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Vitamin D Status in Pregnant Women in Southern China and Risk of Preterm Birth: A Large-Scale Retrospective Cohort Study

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Background: The influence of maternal vitamin D on pregnancy outcomes, including preterm birth (PTB), is unclear due to different experimental designs and study populations (patient race and sample size) of previous studies. We aimed to investigate the relationship between 25-hydroxyvitamin D (25[OH] D) levels and PTB among pregnant women in southern China.





Material/Methods: A total of 11 641 pregnant women were retrospectively enrolled between January 2016 and April 2019. Vitamin D concentrations were evaluated by electrochemiluminescence immunoassay. Logistic regression analysis was used to analyze the association between vitamin D and PTB.

Results: The average 25(OH) D concentration was 59.3 ± 21.5 nmol/L; 34.8% of patients were vitamin D deficient, 43.0% were vitamin D insufficient (25[OH] D <50 nmol/L and 50–74.9 nmol/L, respectively). In total, 3.6% of newborns were born prematurely. Comparing the pre-term and full-term groups, 45.7% versus 42.9% and 29.8% versus 35% were vitamin D deficient and insufficient, respectively. These differences were not significant ($P > 0.05$). However, the mean vitamin D status was significantly different between the pre-term and full-term groups (61.3 ± 21.3 and 59.1 ± 21.5 nmol/L, respectively). No association was found between vitamin D deficiency/insufficiency and PTB in unadjusted or adjusted models, compared with vitamin D sufficiency (adjusted odds ratio, 1.016; 95% confidence interval, 0.794–1.301 and 0.842; 0.641–1.106, respectively).

Conclusions: Low maternal 25(OH) D levels are common in southern China. However, low vitamin D status in pregnant women appears to be unrelated to PTB. Measuring vitamin D level alone is therefore not sufficient to predict PTB.

MeSH Keywords: **Pregnant Women • Premature Birth • Vitamin D**

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Background

Preterm birth (PTB) is the major cause of death among children under the age of 5 years old worldwide, accounting for about 35% of neonatal deaths in 2016 [1]. Vitamin D deficiency is prevalent among all age groups, and the influence of 25-hydroxyvitamin D (25(OH) D) on adverse pregnancy outcomes is an issue of public health significance. Various guidelines provide different cutoff values for the definition of vitamin D deficiency. The National Osteoporosis Society defines 25(OH) D levels of <30 nmol/L as vitamin D deficiency and <50 nmol/L as insufficiency [2]. The Endocrine Society defines 25(OH) D deficiency as <50 nmol/L and insufficiency as 50–72.5 nmol/L [3].

Although poor maternal vitamin D status may contribute to adverse pregnancy outcomes [4–6], discrepancies exist among studies. Low vitamin D levels were not found to increase the risk of PTB after adjusting for potential confounders according to a prospective cohort study that included 200 pregnant women [5]. A study of a population in central Poland reported that very low vitamin D status (<10 ng/mL) may be a risk factor for preterm labor [6]. Since the fetus is completely dependent on the mother for vitamin D, supplementation during pregnancy increases the serum levels of 25(OH) D in both the mother and fetus. A recent systematic review and meta-analysis of 13 randomized controlled trials confirmed the well-established effect of vitamin D supplementation during pregnancy in terms of size at birth. However, a review of 10 randomized controlled trials revealed that vitamin D supplementation during pregnancy does not affect the risk of small-for-gestational-age or preterm birth [7]. Few epidemiological studies have been carried out on vitamin D deficiency among Chinese expectant mothers. This study recruited participants from the Guangzhou district, a typical southern city in China with sufficient sunlight. The geographical position of Guangzhou is $23^{\circ}70'$ N in latitude and $113^{\circ}15'$ E in longitude. We aimed to evaluate the relationship between vitamin D status and premature labor.

Material and Methods

Study design and participants

We recruited all pregnant women who received prenatal care and delivered at Guangdong Women and Children Hospital from January 2016 to April 2019 by voluntary inclusion, which resulted in a total of 11 641 participants. Maternal serum 25(OH) D levels were recorded once for each participant, at any time of pregnancy. Participants were followed up until the third trimester, and the incidence of PTB was analyzed. Participants were divided into a pre-term and full-term groups; PTB was defined as delivery between the 28th and 37th gestational week.

