Maternal Vitamin D Deficiency During Pregnancy Elevates the Risks of Small for Gestational Age and Low Birth Weight Infants in Chinese Population

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Context: Vitamin D deficiency is common in pregnant women. Nevertheless, the association between maternal vitamin D status during pregnancy and the risk of having small for gestational age (SGA) and low birth weight (LBW) infants is uncertain.

Objective: The objective of this study was to investigate whether there is a correlation between maternal vitamin D deficiency during pregnancy and the risk of having SGA and LBW infants in a Chinese population.

Design and Participants: This was a population-based birth cohort study that recruited 3658 eligible mother-and-singleton-offspring pairs.

Main Outcome Measures: Serum 25-hydroxyvitamin D was measured by RIA. The rate and relative risk (RR) for SGA and LBW infants were calculated among subjects with vitamin D deficiency and insufficiency during pregnancy.

Results: There was a positive correlation between maternal serum 25-hydroxyvitamin D level and offspring birth weight ($r = 0.477$; $P < .001$). Further analysis showed that 4.98% of neonates were LBW infants among the subjects with vitamin D deficiency (RR, 12.00; 95% confidence interval [CI], 4.37, 33.00) and 1.32% among the subjects with vitamin D insufficiency (RR, 3.18; 95% CI, 1.07, 9.48). After adjustment for confounders, the RR for LBW infants was 12.31 (95% CI, 4.47, 33.89) among subjects with vitamin D deficiency and 3.15 (95% CI, 1.06, 9.39) among subjects with vitamin D insufficiency. Moreover, 16.01% of neonates were SGA infants among subjects with vitamin D deficiency (RR, 5.72; 95% CI, 3.80, 8.59) and 5.59% among subjects with vitamin D insufficiency (RR, 1.99; 95% CI, 1.27, 3.13). After adjustment for confounders, the RR for SGA infants was 6.47 (95% CI, 4.30, 9.75) among subjects with vitamin D deficiency and 2.01 (95% CI, 1.28, 3.16) among subjects with vitamin D insufficiency.

Conclusion: Maternal vitamin D deficiency during pregnancy elevates the risk of SGA and LBW infants in a Chinese population. **(*J Clin Endocrinol Metab* 100: 1912–1919, 2015)**

Vitamin D, a secosteroid hormone known for its classical functions in calcium uptake and bone metabolism (1), is now well recognized for its nonclassical actions, including modulation of innate immune response and regulation of cell proliferation (2–5). Vitamin D deficiency, defined as lower than 50 nmol/L of 25-hydroxyvitamin D [25(OH)D], is common in pregnant women and is increasingly recognized as a global public

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Abbreviations: BMI, body mass index; CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; 25(OH)D, 25-hydroxyvitamin D; RR, relative risk; SGA, small for gestational age.

health problem (6, 7). Increasing evidence demonstrates that vitamin D deficiency during pregnancy is linked with gestational diabetes mellitus, pre-eclampsia, and bacterial vaginosis (8–10). Moreover, maternal vitamin D deficiency during pregnancy is associated with reduced bone mineral content, impaired muscle development, the increased asthma and schizophrenia in adult offspring (11–15).

Intrauterine growth restriction (IUGR), which manifests as small for gestational age (SGA) and low birth weight (LBW), increases the risk of infant morbidity and metabolic diseases in adulthood (16, 17). Recently, several small epidemiological studies explored the association between vitamin D status during pregnancy and SGA and LBW infants with contradictory results (18–21). Until now, no report analyzed the association between vitamin D status at different gestational stages and the risk of SGA and LBW infants. Therefore, the association between maternal vitamin D status at different gestational stages and the risks of LBW and SGA infants needs to be further determined in a large longitudinal investigation.

The objective of the present study was to analyze whether maternal vitamin D deficiency at different gestational stages elevates the risks of LBW and SGA infants in a Chinese population-based birth cohort study. Our results demonstrate that maternal vitamin D deficiency not only at the first trimester but also at middle and late gestational stages elevates the risks of LBW and SGA infants in a Chinese population.

