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The Correlation Between Serum Vitamin D Deficiency and Preterm Birth

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Preterm birth is an important cause of death and developmental disorder in neonates. Vitamin D deficiency has been shown to regulate body inflammatory factor levels that stimulate elevation of uterine contraction hormones, such as prostaglandin, thus causing preterm birth. However, current observations regarding the relationship between vitamin D and preterm birth are inconsistent. We performed a nested case-control study to investigate the effect of vitamin D on preterm birth.

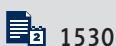
Material/Methods: A prospective cohort study included 200 cases of pregnant women in our hospital from May 2013 to May 2015. Blood samples were collected from early, middle, and late stages of pregnancy. Forty-six patients with preterm delivery were compared with age-matched full-term delivery cases (N=92). High performance liquid chromatography-mass spectrometry (HPLC-MS) was used to detect serum levels of 25(OH)D, 25(OH)D₂, and 25(OH)D₃. Logistic regression was performed to analyze the correlation between 25(OH)D and risk of preterm birth.

Results: No significant difference in age, smoking/drinking, education level, BMI and vitamin D levels was found between the preterm birth group and full-term delivery group. No significant difference was found for vitamin D levels across different stages of pregnancy; no difference in concentration of 25(OH)D related to preterm birth risk was found. After adjusting for potentially confounding factors, serum vitamin D level did not increase the risk of preterm birth.

Conclusions: This study did not found evidence of an increase in preterm birth risk related to vitamin D level during pregnancy.

MeSH Keywords: **24,25-Dihydroxyvitamin D 3 • Pregnant Women • Premature Birth • Statistics as Topic**

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Background

Preterm birth (PTB) refers to the delivery before 37th week of pregnancy. The World Health Organization (WHO) reported that about 15 million neonates are born preterm [1], with about 1 million deaths occurring during infancy [2]. PTB infants who survive frequently suffer from chronic pulmonary diseases and learning deficits, causing heavy burdens for society and family.

Possible risk factors of PTB include unhealthy lifestyle, mental stress, younger or elder age during pregnancy, and malnutrition [3–5]. Changes in lifestyles that contribute to obesity have become a major challenge threatening public health. During pregnancy, the additional intake of nutrients may contribute to obesity and related complications such as hypertension, diabetes, and pre-eclampsia. Current studies report inconsistent findings regarding obesity and PTB. One study showed that women overweight before pregnancy had an increased the risk of PTB more than three-times that of normal weight women [6]. However, another cohort study found that pre-pregnancy obesity could reduce PTB risk [7]. The level of vitamin D has been negatively correlated with the degree of obesity; and overweight people are more at risk for vitamin D deficiency [8]. During pregnancy, vitamin D is necessary; its deficiency may cause PTB, abortion, and abnormal fetal development. Most studies suggest that vitamin D deficiency could increase PTB incidence, however, controversy still exists among some scholars. We thus performed a correlation analysis between vitamin D deficiency and PTB.

Material and Methods

Sample population

We performed a prospective cohort study to recruit a total of 200 pregnant women from May 2013 to May 2015 seen at Zhujiang Hospital, Southern Medical University; study participants had full medical and demographic records (including general characteristics, lifestyle, body height, body mass, and family medical history). Blood samples were collected at early, middle, and late stages of pregnancy. A nested case control analysis (1: 2 model) was performed that included 46 PTB individuals (less than 37 weeks of pregnancy) and 92 full-term birth individuals (37 to 42 weeks of pregnancy); matched by age, parity, and blood collection period. Inclusive criteria included women between 18 and 45 years of age with natural gestation and no malformation of reproductive tract. Exclusive criteria included PTB history or abortion history; drug abuse; elevated white blood cell count or inflammatory diseases; hysteromyoma or ovarian cyst; severe systemic disease, or mental disorders. A smoking history was defined as one cigarette per day for more than one year. A drinking history was

defined as at least one drink per week for more than three months. Body mass index (BMI) was defined as body weight in kg/(height in m²).

The study protocol was approved by the Research Ethics Committee of Zhujiang Hospital, Southern Medical University, and all patients gave their informed consent before study commencement.

Sample collection

Venous blood samples of 5 mL were collected from participants during the early, middle, and late stage of their pregnancy. Blood samples were immediately centrifuged at 1000 rpm for 10 minutes and the upper serum was frozen for future use.

Vitamin D assay

High performance liquid chromatography-mass spectrometry (HPLC-MS) was used to measure the serum level of 25(OH)D, 25(OH)D₂, and 25(OH)D₃ following the standards stipulated by NIH. Experimental protocols were in accordance with previous records.

Statistical analysis

SPSS software package was used to perform analysis. Measurement data were expressed as mean ± standard deviation. Student t-test was used to compare means between two groups. Analysis of variance was performed in enumeration data. Conditional logistic regression analysis was used to reveal the correlation between 25(OH)D and PTB risk. Significance level was defined as $p < 0.05$.

