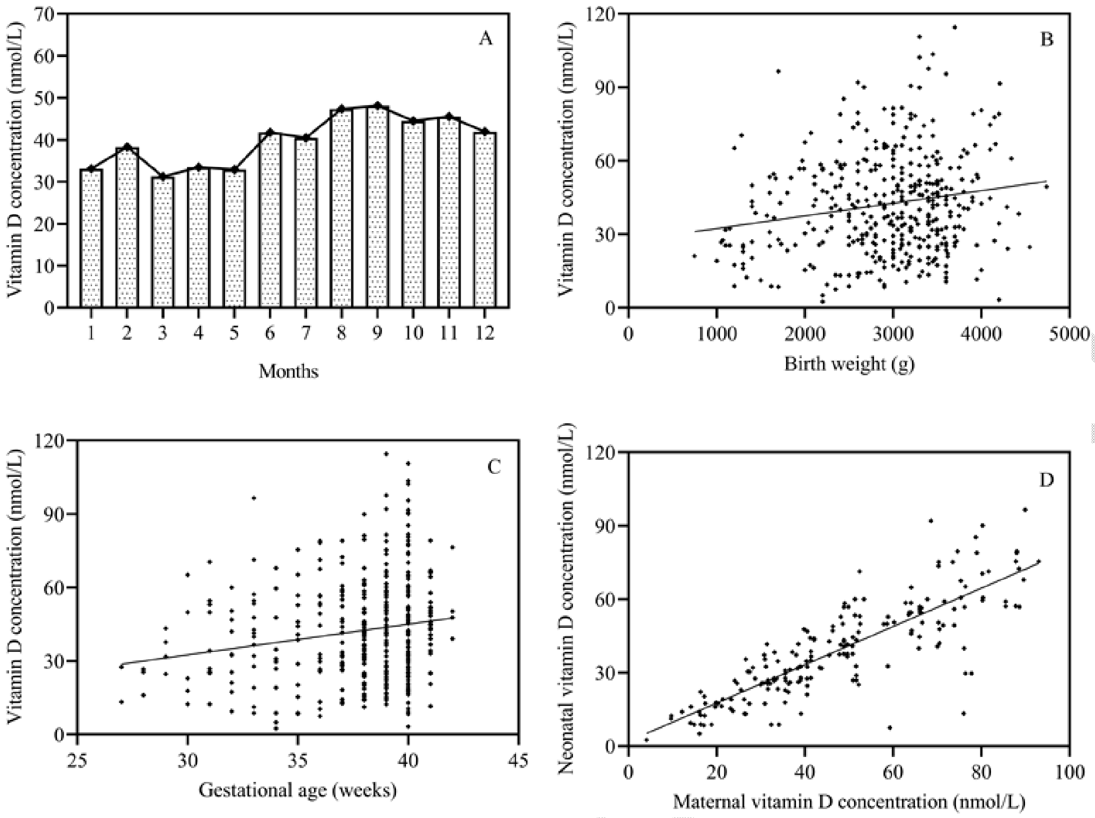

Figure 3. Correlation of neonatal vitamin D concentration with birth weight, gestational age and maternal vitamin D concentration. (A) Trends in neonatal serum vitamin D concentrations in different months. (B) Correlation between birth weight and neonatal vitamin D concentration (r=0.191, $p<0.001$). (C) Correlation between gestational age at birth and neonatal vitamin D concentration (r=0.193, $p<0.001$). (D) Correlation between maternal vitamin D concentration and neonatal vitamin D concentration (r=0.833, $p<0.001$).