Large Retrospective Cohort Study of the Association Between Maternal 25-Hydroxyvitamin D Status and Birth Weight of Neonate

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Research Article

Large retrospective cohort study of the association between maternal 25-hydroxyvitamin D status and birth weight of neonate

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Abstract

Background: The effect of maternal vitamin D status on the birth weight of offspring is controversial as the results are inconsistent between different populations. This large

retrospective cohort study aimed to assess the relationship between maternal vitamin D levels and birth weight of neonate.

Methods: Serum samples were collected from 10,586 Chinese women in the 2nd trimester of pregnancy, and the 25-hydroxyvitamin D [25(OH)D] level of the participants was assessed.

Using the INTERGROWTH-21st standards, the offsprings were classified into three groups based on their gestational age and birth weight, which were as follows: small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA).

Results: The average maternal vitamin D concentration was 61.1 nmol/L. The 25(OH)D concentrations were <75.0, <50.0, and <25.0 nmol/L in 76.6%, 31.1%, and 1.6% of the participants, respectively. Approximately 6.4%, 86.4%, and 7.2% of women delivered SGA, AGA, and LGA infants, respectively. No significant differences were observed in vitamin D levels between the three groups ($P = 0.562$). With the increase in 25(OH)D levels, the risk of SGA and LGA tended to increase and decrease, respectively. However, the results were not precise. AGA was not affected by 25(OH)D levels. The results of the curve fitting and threshold effect analyses did not support the correlation between vitamin D levels and SGA or LGA. Based on the univariate prediction model and the model that adjusted for the risk factors, the area under the curve was extremely small. Thus, 25(OH)D level is not an effective predictor of SGA and LGA.

Conclusions: Low maternal vitamin D levels were not associated with SGA or LGA.

Keywords: Pregnant women, vitamin D, birth weight

Background

Healthy growth from conception until the first 1,000 days of life is considered a critical period as it affects an individual's long-term physical and cognitive development [1]. Fetal growth is significantly correlated to maternal nutrition and uterine environment [2]. Birth weight affects long-term physical and mental development as well as metabolic function [3]. Small for gestational age (SGA) and large for gestational age (LGA) were defined as birth weight <10% or >90% of the average of the sex-specific and gestational age distributions. SGA is a major public health problem, and it is correlated to not only an increase in perinatal morbidity and mortality but also the risk of metabolic complications, such as hypertension, obesity, and glucose metabolism disorder, later in life [4]. LGA is a risk factor of shoulder dystocia, birth canal damage, and postpartum hemorrhage, and it is associated with cardiovascular and metabolic problems [5]. Increasing attention has focused on the association between maternal vitamin D level and birth weight of offsprings. However, the results of previous studies are contrasting. Several reports have shown that maternal 25(OH)D insufficiency is an independent risk factor for low birth weight and SGA [6].

However, higher-quality randomized controlled trials (RCTs) have shown that vitamin D supplementation did not result in weight gain among newborns. In a recent placebo-controlled double-blind RCT trial, researchers assessed the effects of vitamin D supplementation at 17–24 weeks of pregnancy until birth on the primary outcomes of infants. These findings

indicated that in a group of expectant mothers who present with general antepartum 25(OH)D deficiency and who have fetuses and infants with restricted growth, vitamin D supplementation did not improve fetal or infant growth from the 2nd trimester of pregnancy until 6 months after giving birth [7].

In another randomized placebo clinical trial, researchers have found that the daily intake of 2000 IU of vitamin D₃ was associated with significant increases in vitamin D levels. However, vitamin D₃ supplementation did not improve the physical measurements of infants from birth until 8 weeks after birth. No significant difference was found in bone mass measurements between the group of infants whose mothers received vitamin D₃ supplementation and the control group [8]. These studies differed in terms of design, definition of exposure, gestational age at sampling, confounding factors, and analysis methods. In addition, population and geographical location are important factors that influence research results. The number of large-scale studies conducted on the Chinese population is limited. Thus, this study aimed to investigate the relationship between prenatal vitamin D level and birth weight of neonate.

