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Research Article

Relation between Maternal Vitamin D Concentration during Third Trimester and Maternal and Neonatal Health Outcomes: A Cross-Sectional Study in China

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Abstract

Background: Vitamin D is a key nutritional factor for maintenance of maternal and fetal health. Fetal vitamin D acquisition is entirely dependent on the availability of the mother's 25-hydroxyvitamin D, Vitamin D regulates parathyroid hormone level and increases calcium absorption, critical factors in fetal development.

Objective: Vitamin D deficiency occurs frequently in pregnancy and may lead to preeclampsia, gestational diabetes, postpartum depression, and stillbirth. Therefore, it is necessary to establish the risk factors for vitamin D deficiency during pregnancy to enable a preliminary and predictable diagnosis of vitamin D deficiency and its complications.

Materials and Methods: This cross-sectional study was conducted between February 2017 and January 2019 in a referral tertiary hospital in Beijing, China. All data were extracted from the hospital's patient information system. Vitamin D deficiency was defined as total serum 25-hydroxyvitamin-D concentration less than 20 ng/ml, whereas concentrations between 20 and 30 ng/ml were classified as vitamin D insufficiency.

Results: We included 306 participants with singleton pregnancies. The prevalence of vitamin D deficiency was 57.51% (176/306). A significant correlation was found between vitamin D concentration and the gestational week of delivery (P ≤0.001).

Conclusion: Vitamin D deficiency is a common phenomenon among pregnant women in the Chinese mainland, and the concentration of vitamin D in their bodies is significantly correlated with the progress of pregnancy.

Keywords: Infant Health; Maternal Health; Pregnancy Trimester; Vitamin D

Abbreviations

25 hydroxyvitamin D (25(OH)-D)

Gestational diabetes mellitus (GDM)

Small for gestational age (SGA)

Preterm Birth (PTB)

Caesarean section (CS)

Introduction

Two forms of vitamin D can be readily measured, i.e., 25-hydroxyvitamin-D [25(OH)-D] and 1, 25-dihydroxyvitamin-D [1,25(OH)2D] (also known as calcitriol). The serum concentration of 25(OH) D is used to evaluate the nutritional state of persons regarding their vitamin D levels. Conversely, 1, 25(OH) 2D is the active form of vitamin D; its short half-life limits its measurement in serum [1].

Vitamin D can convert from 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D in response to the status of vitamin D in placenta, and this conversion is important for immunoregulation [2]. Deficiency of vitamin D during pregnancy correlates with gestational diabetes mellitus (GDM), preeclampsia, preterm birth, small babies, and other maternal or fetal outcomes [3]. However, it is not clear whether vitamin D deficiency is only a biomarker or whether the deficiency contributes directly to those pathologies and what may be the causative mechanism(s) [4].

A principal cause of perinatal morbidity and mortality is premature birth, which affects maternal health and the emotional and economic wellbeing of the family. Inflammation and/or infection in the placenta is associated with preterm birth [5]. Vitamin D is an important factor that is involved in the suppression or inhibition of such inflammation and infection [6]. For instance, from a meta-analysis, Qin et al. suggested that vitamin D deficiency during pregnancy was linked to an increased risk of preterm birth [7]. However, the results are of this study were inconclusive and controversial because of shortcomings such as limited diversity of the study participants. Thus, the exact effect of vitamin D deficiency in preterm birth is unresolved.

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Hypertensive disorders during pregnancy are another leading cause for maternal and perinatal mortality. For example, preeclampsia accounts for 2-8% of pregnancy related complications worldwide. In Latin America and the Caribbean, 26% of maternal deaths are due to the hypertensive disorders, and hypertensive disorders account for 9% of maternal deaths in Africa and Asia [8]. Woo et al., used meta-analyses to examine the association between maternal vitamin D deficiency and preeclampsia; the results were mixed [9]. Overall, the evidence suggested that vitamin D supplementation reduced the risk of developing pre-eclampsia compared with placebos or no vitamin D supplementation [10].

Gestational diabetes mellitus is the manifestation of carbohydrate intolerance during pregnancy. The incidence of GDM is not rare [11]. The Center of Disease Control (CDC) estimates that the incidence of GDM in the United States (US) is about 10% [12]. Several studies show that Asians have the highest GDM rates [13]. By analyzing the 34-year prevalence trend of gestational diabetes in China, the results show that GDM prevalence based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria was 2 to 3 times higher (15.6%, [95% CI 14.9-16.2%]) in pregnant women post-2010, compared to other criteria (e.g., World Health Organization: 7.1%, [95%CI 4.1-10.0%]) [14]. In a recent systematic review found that low blood vitamin D concentration increased the risk of GDM, and vitamin D supplementation during pregnancy could prevent GDM [15]. However, the World Health Organization still views as low quality the evidence of a positive effect of vitamin D plus calcium on GDM [10]. Therefore, the aim of the present study was to investigate association between serum vitamin D concentration and adverse pregnancy outcomes in Mainland China.