Results

General information of research subjects

In this nested cohort study, statistical analysis was performed between PTB and full term birth groups, and found no statistical significant difference with regards to age, smoking/drinking, education level, BMI, or 25(OH)D₂ (Table 1).

Vitamin D level during different pregnant stages

An analysis was performed to check serum levels of 25(OH)D, 25(OH)D₂, and 25(OH)D₃ across early, middle, and late stages of pregnancy. As shown in Figure 1, no significant difference was found across different stages of pregnancy.

Table 1. General information of research objects.

Index	PTB (N=46)	Full term birth (N=92)	P value
Age	27.4±3.2	27.6±4.2	0.78
Smoking (yes/no)	0/46	1/91	0.48
Drinking (yes/no)	0/46	1/91	0.48
25 (OH) ₂ D	16.54±7.65	17.30±8.32	0.60
BMI	22.13±3.24	23.14±2.30	0.25
Education level			
Elementary	5	12	0.96
High school	12	26	
Collage	18	33	
Undergraduate	11	21	

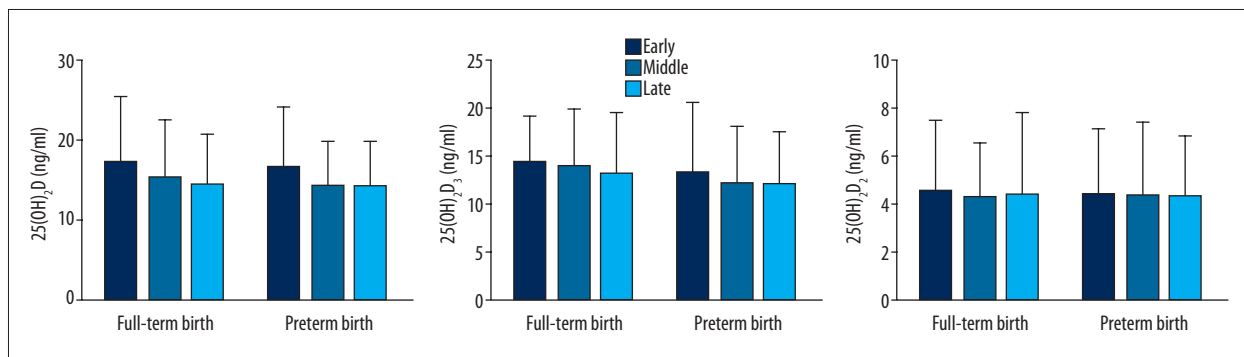


Figure 1. Serum vitamin D levels (in different forms) across pregnant stages.

Vitamin D deficiency and PTB

Serum vitamin D level (in the form of 25(OH)D), were divided into four stages in accordance with international standards [9]: normal (equal or higher than 30 ng/mL), insufficient (between 20 and 30 ng/mL), mild deficiency (between 10 and 20 ng/mL), and moderate to severe deficiency (less than 10 ng/mL). The IOM standard (2011, US) stipulates that higher than 20 ng/mL of 25(OH)D is sufficient for body metabolism. We used 20 ng/mL as the cut-off point for analyzing the correlation between vitamin D deficiency and PTB.

Compared to those individuals with higher than 20 ng/mL 25(OH)D, pregnant women with lower vitamin D (less than 20 ng/mL) had no significant increased PTB risk (OR=0.78, 95% CI, 0.67~1.23) according to IOM standards. Based on international standards of nutrition, OR values between PTB and vitamin D deficiency were 0.43 (95% CI, 0.25~1.01), 0.87 (95% CI, 0.56~1.23) and 0.90 (95% CI, 0.45~1.23) for 25(OH)D values less than 10 ng/mL, between 10 and 20 ng/mL, and between 20 and 30 ng/mL, respectively (Table 2).

Adjusted analysis between vitamin D deficiency and PTB

As PTB can be affected by education level, BMI, smoking or drinking history of pregnant women, we adjusted these factors and re-analyze the correlation. Compared to those individuals with higher than 20 ng/mL 25(OH)D, pregnant women with lower vitamin D (less than 20 ng/mL) had no significant increased PTB risk (OR=0.78, 95% CI, 0.67~1.23). OR values between PTB and vitamin D deficiency were 0.57 (95% CI, 0.25~1.05), 0.75 (95% CI, 0.43~1.19) and 0.95 (95% CI, 0.47~1.32) for those with 25(OH)D values less than 10 ng/mL, between 10 and 20 ng/mL, and between 20 and 30 ng/mL, respectively (Table 3).