Methods

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. The clinical investigation was exempted from the requirement of informed consent because it analyzed a pre-existing dataset and patients remained anonymous. Our research protocol was approved by the Medical Research Ethics Committee of the Guangdong Women

and Children Hospital [201901150]. A retrospective cohort analysis was conducted on women who gave birth at Guangdong Women and Children Hospital between July 1, 2017, and April 30, 2019. The exclusion criteria were as follows: women who had medical or surgical conditions before or during pregnancy, which include high blood pressure, heart disease, diabetes, liver and kidney diseases, abnormal thyroid function, malignant tumor, mental illness, sexually transmitted disease, other diseases requiring surgery, drug or alcohol abuse, fetal abnormalities, or multiple pregnancies. Maternal vitamin D levels were assessed once at 13–27 weeks of gestation. The electronic medical record system of the hospital was used for the review. We obtained the demographic information of the mothers and neonates, which included occupation of the mother, education, age, pre-pregnancy and pregnancy complications, pre-gestational body mass index (BMI, kg/m²), parity, route of birth delivery, gestational age at birth, head circumference of the newborn, height, weight, fetal sex, and season of specimen collection. The follow-up lasted until the participant has delivered her offspring; then, the neonatal birth weight was assessed and used as an outcome variable. The offsprings were categorized according to the 10th and 90th percentiles of birth weight for gestational age with cutoff points derived using the INTERGROWTH-21st standards [9]. SGA, appropriate for gestational age (AGA), and LGA were defined as lower than the 10th, 10th–90th and higher than the 90th sex-specific percentile for weight at birth, respectively. Electrochemiluminescence immunoassay (Abbott Laboratories, IL, USA) was used to measure serum vitamin D concentrations. The inter- and intra-assay coefficients of variation were <10%.

All statistical analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R (<http://www.R-project.org>). A comparison of maternal demographic and clinical features and 25(OH)D concentrations among the three groups were assessed using the Kruskal–Wallis test or Fisher’s exact test. Logistic regression analysis and assessment of smoothing plots were performed to evaluate the crude and adjusted measure of the association between maternal vitamin D concentrations and birth weight of neonate. To assess the predictive accuracy of 25(OH)D levels, the area under the receiver operating characteristic curve was used to compare the models of 25(OH)D with or without adjustment of the risk factors. A two-tailed P value <0.05 was considered statistically significant.

Results

A total of 2359 participants were excluded. Thus, 10586 were finally included in the cohort. The mean value of maternal vitamin D concentrations was 61.1 (range: 13.1–187.8) nmol/L, and the 25(OH)D concentrations were <75.0, <50.0, and <25.0 nmol/L in 8115 (76.6%), 3297 (31.1%), and 169 (1.6%) of the participants. In total, 6,003 (56.7%) women presented with one or more pregnancy complications, such as placenta previa, placental implantation abnormalities, premature rupture of membranes, abruptio placenta, Battledore placenta, fetal growth restriction, fetal distress, umbilical cord torsion, uterine fibroids, and uterine scarring. Meanwhile, 4,583 (43.3%) did not have any pregnancy complications. Of the participants, 681 (6.4%), 9,141 (86.4%), and 764 (7.2%) women delivered SGA, AGA, and LGA infants. Table 1 shows the demographic characteristics of the participants. Compared with other mothers, those who gave birth to SGA infants were younger and had a higher preconception

BMI ($<18.5 \text{ kg/m}^2$) and gestational age at birth (<37 weeks). Moreover, a higher proportion of nulliparous and natural births have been observed in these women ($P < 0.05$). However, contrasting results were observed in those who gave birth to LGA infants. No significant difference was observed in vitamin D concentrations among the three groups ($P = 0.562$). The proportion of individuals with vitamin D deficiency ($<50.0 \text{ nmol/L}$) or insufficiency ($<75.0 \text{ nmol/L}$) did not significantly differ.