Information relating to vitamin D supplementation, vitamin D content of the diet and sunlight exposure were not available. We excluded women with risk factors for premature birth such as history of adverse pregnancy; multiple gestation; placenta-preval; scar uterus; prenatal bleeding; premature rupture of membranes more than 24 hours before labor or ≤ 34 weeks; fetal anomalies; twin transfusion syndrome; maternal-fetal and placental abnormalities; internal or surgical disease such as heart disease, liver disease, chronic hypertension, preeclampsia or diabetes; psychosis, malignant tumor, venereal disease or serious infection or history of drug or alcohol abuse.

Vitamin D measurement

Venous blood samples (2 mL) were collected and transported on ice to the laboratory for measurement. Vitamin D concentration was determined via electrochemiluminescence immunoassay (Abbott Laboratories, IL, USA) within 24 hours of drawing the blood.

Internal quality control measures included repetitive measures for high- and low-quality control, which were provided in the manufacturer's toolkit. Quality control measurements were carried out for each batch of analysis. Inter and intra-assay coefficients of variation (CVs) were less than 10%, and those determined by the kit method were 6.2%. Based on the criteria of the Institution of Medicine and Endocrine Society, participant vitamin D levels were classified as sufficient (≥ 75 nmol/L), insufficient (50–74.9 nmol/L) or deficient (<50 nmol/L) [3]. The following maternal and neonatal data were collected: maternal age, education and profession; pro-gestational body mass index (BMI); gestational weeks and time at blood sampling; mode of delivery; gestational weeks at birth and neonatal birth height, weight, head circumference and Apgar score.

Statistical analysis

The software package SPSS (V20, IBM Corp, Armonk, NY, USA) was used for statistical analysis. Continuous data are presented as mean \pm standard deviation (SD); categorical data are presented as number (%). The Kolmogorov-Smirnov test was used to determine normality of the test data distribution. Maternal demographic and clinical features were compared between the pre-term and full-term groups using the Student's *t*-test, Pearson's chi-square test or Fisher's exact test. Mean 25(OH) D concentration and prevalence of vitamin D deficiency and insufficiency were compared between the pre-term and full-term group. Multivariate variables including maternal age, BMI before pregnancy, gestational weeks and season of blood collection (spring, summer, autumn, winter), delivery mode, number of pre-pregnancies, maternal education and occupation, were controlled for in logistic regression analysis. All *P* values were 2-tailed and $P < 0.05$ was defined as statistically significant.

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the unadjusted and adjusted association between lower vitamin D levels and preterm labor through binary logistic regression analyses.

Ethical information

This study and its protocols were approved by the Medical Research Ethics Committee of the Guangdong Women and Children Hospital and carried out in accordance with the principles of the Helsinki Declaration. We obtained written informed consent from each participant.

Results

In total, 20 703 blood samples were collected. After the exclusion of 9062 women due to the presence of risk factors for PTB, data from 11 641 women were finally included in analysis.

Table 1 details the demographic features of participants and percentile distribution of 25(OH) D concentrations. No significant interaction was identified for 25(OH) D concentrations with BMI before pregnancy or fetal sex. Maternal 25(OH) D levels varied with age, educational level, occupation, gestational week and season in which blood was collected, number of previous pregnancies, mode of birth, and gestational age at delivery (Table 1).

The overall range of vitamin D was 10.5–237.6 nmol/L (mean±SD: 59.3±21.5 nmol/L). Of the entire cohort, 4051 women (34.8%) were 25(OH) D deficient, 5007(43.0%) were insufficient and 2583 (22.2%) had sufficient 25(OH) D levels.

Significantly higher vitamin D status was noted among older mothers or those with college education, compared with others. Domestic workers, unemployed people, students and primiparous woman had poor 25(OH) D status. Significant differences were also found depending on the season of

Table 1. Distribution of maternal demographic characteristics (n=11 641).

