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 levels on the birth weight of the offspring remains 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 neonates in southern China.

Methods: Serum samples were collected from 10,586 Chinese women at 13–27 weeks of pregnancy, and the 25-hydroxyvitamin D (25(OH)D) level of the participants was assessed. Using the INTERGROWTH-21st standards, the offspring were classified into three groups based on their gestational age and birth weight, which were small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). The differences in vitamin D levels among the different groups were compared, and their correlation with newborn birth weight was analyzed.

Results: The average maternal vitamin D concentration was 61.1 nmol/L. The 25(OH)D concentrations were 50–75 nmol/L, 25–50 nmol/L and below 25 nmol/L in 45.5%, 29.5%, and 1.6% of the participants, respectively. No significant differences were observed in the vitamin D levels between the three groups. With the increase in 25(OH)D levels, the risk of SGA and LGA tended to increase and decrease, respectively. AGA was not affected by the 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 adjusted for risk factors, the area under the curve was extremely small. Thus, 25(OH)D levels are not an effective predictor of SGA and LGA.

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

Introduction

Healthy growth from conception until the first 1000 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 with 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 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 disorders, later in life [4]. LGA is a risk factor for shoulder dystocia, birth canal damage, and postpartum hemorrhage, and is associated with cardiovascular and metabolic problems [5].

Vitamin D is a fundamental nutritional factor that is sequentially synthesized in the skin, liver, and kidney of the human body. Its well-known functions are to regulate bone metabolism, absorption of calcium and phosphate, and maintenance of muscle function. Accumulating evidence indicates that sufficient vitamin D status is required during pregnancy to address the growing demand for calcium and to maintain fetal growth. The literature shows that vitamin D is involved in the mineralization and growth of fetal bones, and neonatal vitamin D levels depend on the state of maternal vitamin D [6,7]. Increasing attention has been given to the association between maternal vitamin D levels and birth weight of the offspring; however, the results remain inconsistent. Several reports have shown that maternal 25-hydroxyvitamin
D (25(OH)D) insufficiency is an independent risk factor for low birth weight and SGA [8–10]. High-quality randomized controlled trials (RCTs) have shown that vitamin D supplementation does not result in weight gain in newborns [11,12]. In a recent placebo-controlled double-blind RCT, researchers assessed the effects of vitamin D supplementation at 17–24 weeks of pregnancy until birth on the primary outcomes of infants. These findings indicate 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 second trimester of pregnancy until six months after giving birth [10].

In another randomized placebo clinical trial, researchers found that a 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 [12]. 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 in the Chinese population is limited. Thus, this study aimed to investigate the relationship between prenatal vitamin D levels and birth weight of neonates in southern China.

Materials and methods

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. The clinical investigation was exempted from the requirement of informed consent because it analyzed a preexisting dataset and patients remained anonymous. Our research protocol was approved by the Medical Research Ethics Committee of Guangdong Women and Children Hospital (201901150). A retrospective cohort analysis was conducted on women who gave birth at Guangdong Women and Children Hospital between 1 July 2017 and 30 April 2019. The exclusion criteria were as follows: women who had medical or surgical conditions before or during pregnancy, which included 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 plasma 25(OH)D levels were determined once at 13–27 weeks of gestation via electrochemiluminescence immunoassay (Abbott Laboratories, Lake Bluff, IL) with intra- and inter-assay coefficients of variation less than 10%. Vitamin D deficiency and insufficiency were defined based on widely used clinical cutoff values according to the Endocrine Society’s clinical practice guidelines as 25(OH)D concentrations <50 nmol/L and 50–75 nmol/L, respectively [13].

The electronic medical record system of the hospital was reviewed. We obtained the demographic information of the mothers and neonates, which included occupation of the mother, education, age, pre-pregnancy and pregnancy complications, pro-gestational body mass index (BMI, kg/m²), parity, route of 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 delivered her offspring; then, the neonatal birth weight was assessed and used as an outcome variable. The offspring were categorized according to the 10th and 90th percentiles of birth weight for gestational age with cutoff points derived using the INTERGROWTH-21st standards [14]. SGA, appropriate for gestational age (AGA), and LGA were defined as lower than the 10th, 10th–90th, and 90th percentiles, respectively, for weight at birth.

All statistical analyses were performed using SPSS (V20, IBM Corp., Armonk, NY). Maternal demographic and clinical features and 25(OH)D concentrations among the three groups were compared 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 measures of the association between maternal vitamin D concentrations and birth weight of neonates. To assess the predictive accuracy of 25(OH)D levels, the area under the receiver operating characteristic curve was used to compare the 25(OH)D models with or without adjustment for the risk factors. Statistical significance was defined as a two-tailed p value of <.05.