A vitamin D level $<25 \text{ nmol/L}$ was used as a reference after adjusting for the risk factors. Thus, with the increase in 25(OH)D concentration, the risk for SGA and LGA tended to increase and decrease, respectively. However, the results were not accurate. The risk for AGA did not change with the increase in 25(OH)D concentration (Table 2). To validate whether there is a positive correlation between 25(OH)D level and birth weight, we conducted a statistical analysis using a software to automatically identify the optimal inflection point for the smooth curve fitting and threshold effect analyses. After adjusting for the risk factors, the results of the curve fitting and threshold effect analyses did not show a correlation between 25(OH)D levels and birth weight. The risk prediction models were established to identify women who delivered infants with different birth weights (Table 3). We used 50 and 25 nmol/L as cutoff values, and the results of the statistical analysis revealed that the vitamin D prediction model alone was less effective than the model that only used the risk factors. After adjusting for the risk factors, we found that the area under the curve of the models was still low. Thus, 25 (OH) D concentration was not an effective predictor of SGA and LGA.

Discussion

134 The results of recent studies about the association between maternal vitamin D concentration
135 and birth weight of offspring are inconsistent [10-12]. The number of large-scale studies
136 based on the effect of maternal prenatal vitamin D level on neonatal birth weight in a Chinese
137 population is extremely limited. Thus far, this is the largest study about the association
138 between prenatal vitamin D level and birth weight of neonates among Chinese mothers.

139 After controlling for high-risk factors, such as gestational diabetes and high blood pressure,
140 that might affect birth weight, the subjects were found to be at a low risk of delivering
141 children with abnormal birth weight in this study. In this retrospective cohort study, we
142 classified the neonates into three groups according to birth weight using the
143 INTERGROWTH-21st standards, which were as follows: the SGA, AGA, and LGA groups.

144 The occurrence of prenatal 25(OH)D deficiency is common among pregnant women [13],
145 and this result is consistent with that of the current study. The vitamin D concentrations in all
146 three groups were low, with an average value between 60.7 and 61.8 nmol/L. The occurrence
147 of vitamin D deficiency (<50 nmol/L) was also high at 69.5%, 68.8%, and 68.6% in the SGA,
148 AGA, and LGA groups, respectively.

149 Autonomously synthesizing and activating vitamin D in the skin is dependent on ultraviolet B
150 (UVB) exposure. This study indicated that Chinese mothers did not have adequate 25(OH)D
151 levels in the 2nd trimester of pregnancy even if they had high exposure to sunshine. Our
152 previous research has shown that vitamin D deficiency in children is prevalent in this region
153 [14,15]. Vitamin D synthesis is dependent on the amount of outdoor activities and the direct

exposure of the body's surface to UVB radiation from the sun [16]. Thus, increasing the time spent outdoors, use of vitamin D supplements, and intake of fortified foods are recommended. Surprisingly, the vitamin D levels of the three groups did not significantly differ. Although 25(OH)D levels >75 nmol/L had a weak protective effect against LGA and can increase the risk of SGA after adjusting for the risk factors, a significant linear or non-linear relationship was observed between SGA or LGA and vitamin D concentration.

These results were in accordance with those of a previous study conducted on pregnant women in Indonesia. The 25(OH)D level in the 1st trimester of pregnancy was not correlated to neonatal birth weight, with or without adjusting for pre-pregnancy BMI and maternal age [11]. This outcome was contrasting to that of the study of Huiping Wang, which showed a non-linear correlation between maternal vitamin D level and birth weight of offspring in a cohort of singleton, term, and live births in China. In pregnant women with 25(OH)D levels <20 ng/mL, an elevation of 1 ng/mL in the 25(OH)D concentration was associated with an increase in birth weight by 69 g, which then leveled off [6]. Varying blood collection periods and characteristics of the participants (the latter excluding preterm SGA infants) might have contributed to the differences in the study results.