Maternal characteristics	25(OH) D percentiles (nmol/L)									F value	P value
	5 th	10 th	25 th	50 th	75 th	90 th	95 th				
	11 641	(100)	26.2	32.8	44.4	58.0	72.8	87.5	96.3		
Maternal age (years)										68.166	<0.001
<24 y	1401	(12.0)	23.1	29.7	39.9	53.7	67.1	81.5	90.1		
25–29	4886	(41.9)	24.8	31.6	42.5	56.2	71.1	85.2	94.7		
30–34	3614	(31.0)	27.5	34.5	46.5	59.9	74.9.5	89.0	97.8		
≥35	174.90	(14.9)	30.2	36.9	49.1	62.9	77.8	90.8	99.8		
Education										31.012	<.001
Junior high school or below	3269	(28.1)	24.9	31.7	42.6	56.5	71.1	84.8	93.8		
Senior high school	1889	(16.2)	25.4	31.3	42.8	56.4	70.0	84.9	94.0		
University and above	6483	(55.7)	27.2	34.1	45.4	59.4	74.9.7	89.0	97.7		
Occupation										51.976	<.001
i	1908	(16.3)	25.4	33.2	45.5	60.0	74.9.4	88.5	97.2		
ii	6889	(59.1)	28.0	34.6	46.0	59.0	73.8	88.0	96.5		
iii	2844	(24.4)	22.9	29.4	39.9	53.8	69.1	84.7	94.9		
Season of blood collection										206.680	<.001
Spring (March–May)	3224	(27.7)	18.7	26.6	38.3	51.9	65.8	79.8	88.8		
Summer (June–August)	2999	(25.7)	31.7	36.8	47.2	58.6	71.8	84.3	92.0		
Fall (September–November)	2885	(24.7)	32.7	38.6	50.1	65.2	80.1	95.0	103.3		
Winter (December–February)	2533	(21.7)	22.9	30.4	43.2	57.4	73.4	88.6	97.6		

Table 1 continued. Distribution of maternal demographic characteristics (n=11 641).

Maternal characteristics	25(OH) D percentiles (nmol/L)									F value	P value
	5 th	10 th	25 th	50 th	75 th	90 th	95 th				
Pre-pregnancy BMI (kg/m ²)										1.152	0.094
<18.5	2640	(22.6)	24.8	32.3	43.4	56.7	72.5	87.8	98.1		
18.5–23.9	7713	(66.3)	26.4	32.6	44.5	58.3	73.1	87.7	96.1		
≥24.0	1288	(11.1)	27.5	34.5	46.0	58.2	72.5	85.3	94.5		
Gestational age at blood draw, weeks										37.624	<.001
<13	1803	(15.4)	28.9	33.9	43.0	55.0	68.6	80.3	88.5		
13–27	8817	(75.7)	26.0	32.6	44.7	58.2	73.0	87.4	96.2		
≥28	1021	(8.77)	22.9	32.3	44.4	62.5	80.1	96.6	107.9		
No. of previous pregnancies										91.250	<.001
0	5923	(50.9)	25.3	31.4	42.2	55.3	69.6	83.4	92.2		
1	5068	(43.5)	27.2	34.5	46.7	60.9	76.2	90.5	99.5		
2+	650	(5.6)	28.8	35.7	48.3	61.2	74.9.1	89.2	97.5		
Gestational age at birth, weeks										-1.988	0.047
<37	420	(3.6)	26.8	35.1	47.1	59.4	74.9.4	89.3	97.0		
≥37	11 221	(96.3)	26.1	32.7	44.2	57.9	72.8	87.3	96.3		
Mode of birth										-6.837	<.001
Natural birth	8830	(75.9)	25.0	32.1	43.6	57.2	71.9	86.6	96.1		
Cesarean section	2811	(24.1)	29.4	35.7	47.0	60.6	75.4	89.0	96.8		
Fetal sex										0.115	0.909
Male	6181	(53.1)	26.0	32.9	44.0	57.8	72.8	87.7	96.6		
Female	5460	(46.9)	26.2	32.6	44.6	58.2	72.8	87.3	95.9		

Data are presented as number (%). Key: i: self-employed, freelancer, civil servant, business manager; ii: workers, teachers, business services, serviceman, medical staff, fisherman, clerk, professional technical personnel; iii: housework, unemployed, student, other. 25(OH) D – 25-hydroxyvitamin D; BMI – body mass index.

sampling ($P<0.001$), with the lowest mean concentrations recorded in the spring (52.8 ± 21.0 nmol/L) and the highest in the fall (66.1 ± 21.7 nmol/L).

Table 2 details maternal demographic and clinical features of the preterm and full-term groups. On average, premature women gave birth 4 weeks earlier than the full-term group. No significant differences in mean gestational age at blood sampling and vitamin D status were found between the pre-term and full-term groups, although the average vitamin D status was significantly different between the 2 groups.

No association was found between maternal 25(OH) D deficiency or insufficiency and PTB in the unadjusted model (Table 3)

when using ≥ 75 nmol/L as a reference. After adjusting for maternal age, pre-pregnancy BMI, gestational weeks/season at the time of blood collection, number of previous pregnancies, mother's education and occupation and fetal sex, no association was identified between maternal vitamin D deficiency or insufficiency and preterm labor.

Discussion

This study was conducted in the Guangzhou area of southern China ($23^{\circ}70$ N latitude, $113^{\circ}15$ E longitude) which has sufficient sunlight and a typical subtropical climate. To date, this is the largest hospital-based retrospective cohort study about

Table 2. Maternal characteristics in pre-term and term birth in the total population.