Results

A total of 2359 participants were excluded based on the exclusion criteria. Finally, 10,586 patients were included in the cohort. The mean value of maternal 25(OH)D concentrations was 61.1 (range: 13.1–187.8) nmol/L, and the 25(OH)D concentrations were
Table 1. Baseline characteristics of the participants (N = 10,586).

|                          | SGA infants (N = 681) | AGA infants (N = 9141) | LGA infants (N = 764) | p Value |
|--------------------------|-----------------------|------------------------|-----------------------|---------|
| Maternal age             |                       |                        |                       | <.001   |
| <30 years                | 423 (62.1%)           | 4856 (53.1%)           | 312 (40.8%)           |         |
| ≥30 years                | 258 (37.9%)           | 4265 (46.9%)           | 452 (59.2%)           |         |
| Education level          |                       |                        |                       | .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               |                       |                        |                       | .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/m²) |                       |                        |                       | <.001   |
| <18.5                    | 226 (33.2%)           | 1961 (21.5%)           | 76 (9.9%)             |         |
| ≥18.5                    | 453 (66.8%)           | 7180 (78.5%)           | 688 (90.1%)           |         |
| Parity                   |                       |                        |                       | <.001   |
| Multipara                | 345 (50.7%)           | 6160 (67.4%)           | 620 (81.2%)           |         |
| Nullipara                | 336 (49.3%)           | 2981 (32.6%)           | 144 (18.8%)           |         |
| Complications            |                       |                        |                       | .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  |                       |                        |                       | <.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             |                       |                        |                       | .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 | .095 |
| Preterm or not           |                       |                        |                       | <.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 | <.001 |
| Height at birth          | 47.6 ± 2.0            | 49.6 ± 1.9             | 52.0 ± 1.8            | <.001   |
| Weight at birth          | 2.6 ± 0.3             | 3.2 ± 0.4              | 4.0 ± 0.3             | <.001   |
| Season of blood collection |                   |                        |                       | .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 (nmol/L) | 61.8 ± 20.8 | 61.1 ± 20.1 | 60.7 ± 21.0 | .562 |
| 25(OH)D                  |                       |                        |                       | .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 (45.5%)           | 4167 (45.6%)           | 349 (45.7%)           |         |
| ≥75.0 nmol/L             | 170 (25.0%)           | 2126 (23.3%)           | 175 (22.9%)           |         |

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, service man, fisherman, professional technical personnel medical staff, clerk, and teacher.

≥75 nmol/L, 50–75 nmol/L, 25–50 nmol/L, and <25 nmol/L in 2471 (23.3%), 4819 (45.5%), 3127 (29.5%), and 169 (1.6%) of the participants. In total, 681 (6.4%), 9141 (86.4%), and 764 (7.2%) delivered SGA, AGA, and LGA infants, respectively. Table 1 presents 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 kg/m²) and gestational age at birth (<37 weeks). Moreover, a higher proportion of nulliparous and natural births was observed in these women (p < .05). However, contrasting results were observed in those who gave birth to infants with LGA. No significant difference was observed in vitamin D concentrations among the three groups (p = .562). The proportion of individuals with vitamin D deficiency (<50 nmol/L) or insufficiency (50–75 nmol/L) did not significantly differ (p = .857).

A vitamin D level of <25 nmol/L was used as a reference after adjusting for risk factors. Thus, with the increase in 25(OH)D concentration, the risk for SGA and LGA tended to increase and decrease, respectively. The probability of AGA did not change with an increase in the 25(OH)D concentration (Table 2). To validate whether there is a positive correlation between 25(OH)D levels and birth weight, we conducted a statistical analysis 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. 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 (AUC) of the models was still low. Thus, 25(OH)D concentration was not an effective predictor of SGA or LGA.

Discussion

The results of recent studies on the association between maternal vitamin D concentration and the birth weight of the offspring are inconsistent [15–17]. The number of large-scale studies based on the effect of maternal prenatal vitamin D levels on neonatal birth weight in a Chinese population is extremely limited. To date, this is the largest study on the association between prenatal vitamin D levels and birth weight of neonates among Chinese mothers.

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

The occurrence of prenatal 25(OH)D deficiency is common among pregnant women [18], and this result is consistent with that of the current study. The vitamin D concentrations in all three groups were low, with an average value between 60.7 and 61.8 nmol/L. The occurrence of vitamin D deficiency (<50 nmol/L) was 30.5%, 31.2%, and 31.4% in the SGA, AGA, and LGA groups, respectively.

Autonomous synthesis and activation of vitamin D in the skin are dependent on ultraviolet B (UVB) exposure. This study indicated that mothers did not have adequate 25(OH)D levels at 13–27 weeks of pregnancy, even if they had high exposure to sunshine in southern China. Our previous research has shown that vitamin D deficiency in children is

| Table 2. Association between serum 25(OH)D concentrations and birth weight. |
|--------------------------|----------------|----------------|----------------|
|                         | SGA infants    | AGA infants    | LGA infants    |
| Unadjusted OR (95% CI)  |                |                |                |
| Continuous              | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) |
| <25 nmol/L              | 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 nmol/L            | 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 OR (95% CI)    |                |                |                |
| Continuous              | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) |
| <25 nmol/L              | 1              | 1              | 1              |
| 25–50 nmol/L            | 1.2 (0.6, 2.4) | 1.1 (0.7, 1.7) | 0.7 (0.4, 1.2) |
| 50–75 nmol/L            | 1.3 (0.6, 2.5) | 1.1 (0.7, 1.8) | 0.7 (0.4, 1.1) |
| ≥75 nmol/L              | 1.4 (0.7, 2.9) | 1.1 (0.7, 1.7) | 0.6 (0.4, 1.1) |