The predictive value of vitamin D for SGA and LGA was assessed by evaluating the area under the curve (AUC) using the logistic regression models. After using low 25(OH)D concentrations (25 and 50 nmol/L), the predictive value of vitamin D concentration alone and that of vitamin D after adjusting for the clinical risk factors was assessed. After comparing the AUC of each model and indicator, such as specificity, sensitivity, and negative and positive

predictive values, our findings indicated that a lower 25(OH)D concentration was not better than the clinical risk factors in predicting SGA and LGA. In the study of Mendel, the results of a randomized analysis of 190,406 mothers showed that maternal 25(OH)D concentrations did not affect the birth weight of healthy newborns [12]. Previously, a meta-analysis of randomized trials of vitamin D supplementation has been conducted. Results showed that none of the moderate- or high-quality studies have found an association between vitamin D supplementation and improvement of glucose metabolism in pregnant women [17]. Moreover, a cohort study based on a prospective community research did not find any evidence showing that vitamin D status during early pregnancy was associated with pregnancy-related hypertension in women who did not have children [18]. In one of our previous studies, prenatal vitamin D levels did not have any effect on the birth weight of premature infants [19]. Preterm labor, gestational diabetes, and preeclampsia are the factors that influence birth weight. Similar to previous studies, this research found that maternal vitamin D levels do not affect birth weight.

The current study had several limitations. First, this was a retrospective study that did not collect information about diet and vitamin D supplementation, which are important factors that can affect the vitamin D levels of pregnant woman. A previous study has assessed the nutrition and health status of pregnant women in China for nearly a decade, and results showed that the most common problems observed in the participants were unbalanced diet, micronutrient intake below the recommended value, and extremely low intake of vitamins, including vitamin D [20]. In addition, our study only focused on pregnant women in southern

China, and the results reflected the effect of maternal vitamin D concentration on the birth weight of offsprings in this region. Thus, the results may not be representative of other populations. A previous meta-analysis revealed differences in study design, population, geographical location, and definition of cutoff values, which resulted in heterogeneity among the studies [21]. Third, we evaluated vitamin D levels in the blood but did not consider the diversity of vitamin D receptor (VDR) polymorphisms. Recent studies have shown that single nucleotide polymorphisms (SNPs) in the VDR gene affect maternal vitamin D concentrations and pregnancy outcomes. The vitamin D concentration of pregnant women with low-frequency allele GG of SNP TaqI was higher than that of women with higher-frequency homozygotes AA. Women with ApaI SNP (GA) heterozygotes give birth to children with lower weight [22]. Meanwhile, Barchitta M has found that the birth weight of offsprings is lower in women with FokI polymorphism who have a higher number of A allele [23]. Fourth, blood sampling during pregnancy was conducted only once. Thus, it may not accurately reflect vitamin D status and its changes throughout pregnancy [24].

Conclusions

In summary, maternal 25(OH) D concentration did not affect the birth weight of neonates, and low vitamin D levels were not associated with SGA or LGA. Thus, well-designed prospective cohort studies must be conducted to longitudinally measure vitamin D concentration and to assess the diversity of VDR polymorphisms.

216 **List of abbreviations**

217 SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for
218 gestational age; 25(OH)D :25-hydroxyvitamin D; RCTs: randomized controlled trials ; BMI:
219 body mass index; UVB :ultraviolet B; AUC: area under the curve; VDR: vitamin D receptor ;
220 SNPs: single nucleotide polymorphisms**Declarations**

221 **Ethics approval and consent to participate**

222 This study was approved by the Medical Research Ethics Committee of Guangdong Women
223 and Children Hospital and was conducted in accordance with the Declaration of Helsinki. The
224 clinical investigation was exempted from the requirement of informed consent requirement
225 because it analyzed a pre-existing dataset and patients remained anonymous.

226 **Consent for Publication**

227 Not applicable.

228 **Availability of data and materials**

229 The datasets used and/or analysed during the current study are available from the
230 corresponding author on reasonable request.

231 **Competing interests**

232 The authors declare that they have no competing interests.

233

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236

237 **Authors' contributions**

238 Conception and design were done by LY, HK and JW. Data analysis and interpretation were
239 done by LY and DC. Drafts were prepared by LY and YG. Revision of the manuscript was
240 done by LY, HK, DC and JW. All authors have approved the final article.