Subjects and Methods

Cohort study

The China-Anhui Birth Cohort Study (C-ABCS) is a prospective population-based cohort study that recruited 16 766 pregnant women from six major cities of Anhui province in China between November 2008 and October 2010. A total of 13 454 singleton live births were followed up from this cohort (22). The present study analyzed a subsample of the C-ABCS cohort that recruited 4358 pregnant women from Hefei city of Anhui province between January 2009 and December 2009. For this study, eligible participants were mother-and-singleton-offspring pairs in which serum samples from mothers were available for analysis of 25(OH)D and offspring had detailed birth records. Excluded from the study were 36 pregnant women giving birth to twins, 15 fetal deaths, two stillbirths, 58 abortions, and 589 subjects who withdrew. A total of 3658 mother-and-singleton-offspring pairs were eligible for this study. The demographic characteristics of pregnant women from mother-offspring pairs are presented in Table 1. No subjects were drinking alcohol or smoking cigarettes throughout their pregnancies. The present study obtained ethics approval from the ethics committee of Anhui Medical University. Oral and written consent was obtained from all pregnant women.

Table 1. Maternal Demographic Characteristics

Characteristics	Variables
Pregnant women, n	3658
Maternal age (means ± SD), y	27.5 ± 3.2
<25	579 (15.83)
25–34	1137 (81.08)
≥35	113 (3.09)
Maternal BMI, kg/m^2	
<18.5	788 (21.54)
18.5 to 24.9	2754 (75.29)
≥25.0	116 (3.17)
Season of blood sample	
Spring (March–May)	1341 (36.66)
Summer (June–August)	822 (22.47)
Fall (September–November)	755 (20.64)
Winter (December–February)	740 (20.23)
Periconceptional multivitamin use	
None	3053 (83.46)
<1 mo	291 (7.96)
>1 mo	314 (8.58)
Family monthly income (RMB/yuan)	
Low (<2000)	1655 (45.24)
Middle (2000–4000)	1483 (40.54)
High (>4000)	520 (14.22)
Parity	
1	3510 (95.95)
>1	148 (4.05)
Gestational week of blood sample	
First trimester, <wk 13	1284 (35.10)
Second trimester, wk 13–27	2268 (62.00)
Third trimester, wk 28 or later	106 (2.90)

Data are expressed as number (percentage), unless otherwise specified.

Definition of SGA and LBW

In this study, SGA births were live-born infants that were <10th percentile of birth weight according to nomograms based on gender and gestational age from a reference population of 13 454 infants delivered at C-ABCS (23). LBW births were live-born infants that weighed <2500 g at birth.

Measurement of 25(OH)D

Maternal nonfasting blood samples taken as part of routine antenatal care were collected and stored initially at −20°C, and then at −80°C, with no further freeze-thaw cycles until 25(OH)D measurement. Serum samples could be from any stage of pregnancy. Serum 25(OH)D was measured by RIA using a kit from Diasorin Inc, following the manufacturer's instructions (24). The serum 25(OH)D level is expressed as nanograms per milliliter. The quality and reproducibility were determined using quality controls provided with the kits. Two controls (low control, 14.1 ng/mL; high control, 54.1 ng/mL) were provided, and the coefficient of variation for all kits used was 12.54% for the low control and 12.95% for the high control. The controls fell within the acceptable range given by the manufacturer.