Maternal characteristics	Gestational age at birth, weeks		χ^2 value or T value	P value
	<37 (n=420)	≥37 (n=11 221)		
25-hydroxyvitamin D levels			4.988	0.083
<50	125 (29.8)	3926 (35.0)		
50–74.9	192 (45.7)	4815 (42.9)		
≥75	103 (24.5)	2480 (22.1)		
Education			0.652	0.722
Junior high school or below	124 (29.5)	3145 (28.0)		
Senior high school	70 (16.7)	1819 (16.2)		
University and above	226 (53.8)	6257 (55.8)		
Occupation			0.423	0.809
i	69 (16.4)	1839 (16.4)		
ii	243 (57.9)	6646 (59.2)		
iii	108 (25.7)	2736 (24.4)		
Season of blood collection			7.094	0.069
Spring (March–May)	102 (24.3)	3122 (27.8)		
Summer (June–August)	96 (22.9)	2903 (25.9)		
Fall (September–November)	116 (27.6)	2769 (24.7)		
Winter (December–February)	106 (25.2)	2427 (21.6)		
Mode of delivery			19.046	<.001
Natural birth	281 (66.9)	8549 (76.2)		
Cesarean section	139 (33.1)	2672 (23.8)		
No. of previous pregnancies			7.417	0.025
0	205 (48.8)	5718 (51.0)		
1	179 (42.6)	4889 (43.6)		
2+	36 (8.6)	614 (5.5)		
Fetal sex			4.798	0.028
Female	175 (41.7)	5285 (47.1)		
Male	245 (58.3)	5936 (52.9)		
25-hydroxyvitamin D concentration	61.3±21.3	59.1±21.5	–1.988	0.047
Maternal age	29.8±4.8	29.5±4.5	–1.380	0.168
Pre-pregnancy BMI*	20.7±2.7	20.5±2.7	–0.923	0.356
Gestational age of specimen draw	18.3±6.0	17.8±6.1	–1.437	0.151
Gestational age at birth	35.0±1.4	39.0±1.0	57.376	<.001
2-hour postpartum hemorrhage	220.2±101.0	217.4±77.2	–0.562	0.575
1-minute Apgar score	8.8±0.5	8.9±0.2	4.212	<.001

Table 2 continued. Maternal characteristics in pre-term and term birth in the total population.

Maternal characteristics	Gestational age at birth, weeks		χ^2 value or T value	P value
	<37 (n=420)	≥37 (n=11 221)		
5-minute Apgar score	9.8±0.4	9.9±0.1	4.599	<.001
Neonatal birth weight	2.4±0.4	3.2±0.3	35.392	<.001
Neonatal birth height	46.4±2.9	49.9±1.6	23.940	<.001
Neonatal birth head circumference	31.6±1.6	33.5±1.1	22.485	<.001

Categorical data are presented as number (%), continuous data are presented as mean±standard deviation. Key: i: self-employed, freelancer, civil servant, business manager; ii: worker, teacher, business services, serviceman, medical staff, fisherman, clerk, professional technical personnel; iii: housework, unemployed, student, other. BMI – body mass index.

Table 3. Unadjusted and adjusted odds ratios for pre-term birth according to vitamin D status.

Vitamin D status	≥37 weeks number (%)	<37 weeks number (%)	Unadjusted OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
≥75	2,480 (96.9)	103 (3.1)	1.00 (Reference)	–	1.00 (Reference)	–
50–74.9	4815 (96.2)	192 (3.8)	0.767 (0.588–1)	0.05	0.842 (0.641–1.106)	0.164
<50	3926 (96.0)	125 (4.0)	0.96 (0.752–1.226)	0.749	1.016 (0.794–1.301)	0.961

Data are presented as number (%). * Adjusted for maternal age (categorical variable), body mass index (categorical variable), gestational age at serum collection (categorical variable), and season of blood draw (winter, spring, summer, fall), number of previous pregnancies (categorical variable), mode of delivery (categorical variable), mother’s education and occupation. OR – odds ratio; CI – confidence interval.

the impact of maternal 25(OH) D on preterm delivery among Chinese women. Consistent with previous literature [4,8], we found maternal vitamin D deficiency to be highly prevalent; only 22.2% of expectant mothers in the present study had sufficient 25(OH) D levels.