Material and Methods

Patients

This cross-sectional study was conducted between February 2017 and January 2019 at the Anzhen Hospital, a comprehensive tertiary hospital in Beijing, China. The inclusion criteria were the following: (1) women aged 18-50 years at the expected date of delivery; (2) singleton pregnancy; (3) regular prenatal care and delivery planned in Anzhen Hospital; (4) signed informed consent. We excluded women with pre-pregnant diabetes, multiple pregnancies, chronic hypertension, calcium or vitamin D metabolism disorders, active thyroid disease, eating disorders (anorexia, bulimia), emotional disorders (depression, bipolar disorder, anxiety), or drug addiction (Figure 1). All data were extracted from the hospital's patient information system. The Research and Ethics Committee of Anzhen Hospital approved the study (Anzhen 18029X). The investigators ensured strict confidentiality of participant information by delinking patient identifiers and by using study codes. Preterm birth was defined as delivery before 37 weeks of pregnancy.

Vitamin D measurement

A venous blood sample (5 mL) was collected during prenatal examination after 36 weeks or immediately after delivery. The concentration of 25(OH)-D was measured by ChemiLuminescence (DiaSorin Inc., Saluggia, Italy). Total serum 25(OH)-D concentration between 20 and 30 ng/ml and concentration less than 20 ng/ml were considered as vitamin D insufficiency and deficiency, respectively [16].

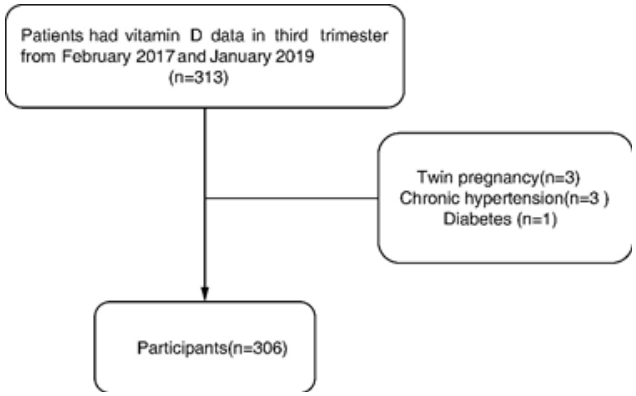

Figure 1: Recruitment of records for study participants.

Recruitment of records for study participants, Preterm birth was defined as delivery before 37 weeks of pregnancy.

Statistical analysis

Data analysis was performed with SPSS 23 and Empower software (X&Y Solutions, Inc. Boston, USA). Descriptive statistics were conducted for relevant data. One way analysis of variances (ANOVA) and Kruskal Wallis test were used for quantitative data. Either the independent sample t-test or Mann–Whitney U test was used to compare continuous variables. The $\chi 2$ test was used to analyze the association between categorical variables and maternal and neonatal health outcomes. Linear regression was used to analyze the association between birth week and vitamin D concentration. A value of $P < 0.05$ was considered to represent statistical significance.

Results

Among the 313 records that were initially examined for this study, 306 (97.7%) were included in the analysis. Table 1 lists the characteristics of the participants. Most of the expectant women (176, 57.5%) had vitamin D deficiency with about a quarter of them (79, 25.8%) displaying vitamin D insufficiency. There was a significant difference in the BMI of the women stratified according to their vitamin D concentrations. The mean BMI in vitamin D sufficiency group was 21.82kg/m^2， while the mean BMI in vitamin D deficiency was 22.96 kg/m^2 and insufficiency group was 22.23 kg/m^2.

We noticed that there were significant differences in the maternal 25-hydroxy vitamin D serum concentrations between women who were at less than 39 weeks of pregnancy and women who were at or beyond 39 weeks of gestation (17.23 ± 6.65 vs 22.83 ± 14.38, P=0.022). Similarly, in the subgroup of participants who had a vaginal delivery the maternal serum 25-hydroxy vitamin D concentration in the preterm delivery subgroup (<37 weeks) was lower compared with that of the full term delivery subgroup (15.17 ± 7.18 vs 21.55 ± 13.17, p=0.40) (Table 2).

Significant linear correlations were noticeable between the maternal vitamin D status and either the gestational period (Figure 2) or the BMI. However, there was no correlation between the maternal vitamin D status and either the gestational weight gain, method of delivery, newborn weight, or GDM (Table 1).