Statistical analysis

We used means (SD or 95% confidence interval [CI]) and proportions to describe all variables for included mothers and offspring. The differences between included mother-and-offspring pairs and those excluded because of missing data were investigated with *t* tests for continuously measured variables

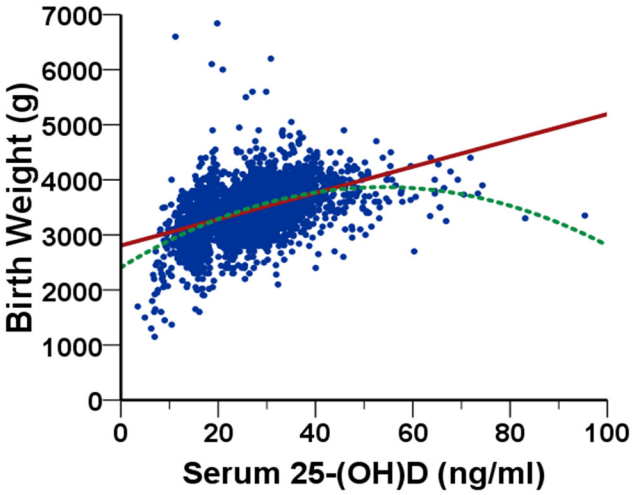

Figure 1. Correlation between maternal 25(OH)D level during pregnancy and birth weight. Serum 25(OH)D level during pregnancy was assessed among 3658 pregnant women. The correlation between maternal serum 25(OH)D level and birth weight was analyzed. Correlation coefficient r = 0.477; $P < .001$.

(with those variables that were right-skewed being logged) and χ^2 tests for categorical variables. Pearson's correlation coefficients were used to assess whether maternal serum 25(OH)D levels were correlated with offspring birth weight. Linear regression was used to explore the association between birth weight (dependent variables) and maternal serum 25(OH)D level during pregnancy (independent variables): model A was minimally adjusted (included body mass index [BMI] before pregnancy, maternal age, and season of blood sample); model B was the main confounder-adjusted model, and was model A plus adjustment for maternal socioeconomic status, maternal periconceptional multivitamin use, and parity (25). Maternal serum 25(OH)D level was divided into three groups according to following criteria: <20 ng/mL (50 nmol/L), for vitamin D deficiency; 20–29.9 ng/mL (50–75 nmol/L), for vitamin D insufficiency; and ≥30 ng/mL (75 nmol/L), for vitamin D sufficiency (6). The rate and relative risk (RR) of LBW and SGA infants were calculated among different groups. For adjustment of maternal BMI before pregnancy, maternal age, and season and gestational week of blood sample, a multiple logistic regression model was used to calculate adjusted RR with 95% CI with respect to LBW and SGA infants. A P value of <.05 (two-tailed) or a 95% CI not including the null point (for linear regression) or 1 (for logistic regression and RR) was considered statistically significant.

Results

Correlation between maternal serum vitamin D level during pregnancy and birth weight

The correlation between maternal serum 25(OH)D level during pregnancy and birth weight were analyzed. As shown in Figure 1, there was a positive correlation between maternal serum 25(OH)D level and birth weight (r = 0.477; $P < .001$). Further analysis showed that there was a threshold (about 40 ng/mL) below which maternal serum 25(OH)D level is an important predictor for offspring birth weight (Figure 1 and Table 2). Linear regression was used to further explore the correlation between maternal serum 25(OH)D level during pregnancy and birth weight. After minimal adjustment for BMI before pregnancy, maternal age, and season of blood sample (model A), the maternal serum 25(OH)D level, as a continuous variable, was a significant predictor of birth weight with each additional 1 ng/mL 25(OH)D associated with an additional 23.87 g of birth weight (Figure 2). After further adjustment for main confounders including model A plus adjustment for maternal socioeconomic status and parity (model B), the mean difference was 23.66 g in birth weight per 1 ng/mL 25(OH)D (Figure 2).