Season, latitude, and exposure to sunlight affect the synthesis of vitamin D, and 25(OH) D deficiency is therefore common at high latitudes. However, living in low-latitude regions with plenty of sunshine does not seem to decrease the prevalence of deficiency. Despite Guangzhou receiving sufficient sunlight, our results reveal that the 25(OH) D levels of residents of this district did not exceed those of people living in high-latitude areas with insufficient sunlight, whether adults or children. A study by Guo involving 16 755 children aged 0–6 years in the Guangzhou region found vitamin D insufficiency and deficiency to be very prevalent (49.8%) [9]. We found that maternal 25(OH) D levels increased significantly from summer, peaking in September and declining in winter to reach the lowest levels in April. Outdoor activities and sunshine in exposure are limited the spring in Guangzhou due to the wet and rainy weather during this season. Seasonal variation of 25(OH) D levels has also been reported in other studies [10,11] Chen et al. [4] demonstrated that, compared with normal or overweight individuals,

underweight subjects had lower vitamin D levels; each additional unit (1 kg/m²) of pre-pregnancy BMI was associated with a 0.23 ng/mL increase in 25(OH) D concentration. In contrast to earlier findings, however, we did not find a significant association of pre-pregnancy BMI with maternal vitamin D status in the present study. Our observations of vitamin D status of older mothers or mothers with college education compared with domestic workers, unemployed people, students, or primipara lead us to speculate that older who mothers or those have given birth before have more experience in taking vitamin D supplements or adjusting their diet, outdoor activities and sunshine exposure than younger or first-time mothers. Well-educated mothers have more opportunities to use healthcare services and guidance in an urban setting where pre-labor healthcare systems are established. The inability of unemployed women or students to afford vitamin D supplements may be the main reason for their lower 25(OH) D levels.

A growing number of studies have been devoted to studying the impact of vitamin D levels of pregnant woman on adverse pregnancy outcomes. However, results vary in terms of study participants and the relationship of PTB to vitamin D status [12–15]. The results will also be affected by sample size, research methods and confounding factors. Observational and

longitudinal studies support the relevance of vitamin D insufficiency to preterm delivery [16,17], while a randomized trial did not report that vitamin D supplementation reduced the rate of preterm birth [18]. The strength of our study is the cohort of healthy females who should have a relatively low risk of pregnancy complications due to the exclusion of participants with comorbidities or complications that may be associated with PTB, such as diabetes and pre-existing hypertension. Interestingly, no difference was noted in the incidence of vitamin D insufficiency or deficiency in mothers in the preterm group compared with mothers in the full-term group. Surprisingly, in both the unadjusted and adjusted models, maternal vitamin D deficiency or insufficiency showed no relationship with PTB. This supports previous studies; for example, no association was reported between 25(OH) D levels at 15 weeks gestation with pre-eclampsia or spontaneous PTB in a study of 1710 New Zealand women [19].

Differences in 25(OH) D cutoffs; population characteristics such as race, maternal age and/or gestational age at blood collection, and methods for assessing vitamin D status may explain the variations in findings between studies. A prospective study reported that the rate of PTB among Chinese women with 25(OH) D levels of over 30 ng/mL increased by 3.8% between the 16th and 20th gestational week [20]. A recent study revealed that both fetal and maternal vitamin D receptor (VDR) polymorphisms are associated with the development of preterm labor and pointed out that 25(OH) D may contribute to PTB via the VDR [21,22]. Vitamin D metabolism may be influenced by single nucleotide polymorphisms of VDR genes such as BsmI, FokI, TaqI, and Apal, possibly contributing to premature birth. A Brazilian cohort study found that maternal

homozygotes with the low-frequency (CD) allele of Apal single nucleotide polymorphism may be at increased risk of preterm birth [23]. Therefore, the VDR should be considered when exploring the impact of 25(OH) D on premature delivery. Most previous studies – including the present study – have not considered this, which may be one of the reasons for the inconsistent results. There are also other limitations in the present study. First, our study was a single-center retrospective study, and the generalizability of results is low. Second, information on dietary and supplemental vitamin D intake and sunlight exposure were not available, both of which may affect maternal vitamin D status. Third, using only single measurements of each study participant and inconsistent gestational week at the time of blood collection both made it impossible to evaluate fluctuations of vitamin D status over time.

Conclusions

Low 25(OH) D is common among pregnant women in southern China. Serum 25(OH) D concentrations vary depending on maternal characteristics and season. However, maternal vitamin D insufficiency or deficiency does not appear to be associated with PTB. Therefore, evaluating vitamin D level alone is not sufficient to predict PTB. To further investigate the impact of maternal 25(OH) D levels on PTB, well-designed prospective case-control or cohort studies involving multiple measurements are required.

Conflicts of interest

None.

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