No participant who had an adequate concentration of vitamin D had preeclampsia. However, one and two individuals incurred

Characteristics	All participants	Vitamin D deficiency	Vitamin D insufficiency	Vitamin D sufficiency	P value
	N=306	N=176 (57.51%)	N=79 (25.82%)	N=51 (16.67%)	
Age (yr) *	31.02 ± 3.85	31.00 ± 3.86	31.22 ± 4.24	30.78 ± 3.13	0.82
BMI (kg/m2) *	22.58 ± 3.56	22.96 ± 3.49	22.23 ± 3.78	21.82 ± 3.34	0.038
GWG (kg) *	14.05 ± 4.91	13.85 ± 4.80	14.45 ± 5.13	14.08 ± 4.99	0.67
GDM**	81 (26.47%)	46 (26.14%)	21 (26.58%)	14 (27.45%)	0.982
HD**	29 (9.48%)	14 (7.95%)	12 (15.19%)	3 (5.88%)	0.119
PE**	3 (0.98%)	1 (0.57%)	2 (2.53%)	0 (0.00%)	0.25
PB**	13 (4.25%)	9 (5.1%)	3 (3.8%)	1 (2.0%)	0.601
Newborn weight (g) *	3378.73± 450.50	3372.39 ± 477.40	3411.52 ± 414.45	3349.80 ± 411.90	0.719
Serum 25(OH)-D (ng/ml) *	20.65 ± 12.23	12.84 ±4.25	23.84± 2.73	42.63 ± 10.70	

Table 1: Baseline characteristics of the participants.

Note: * Data are mean ± SD. ** Data presented as n (%). One way analysis of variances or Kruskal Wallis test. BMI: Body Mass Index; GWG: Gestational Weight Gain; GDM: Gestational Diabetes Mellitus; HD: Heart Disease; PE: Preeclampsia; VD: Vaginal Delivery; PB: preterm birth.

Characteristics	< 37 weeks	≥ 37 weeks	p-value	< 39 weeks	≥ 39 weeks	P-value
	N=3	N=149		N=38	N=114	
Age*a	27.67 ± 5.51	30.38 ± 3.76	0.222	30.84 ± 4.20	30.15 ± 3.65	0.331
BMI* a	27.50 ± 5.55	22.18 ± 3.57	0.012	23.17 ± 4.06	21.99 ± 3.50	0.062
GWG* a	11.67 ± 2.89	13.90 ± 4.38	0.259	12.72 ± 3.79	14.24 ± 4.49	0.024
GDM**b	1 (33.33%)	29 (19.46%)	0.485	8 (21.05%)	22 (19.30%)	0.814
PE** b	1(33.33%)	0 (0.00%)	< 0.001	1 (2.63%)	0 (0.00%)	0.082
Serum 25(OH)-D*a	15.17 ± 7.18	21.55 ± 13.17	0.4	17.23 ± 6.65	22.83 ± 14.38	0.022

Table 2: Baseline characteristics of participants with vaginal delivery.

Note: * Data are mean ± SD. ** Data present as n (%). a: T-test; b: $\chi 2$ test. BMI: Body Mass Index; GWG: Gestational Weight Gain; GDM: Gestational Diabetes Mellitus; PE: Preeclampsia

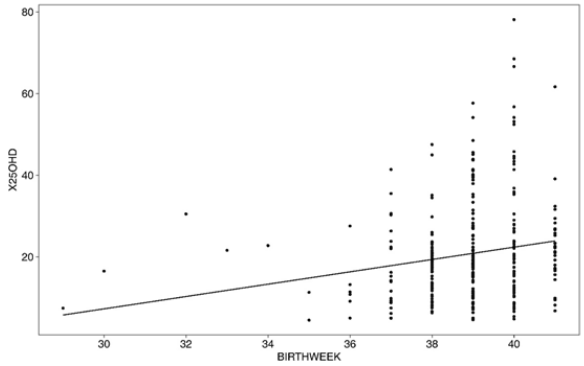

Figure 2: Linear relationship between serum 25(OH)-D and birth week.

Significant linear correlations were noticeable between the maternal vitamin D status and the gestational period. (Correlation=0.1907(0.0803,0.2965); P=0.0008).

preeclampsia among women with vitamin D deficiency and insufficiency, respectively. Adjusted by age, BMI and gestational weight gain, there was no significant aOR for maternal vitamin D status with pregnancy complications including gestational diabetes mellitus, preterm birth and Caesarean section (Table 3).

Discussion

Vitamin D is a fat-soluble vitamin well known for its function in maintaining calcium homeostasis. Vitamin D has been implicated in modulation of other critical functions such as immune response, metabolism, and cell growth [17,18].