Association between vitamin D status during pregnancy and the risks of LBW and SGA infants

The rate and RR of SGA were analyzed. As shown in Table 3, 16.01% of neonates were SGA infants among subjects with vitamin D deficiency and 5.59% among subjects with vitamin D insufficiency, significantly higher than 2.80% among subjects with vitamin D sufficiency. The RR for SGA infants was 5.72 (95% CI, 3.80, 8.59) among subjects with vitamin D deficiency and 1.99 (95% CI, 1.27, 3.13) among subjects with vitamin D insufficiency. The adjusted RR for SGA infants was 6.47 (95% CI, 4.30, 9.75) among subjects with vitamin D deficiency and 2.01 (95% CI, 1.28, 3.16) among subjects with vitamin D insufficiency using a multiple logistic regression model. The rate and RR of LBW infants were then ana-

Table 2. Distribution of Maternal 25(OH)D Levels During Pregnancy and Its Correlation With Birth Weight

Serum 25(OH)D, ng/mL	n	Cumulative %	Birth Weight, g (95%CI)
<10	46	1.26	2430.1 (2249.9, 2610.3)
10–14	303	9.54	3095.8 (3049.6, 3142.1)
15–19	1056	38.41	3244.1 (3218.8, 3269.4)
20–24	545	53.31	3292.5 (3261.6, 3323.5)
25–29	744	73.65	3499.9 (3472.0, 3527.7)
30–34	488	86.99	3614.2 (3577.6, 3650.7)
35–39	273	94.45	3789.5 (3743.8, 3835.2)
40–44	99	97.16	3804.2 (3729.3, 3879.1)
45–49	49	98.50	3779.0 (3659.0, 3899.0)
≥50	55	100.00	3793.5 (3685.4, 3901.6)

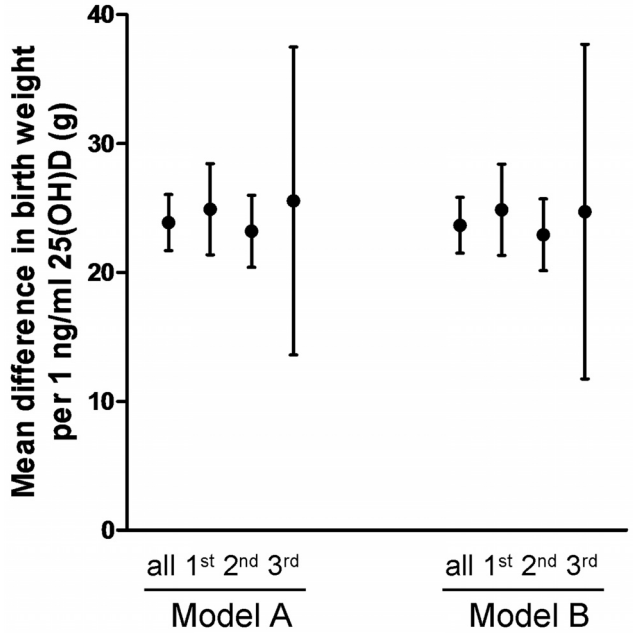

Figure 2. Mean difference in birth weight in relation to maternal serum 25(OH)D level during pregnancy. Linear regression was used to explore the association between birth weight (dependent variables) and maternal serum 25(OH)D level during pregnancy (independent variables). Model A was minimally adjusted (included BMI before pregnancy, maternal age, and season of blood sample). Model B was further adjusted for main confounders, and was model A plus adjustment for maternal socioeconomic status and parity. 1st, First trimester (n = 1284); 2nd, second trimester (n = 2268); 3rd, third trimester (n = 106); All, first plus second plus third trimesters (n = 3658). Data represent mean difference (mean, 95% CI) in birth weight.

lyzed. As shown in Table 3, 4.98% of neonates were LBW infants among subjects with vitamin D deficiency and 1.32% among subjects with vitamin D insufficiency, significantly higher than 0.41% among subjects with vitamin D sufficiency. The RR for LBW infants was 12.00 (95% CI, 4.37, 33.00) among subjects with vitamin D deficiency and 3.18 (95% CI, 1.07, 9.48) among subjects with vitamin D insufficiency. Adjusted RR for LBW infants was 12.31 (95% CI, 4.47, 33.89) among subjects with vitamin D deficiency and 3.15 (95% CI, 1.06, 9.39) among subjects with vitamin D insufficiency using a multiple logistic regression model.