241

242 **Acknowledgement**

243 Not applicable

244

245 **References**

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323

324 Table 1. Baseline characteristics of the participants (N = 10586)

	SGA infants	AGA infants	LGA infants	P value
	(n = 681)	(n = 9141)	(n = 764)	

Maternal age				<0.001
<30 years	423 (62.1%)	4856 (53.1%)	312 (40.8%)	
≥30 years	258 (37.9%)	4285 (46.9%)	452 (59.2%)	
Education level				0.108
Senior high school or lower	313 (46.0%)	4031 (44.1%)	311 (40.7%)	
University graduate or higher	368 (54.0%)	5110 (55.9%)	453 (59.3%)	
Occupation				0.042
I	434 (63.7%)	5456 (59.7%)	478 (62.6%)	
II	247 (36.3%)	3685 (40.3%)	286 (37.4%)	
Pre-pregnancy BMI (kg/m ²)				<0.001
<18.5	226 (33.2%)	1961 (21.5%)	76 (9.9%)	
≥18.5	455 (66.8%)	7180 (78.5%)	688 (90.1%)	
Parity				<0.001
Multipara	345 (50.7%)	6160 (67.4%)	620 (81.2%)	
Nullipara	336 (49.3%)	2981 (32.6%)	144 (18.8%)	
Complications				0.009
Yes	412 (60.5%)	5130 (56.1%)	461 (60.3%)	
No	269 (39.5%)	4011 (43.9%)	303 (39.7%)	
Route of birth delivery				<0.001
Caesarean section	210 (30.8%)	2735 (29.9%)	370 (48.4%)	
Natural birth	471 (69.2%)	6406 (70.1%)	394 (51.6%)	

Neonatal sex				0.301
Male	357 (52.4%)	4946 (54.1%)	431 (56.4%)	
Female	324 (47.6%)	4195 (45.9%)	333 (43.6%)	
Gestational age at birth (weeks)	38.9 ± 1.4	38.8 ± 1.5	38.9 ± 1.3	0.095
Preterm or not				<0.001
Term birth	648 (95.2%)	8653 (94.7%)	749 (98.0%)	
Preterm birth	33 (4.8%)	488 (5.3%)	15 (2.0%)	
Head circumference at birth	32.1 ± 1.3	33.4 ± 1.3	35.2 ± 1.2	<0.001
Height at birth	47.6 ± 2.0	49.6 ± 1.9	52.0 ± 1.8	<0.001
Weight at birth	2.6 ± 0.3	3.2 ± 0.4	4.0 ± 0.3	<0.001
Season of blood collection				0.510
Spring and winter	313 (46.0%)	4207 (46.0%)	335 (43.8%)	
Summer and fall	368 (54.0%)	4934 (54.0%)	429 (56.2%)	
25(OH)D concentration	61.8 ± 20.8	61.1 ± 20.1	60.7 ± 21.0	0.562
25(OH)D				0.857
<25.0 nmol/L	9 (1.3%)	144 (1.6%)	16 (2.1%)	
25.0–50.0 nmol/L	199 (29.2%)	2704 (29.6%)	224 (29.3%)	
50.0–75.0 nmol/L	303 (44.5%)	4167 (45.6%)	349 (45.7%)	
≥75.0 nmol/L	170 (25.0%)	2126 (23.3%)	175 (22.9%)	

325 BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

I: unemployed, houseworker, student and others. II: business manager, freelancer, Self-employed, civil servant, worker, business service provider, serviceman, fisherman, professional technical personnel medical staff, clerk and teacher

329

330

Table 2. Association between serum 25(OH)D concentrations and birth weight

		SGA	AGA	LGA
		infants	infants	infants
Unadjusted β /OR (95% CI), P value	Continuous	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
	<25	1	1	1
	25–50 nmol/L	1.2 (0.6, 2.4)	1.1 (0.7, 1.7)	0.7 (0.4, 1.3)
	50–75	1.2 (0.6, 2.4)	1.1 (0.7, 1.7)	0.7 (0.4, 1.3)
	≥ 75 nmol/L	1.3 (0.7, 2.6)	1.1 (0.7, 1.7)	0.7 (0.4, 1.2)
Adjusted β /OR (95% CI), P value	Continuous	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
	<25	1	1	1