Discussion

Vitamin D is a liposoluble vitamin with important functions. Two important members of the vitamin D family are ergocalciferol (VitD₂) and cholecalciferol (VitD₃), neither, however, have biological effects until they undergo activation in the liver by chylomicron or vitamin D binding protein, with further catalytic reaction by 25-hydrogenase [10] and then transformation into 24, 25(OH)D₂ and 1α, 24, 25(OH)D₂ in the kidneys [11].

Table 2. Correlation between 25(OH)D deficiency and PTB.

Vitamin D (ng/ml)	PTB (N=46)	Full-term (N=92)	OR (95% CI)	P value
IOM standard				
≥20	16 (34.8%)	38 (41.3%)	1.00	–
<20	30 (65.2%)	54 (58.7%)	0.78 (0.67–1.23)	0.86
International nutrition guideline				
<10	8 (17.3%)	6 (6.5%)	0.43 (0.25–1.01)	0.06
10 ≤25(OH)D <20	26 (56.5%)	45 (48.9%)	0.87 (0.56–1.23)	0.58
20 ≤25(OH)D <30	10 (21.7%)	24 (26%)	1.00	–
≥30	2 (4.3%)	17 (18.4%)	0.90 (0.45–1.23)	0.67

Table 3. Correlation between Vitamin D deficiency and PTB.

Vitamin D (ng/ml)	Full-term birth	PTB	OR (95%CI)	P value
IOM standard				
≥20	16 (34.8%)	38 (41.3%)	1.00	–
<20	30 (65.2%)	54 (58.7%)	0.78 (0.67–1.23)	0.86
International nutrition guideline				
<10	8 (17.3%)	6 (6.5%)	0.57 (0.25–1.05)	0.32
10 ≤25(OH)D <20	26 (56.5%)	45 (48.9%)	0.75 (0.43–1.19)	0.84
20 ≤25(OH)D <30	10 (21.7%)	24 (26%)	1.00	–
≥30	2 (4.3%)	17 (18.4%)	0.95 (0.47–1.32)	0.74

As 25(OH)D₂ is the most important metabolite, it is frequently employed as the optimal index evaluating vitamin D condition [12]. Our study performed a correlation analysis between 25(OH)D₂ level in pregnant women and PTB.

Vitamin D deficiency varies in different countries and ethnic groups; the percentage of insufficiency ranges from 26% to 78.5% [13]. Possible reasons for vitamin D deficiency-induced PTB include pregnant hypertension, diabetes, pre-rupture of fetal membrane, and the higher risk of bacterial vaginitis with low serum 25(OH)D₃ levels [14]. Surprisingly, our study showed no statistically significant difference of 25(OH)D, 25(OH)D₂, and 25(OH)D₃ levels across early, middle, and late stages of pregnancy. Comparing individuals with higher than 20 ng/mL 25(OH)D, pregnant women with lower vitamin D (less than 20 ng/mL) had no significant increased PTB risk. The risk of PTB in pregnant women with 25(OH)D levels was not significantly elevated for less than 10 ng/mL, between 10 and 20 ng/mL, or between 20 and 30 ng/mL.

A study of Japanese women found the level of 25(OH)D significantly different in a PTB group compared to a full-term group [15]. A twin study in the USA also found that pregnant

women with 25(OH)D higher than 75 nmol/L had lower incidence of PTB [16]. The replenishment of vitamin D during pregnancy can significantly decrease the risk of PTB [17]. Another prospective study in China, however, found a 3.8% increase of PTB incidence in pregnant women with serum 25(OH)D higher than 30 ng/mL between 16th and 20th gestation week [18]. This observation agrees with one meta-analysis that found no decrease of PTB by replenishing vitamin D [19]. Furthermore, in one observational study of Spanish pregnant women, no significant change of PTB risk was found in those women with 25(OH)D levels lower than 20 ng/mL [20].

Vitamin D deficiency is related to multiple adverse pregnancy complications such as hypertension and low infant body weight. However, whether vitamin D plays a direct or indirect role in regulating hormonal factors of pregnant women is still unclear. Moreover, vitamin D levels show a seasonal pattern with higher synthesis in summer due to more sun exposure. Such environmental complexities make it difficult to directly compare different studies, which might account for the inconsistencies. In addition, the relatively small sample size and confounding factors in studies should be taken into account. Furthermore, in the future, measurement of thyroid function in patients with

PTB could be important due to the close relationship between thyroid function and PTB, as demonstrated by low serum concentrations of thyroid hormone in the early life of infants is associated with poor developmental outcomes [21,22].

Conclusions

Our study found no significant correlation between PTB and insufficiency of vitamin D, suggesting other factors might be

involved in the pathogenesis of PTB rather than vitamin D. However, due to the limited number of individuals enrolled in our study, large cohort clinical studies are required to confirm this finding in order to provide some guidelines on whether replenishment of vitamin D during pregnancy is necessary.

Disclosure of conflict of interest

The authors declare no competing financial or commercial interests in this manuscript.

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