Association between vitamin D status at early gestational stage and the risks of LBW and SGA infants

The association between vitamin D status at the first trimester and the risk of SGA infants was analyzed. As shown in Table 4, 15.94% of neonates were SGA infants among subjects with vitamin D deficiency and 6.11% among subjects with vitamin D insufficiency, significantly higher than the 2.10% among subjects with vitamin D sufficiency. The RR for SGA infants was 7.61 (95% CI, 3.47, 16.67) among subjects with vitamin D deficiency and 2.92 (95% CI, 1.25, 6.77) among subjects with vitamin D insufficiency. The adjusted RR for SGA infants was 8.75 (95% CI, 3.98, 19.22) among subjects with vitamin D deficiency and 2.99 (95% CI, 1.29, 6.96) among subjects with vitamin D insufficiency using a multiple logistic regression model. The association between vitamin D status at the first trimester and the risk of LBW infants was then analyzed. As shown in Table 4, 4.53% of neonates were LBW infants among subjects with vitamin D deficiency and 0.90% among subjects with vitamin D insufficiency, significantly higher than the 0.30% among subjects with vitamin D sufficiency. The RR for LBW infants was 15.12 (95% CI, 2.03, 112.51) among subjects with vitamin D deficiency and 3.02 (95% CI, 0.34, 27.17) among subjects with vitamin D insufficiency. The adjusted RR for LBW infants was 15.03 (95% CI, 2.01, 112.15) among subjects with vitamin D deficiency and 2.95 (95% CI, 0.33, 26.54) among subjects with vitamin D insufficiency using a multiple logistic regression model.

Association between vitamin D status at middle and late gestational stages and the risks of LBW and SGA infants

The association between vitamin D status in the second and third trimesters and the risk of SGA infants was analyzed. As shown in Table 4, 16.05% of neonates were SGA infants among subjects with vitamin D deficiency and 5.31% among subjects with vitamin D insufficiency, significantly higher than the 3.17% among subjects with vitamin D sufficiency. The RR for SGA infants was 5.06 (95% CI, 3.13, 8.16) among subjects with vitamin D deficiency and 1.67 (95% CI, 0.98, 2.86) among subjects with vitamin D insufficiency. The adjusted RR for SGA infants was 5.58 (95% CI, 3.45, 9.04) among subjects with vitamin D deficiency and 1.65 (95% CI, 0.97, 2.83) among subjects with vitamin D insufficiency using a multiple logistic regression model. The association between vitamin D status in the second and third trimesters and the risk of LBW infants was then analyzed. As shown in Table 4, 5.24% of neonates were LBW infants among subjects with vitamin D deficiency and 1.53% among subjects with vitamin D insufficiency, significantly higher than the 0.48% among subjects with vitamin D sufficiency. The RR for LBW infants was 11.00 (95% CI, 3.41, 35.51) among subjects with vitamin D deficiency and 3.22 (95% CI, 0.92, 11.36) among subjects with vitamin D insufficiency. The adjusted RR for LBW infants was 11.03 (95% CI, 3.41, 35.68) among subjects with vitamin D deficiency and 3.18 (95% CI, 0.90, 11.23) among subjects with vitamin D insufficiency using a multiple logistic regression model.

Table 3. Association Between Maternal Vitamin D Status and Its Association With LBW and SGA