25–50nmol/L	1.2 (0.6,	1.1 (0.7,	0.7 (0.4,
	2.4)	1.7)	1.2)
50–75	1.3 (0.6,	1.1 (0.7,	0.7 (0.4,
	2.5)	1.8)	1.1)
≥75 nmol/L	1.4 (0.7,	1.1 (0.7,	0.6 (0.4,
	2.9)	1.7)	1.1)

332 Values were adjusted for parity, pre-pregnancy BMI (kg/m²), maternal age, occupation,
333 education, gestational age at birth, fetal sex, complications, and season of blood collection

334

335

336 Table 3. Accuracy of 25(OH)D levels in predicting birth weight

		AU	95%	Specific	Sensitiv	LR	LR	PP	NP
		C	CI	ity	ity	(+)	(–)	V	V
SGA	25(OH)D < 50	0.50	(0.48	0.3118	0.6946	1.00	0.979	0.06	0.93
infants	nmol/L	32	53,			92	7	49	69
			0.521						
			1)						
	25(OH)D < 25	0.50	(0.49	0.0162	0.9868	1.00	0.818	0.06	0.94
	nmol/L	15	7,			3	1	45	67

				0.505				
				9)				
	Risk factors	0.63	(0.61	0.5745	0.649	1.52	0.610	0.09 0.95
		38	23,			52	9	49 97
				0.655				
				2)				
	25(OH)D < 50	0.63	(0.61	0.6165	0.6079	1.58	0.636	0.09 0.95
	nmol/L + risk	53	4,			5		83 81
	factors			0.656				
				6)				
	25(OH)D < 25	0.63	(0.61	0.5754	0.6476	1.52	0.612	0.09 0.95
	nmol/L + risk	35	2,			5	5	49 96
	factors			0.655				
				)				
AGA	25(OH)D < 50	0.50	(0.48	0.69	0.3116	1.00	0.997	0.86 0.13
infants	nmol/L	08	79,			49	8	41 68
				0.513				
				6)				
	25(OH)D < 25	0.50	(0.49	0.0173	0.9842	1.00	0.910	0.86 0.14
	nmol/L	08	72,			16	5	37 79

				0.504				
				4)				
	Risk factors	0.53	(0.51	1.8768	0.6332	0.41	0.447	1.14 0.91
		18	6,			86	9	12 82
				0.547				
				6)				
	25(OH)D nmol/L	0.53	(0.51	1.8754	0.6332	0.41	0.447	1.14 0.91
	<50 + risk factors	17	58,			86	9	12 82
				0.547				
				6)				
	25(OH)D nmol/L	0.53	(0.51	1.8777	0.6381	0.41	0.444	1.14 0.91
	<25 + risk factors	22	64,			43	8	46 8
				0.548				
				1)				
LGA	25(OH)D < 50	0.50	(0.48	0.6889	0.3141	1.00	0.995	0.07 0.92
infants	nmol/L	15	44,			96	6	28 81
				0.518				
				6)				
	25(OH)D < 25	0.50	(0.49	0.9844	0.0209	1.34	0.994	0.09 0.92
	nmol/L	27	75,			44	5	47 82

				0.507				
				9)				
Risk factors	0.62	(0.60	-2.7492	0.4398	0.77	0.463	1.38	0.51
	63	73,			36	9	09	48
				0.645				
				2)				
25(OH)D < 50 nmol	0.62	(0.60	-2.4948	0.4962	0.72	0.512	1.43	0.55
/L + risk factors	77	87,			38	7	68	65
				0.646				
				8)				
25(OH)D < 25	0.62	(0.60	-2.7643	0.4346	0.77	0.459	1.37	0.51
nmol/L + risk	79	89			75	4	52	2
factors				0.646				
				9)				

337 The risk factors were adjusted for parity, pre-pregnancy BMI (kg/m²), maternal occupation,
338 and complications.

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