Except exposure to lack of sunlight, such as live in northern latitudes, wear long robes or head coverings for religious reasons et al, several factors are known to cause vitamin D deficiency, including age, kidney failure, malabsorption in the intestine, liver failure, and chronic inflammatory disease [19]. In addition, polypharmacy, the use of multiple medications in the management of diseases, can increase the risk of developing vitamin D deficiency. The prevalence of vitamin D deficiency is higher during pregnancy [20,21], and according to a systematic literature review, this prevalence is 54% worldwide [22]. Our study findings concur with this observation because more than half (57.5%) of pregnant women were found to have vitamin D deficiency. There is a large variation in the prevalence of vitamin D deficiency in pregnant women according to geographical location. The prevalence of deficiency in the UK is 20% [23], 78% in Iran [24], 86% in northern India [25], 28% in Australia and New Zealand [26], and 60–84% of pregnant non-Western women in the Netherlands [27].

Serum 25(OH)-D n (%)		GDM		PB		CS	
		n(%)	aoR	n(%)	aoR	n(%)	aoR
Deficiency	176 (57.52%)	46 (56.79%)	0.74 (0.35, 1.56)	9 (5.11%)	2.14 (0.26, 17.76)	91 (51.7%)	1.07 (0.56, 2.02)
Insufficiency	79 (25.82%)	21 (25.93%)	0.87 (0.37, 2.01)	3 (3.80%)	1.64(0.16, 16.99)	38 (48.1%)	0.93(0.45, 1.92)
Sufficiency	51 (16.67%)	14 (17.28%)	1	1 (1.96%)	1	25 (49.0%)	1

Table 3: Adjusted relative risks for pregnancy complications*.

Note: Data presented as n (%). $\chi 2$ test analysis of variances. * Adjusted for age, BMI and GWG. BMI: Body Mass Index; GWG: Gestational Weight Gain; GDM: Gestational Diabetes Mellitus; PB: preterm birth; CS: Cesarean section. There was no significant aOR for maternal vitamin D status with pregnancy complications including gestational diabetes mellitus (GDM), preterm birth (PB) and Caesarean section (CS).

Studies of vitamin D status (maternal serum 25(OH) D concentration) in pregnancy have mostly focused on the later stages of pregnancy and the associated adverse events such as preterm birth, gestational diabetes, and preeclampsia [28]. In a recent critical review, Woo et al. reported a positive correlation between vitamin D deficiency and preterm births [9]. However, the findings of the relationship between vitamin D deficiency and preeclampsia were inconclusive [9]. In an observational cohort study, Vivanti et al., found that a significant decrease in the risk of preeclampsia was associated with maternal vitamin D concentration ≥ 30 ng/mL in the third trimester (OR=0.34; 95% CI: 0.13-0.86. P=0.023) [29]. In our study, we found there was no preeclampsia in the vitamin D sufficiency group compared with two occurrences of preeclampsia in the vitamin D insufficiency group and one in the deficiency group. There was no significant difference for maternal vitamin D status with pregnancy complications including gestational diabetes mellitus, preterm birth, and Caesarean section.

However, we found an interesting phenomenon in our study. The maternal vitamin D concentrations in the group of mothers who delivered before the 39th gestational week were significantly lower than in the group of mothers who delivered after 39 weeks of gestation. And significant linear correlations were noticeable between the maternal vitamin D status and the gestational period in the vaginal delivery group. These findings suggest that vitamin D concentration may be related to the onset of labor.

The fact that CYP27B1 and VDR are expressed in placenta at early stages indicates the importance of vitamin D for placenta function and physiology. In addition to its potential antimicrobial and inflammatory activities, vitamin D might have a much broader functional spectrum in placenta. A study by Ganguly et al., performed trophoblast cells, ex vivo and in vitro, supports this concept [30].

Wagner et al. found that maternal vitamin D status in the third trimester was most significantly associated with preterm birth, thereby proposing that later intervention could be a rescue treatment to decrease the risk of preterm deliveries [31]. Vitamin D and its receptors may have an important function in the maintenance of pregnancy or the initiation of labor.

Our study was an observational design; thus, it was not possible to demonstrate causal relationships. We will increase the sample size in our next study and measure vitamin D concentration throughout the pregnancy with maternal and neonatal health outcomes and labor initiation.

Conclusion

Our study demonstrates that vitamin D deficiency is common among pregnant Chinese women and that the concentration of vitamin D may correlate with the advancement in pregnancy. Thus, Vitamin D and its receptor may have an important function in the initiation of labor, a proposal that requires further investigation.

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Disclosure Statement

The authors whose names are listed certify that they have no affiliations with, or involvement in, any organization or entity with a financial interest or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials presented in this manuscript.

Ethical Consideration

This cross-sectional study was conducted between February 2017 and January 2019 at the Anzhen Hospital, China. All data were extracted from the hospital's patient information system. The Research and Ethics Committee of Anzhen Hospital approved this study (Anzhen 18029X), and all study participants provided required informed consent. The investigators ensured strict confidentiality of participant information by delinking patient identifiers and by using study codes.

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