	Maternal Vitamin D Status During Pregnancy[a]			
	Deficiency	**Insufficiency**	**Sufficiency**	P_{trend}
Mother-offspring pairs eligible, n (%)	1405 (38.41)	1289 (35.24)	964 (26.35)	
Rate and RR for LBW				
Infants with LBW, n	70	17	4	
Rate for LBW, %	4.98	1.32	0.41	<.001
Unadjusted RR for LBW (95% CI)	12.00 (4.37, 33.00)	3.18 (1.07, 9.48)	1.00	<.001
Adjusted RR for LBW (95% CI)[b,c]	12.31 (4.47, 33.89)	3.15 (1.06, 9.39)	1.00	<.001
Rate and RR for SGA				
Infants with SGA, n	225	72	27	
Rate for SGA, %	16.01	5.59	2.80	<.001
Unadjusted RR for SGA (95% CI)	5.72 (3.80, 8.59)	1.99 (1.27, 3.13)	1.00	<.001
Adjusted RR for SGA (95% CI)[b,d]	6.47 (4.30, 9.75)	2.01 (1.28, 3.16)	1.00	<.001

[a] 25(OH)D < 20 ng/mL for deficiency; 20 ≤ 25(OH)D < 30 ng/mL for insufficiency; and 25(OH)D ≥ 30 ng/mL for sufficiency.

[b] Adjusted for BMI before pregnancy, maternal age, season, and gestational week of blood sample.

[c] Dependent variables: LBW (yes or no). Independent variables: maternal vitamin D status (sufficiency, insufficiency and deficiency).

[d] Dependent variables: SGA (yes or no). Independent variables: maternal vitamin D status (sufficiency, insufficiency and deficiency).

Discussion

In the cohort study, no subjects smoked cigarettes, drank alcohol, or were pre-eclamptic throughout pregnancy (data not shown). Several reports show that maternal age and the season of sampling influence maternal vitamin D status during pregnancy (26–28). In the present study, maternal age, family monthly income, parity, and gestational week of blood sampling did not influence serum 25(OH)D level during pregnancy. By contrast, the serum 25(OH)D level was slightly higher among subjects with BMI of 18.5–24.9 kg/m^2 than subjects with either BMI < 18.5 kg/m^2 or BMI ≥ 25.0 kg/m^2. Moreover, the serum 25(OH)D level was increased among multivitamin users. As expected, the serum 25(OH)D level during pregnancy was slightly higher in the spring and summer than in the fall and winter.

The present study analyzed the association between maternal vitamin D status during pregnancy and birth weight in a Chinese population-based birth cohort study that recruited 3658 eligible mother-and-singleton-offspring pairs. We demonstrated that there was a positive correlation between maternal serum 25(OH)D level and birth weight in this Chinese population ($r = 0.477$; $P < .001$). Further analysis showed that there was a threshold of about 40 ng/mL, below which the maternal serum 25(OH)D level is an important predictor for birth weight in offspring. After adjustment for main confounders, such as BMI before pregnancy, maternal age, maternal socioeconomic status, parity, and season of blood sample, maternal serum 25(OH)D level, as a predictor of birth weight, was with each additional 1 ng/mL 25(OH)D in maternal serum associated with an additional 23.66 g birth weight in offspring. These results provide strong evidence that maternal vitamin D status during pregnancy is associated with intrauterine fetal growth in offspring.

It remains uncertain whether maternal vitamin D deficiency during pregnancy elevates the risks of SGA and LBW infants. Several studies explored the association between maternal vitamin D status during pregnancy and the risks of SGA and LBW infants with contradictory results. Some reports showed that there was no association between maternal serum 25(OH)D level and a child's body size and birth weight (18, 19). Other studies found that maternal vitamin D status during pregnancy was associated with the risk of SGA infants (20, 21). The inconsistency of past findings may be related to the following reasons. First, negative results came most frequently from small samples (18, 19). Second, maternal vitamin D status during pregnancy is a link to ethnic disparities in adverse birth outcomes (20, 21). The present study analyzed the association between maternal vitamin D status during pregnancy and the risks of SGA and LBW infants in a Chinese population. Our results showed that 4.98% of neonates were LBW infants among subjects with vitamin D deficiency (RR, 12.00; 95% CI, 4.37, 33.00) and 1.32% among subjects with vitamin D insufficiency (RR, 3.18; 95% CI, 1.07, 9.48). Moreover, 16.01% of neonates were SGA infants among subjects with vitamin D deficiency (RR, 5.72; 95% CI, 3.80, 8.59) and 5.59% among subjects with vitamin D insufficiency (RR, 1.99; 95% CI, 1.27, 3.13). To our knowledge, the present study is the first to demonstrate that maternal vitamin D deficiency during pregnancy elevates the risks of LBW and SGA infants in a Chinese population-based birth cohort study.