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

| Table 3. Accuracy of 25(OH)D levels in predicting birth weight. |
|-----------------------|----------------|----------------|----------------|
|                       | SGA infants    | AGA infants    | LGA infants    |
|                       |                |                |                |
| AUC                   |                |                |                |
| Continuous            | 0.5032 (0.4853, 0.5211) | 0.5015 (0.497, 0.5059) | 0.5032 (0.4853, 0.5211) |
| Risk factors          | 0.6338 (0.6123, 0.6552) | 0.6353 (0.614, 0.6566) | 0.6335 (0.612, 0.655) |
| AGA infants           | 0.5008 (0.4879, 0.5136) | 0.5008 (0.4972, 0.5044) | 0.5008 (0.4972, 0.5044) |
| Risk factors          | 0.5318 (0.516, 0.5476) | 0.5317 (0.5138, 0.5476) | 0.5322 (0.5164, 0.5481) |
| LGA infants           | 0.5015 (0.4844, 0.5186) | 0.5027 (0.4975, 0.5079) | 0.5027 (0.4975, 0.5079) |
| Risk factors          | 0.6263 (0.6073, 0.6452) | 0.6277 (0.6087, 0.6468) | 0.6279 (0.6089, 0.6469) |
|                       |                |                |                |
| Specificity           | 0.3118         | 0.0162         | 0.6354         |
| Sensitivity           | 0.6946         | 0.9868         | 0.6079         |
| LR (+)                | 1.0092         | 1.003          | 1.585          |
| LR (−)                | 0.9797         | 0.8181         | 0.636          |
| PPV                   | 0.0649         | 0.0645         | 0.9983         |
| NPV                   | 0.9369         | 0.9467         | 0.9581         |

The risk factors were adjusted for parity, pre-pregnancy BMI (kg/m²), maternal age, occupation, gestational age at birth, fetal sex, complications, and season of blood collection.
prevalent in this region [19,20]. Vitamin D synthesis is dependent on the frequency of outdoor activities and direct exposure of the body’s surface to UVB radiation from the sun [21]. Thus, increasing the time spent outdoors, use of vitamin D supplements, and intake of fortified foods are recommended. Surprisingly, the vitamin D levels in the three groups did not differ significantly. Although 25(OH)D levels of >75 nmol/L had a weak protective effect against LGA and increased the risk of SGA after adjusting for the risk factors, no 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 first trimester of pregnancy was not correlated with neonatal birth weight, with or without adjusting for pre-pregnancy BMI and maternal age [16]. This outcome was in contrast to that of the study by Wang H, who 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 of <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 [8]. Varying blood collection periods and characteristics of the participants (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 AUC using 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 by mendelian randomisation, 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 [17]. A meta-analysis of randomized trials of vitamin D supplementation was 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 [22]. 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 [23]. In one of our previous studies, prenatal vitamin D levels did not affect the birth weight of premature infants [24]. Preterm labor, gestational diabetes, and preeclampsia are factors that influence birth weight. These factors do not change with maternal vitamin D levels during pregnancy, which may provide clues to explain the negative correlation between maternal vitamin D levels and 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 vitamin D levels in pregnant women. A previous study assessed the nutrition and health status of pregnant women in China for nearly a decade, and the 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 [25]. 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 the offspring 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 [26]. Third, we evaluated vitamin D levels in 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 outcomes of pregnancy. The vitamin D concentration of pregnant women with low-frequency allele GG of SNP TaqI was higher than that of women with higher-frequency homozygote AA. Women with Apal SNP (GA) heterozygotes give birth to children of lower weight [27]. Meanwhile, Barchitta M et al. found that the birth weight of offspring is lower in women with FokI polymorphism who have a higher number of A alleles [28]. Fourth, blood sampling during pregnancy was conducted only once. Thus, it may not accurately reflect the vitamin D status and its changes throughout pregnancy [29]. Finally, the sample collection of the subjects in this study spanned a large gestational period, from 13 to 27 weeks. The vitamin D levels of mothers at different gestational weeks may have different effects on the birth weight of the offspring, which may have caused bias.
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 concentrations and to assess the diversity of VDR polymorphisms.

Ethics approval and consent to participate

This study was approved by the Medical Research Ethics Committee of Guangdong Women and Children Hospital and was conducted in accordance with the Declaration of Helsinki. This study was exempted from the requirement of informed consent because it analyzed a preexisting dataset, and the patients remained anonymous.

Disclosure statement

The authors report no conflict of interest.

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