Most of the earlier studies analyzed the association between maternal vitamin D status at the first trimester and

Table 4. Incidence and RR for LBW and SGA Infants Based on Maternal Vitamin D Status in Different Trimesters

	Maternal Vitamin D Status During Pregnancy[a]			
	Deficiency	**Insufficiency**	**Sufficiency**	P_{trend}
First trimester[b]				
LBW				
Infants, n	508	442	334	
Infants with LBW, n	23	4	1	
Rate for LBW, %	4.53	0.90	0.30	<.001
Unadjusted RR for LBW (95% CI)	15.12 (2.03, 112.51)	3.02 (0.34, 27.17)	1.00	<.001
Adjusted RR for LBW (95% CI)[c,d]	15.03 (2.01, 112.15)	2.95 (0.33, 26.54)	1.00	<.001
SGA				
Infants, n	508	442	334	
Infants with SGA, n	81	27	7	
Rate for SGA, %	15.94	6.11	2.10	<.001
Unadjusted RR for SGA (95% CI)	7.61 (3.47, 16.67)	2.92 (1.25, 6.77)	1.00	<.001
Adjusted RR for SGA (95% CI)[c,e]	8.75 (3.98, 19.22)	2.99 (1.29, 6.96)	1.00	<.001
Second and third trimesters[b]				
LBW				
Infants, n	897	847	630	
Infants with LBW, n	47	13	3	
Rate for LBW, %	5.24	1.53	0.48	<.001
Unadjusted RR for LBW (95% CI)	11.00 (3.41, 35.51)	3.22 (0.92, 11.36)	1.00	<.001
Adjusted RR for LBW (95% CI)[c,d]	11.03 (3.41, 35.68)	3.18 (0.90, 11.23)	1.00	<.001
SGA				
Infants, n	897	847	630	
Infants with SGA, n	144	45	20	
Rate for SGA, %	16.05	5.31	3.17	<.001
Unadjusted RR for SGA (95% CI)	5.06 (3.13, 8.16)	1.67 (0.98, 2.86)	1.00	<.001
Adjusted RR for SGA (95% CI)[c,e]	5.58 (3.45, 9.04)	1.65 (0.97, 2.83)	1.00	<.001

[a] 25(OH)D < 20 ng/mL for deficiency; 20 ≤ 25(OH)D < 30 ng/mL for insufficiency; 25(OH)D ≥ 30 ng/mL for sufficiency.

[b] First trimester: gestational week <13 week; second and third trimesters: gestational week ≥13 week.

[c] Adjusted for BMI before pregnancy, season of blood sample, and maternal age.

[d] Dependent variables: LBW (yes or no). Independent variables: maternal vitamin D status during pregnancy (sufficiency, insufficiency, and deficiency).

[e] Dependent variables: SGA (yes or no). Independent variables: maternal vitamin D status during pregnancy (sufficiency, insufficiency, and deficiency).

the risks of SGA and LBW infants (28, 29). The present study analyzed the association between maternal vitamin D status at different gestational stages and the risks of SGA and LBW infants. In the first trimester, 4.53% of neonates were LBW infants among subjects with vitamin D deficiency (RR, 15.12; 95% CI, 2.03, 112.51) and 0.90% among subjects with vitamin D insufficiency (RR, 3.02; 95% CI, 0.34, 27.17). Moreover, 15.94% of neonates were SGA infants among subjects with vitamin D deficiency (RR, 7.61; 95% CI, 3.47, 16.67) and 6.11% among subjects with vitamin D insufficiency (RR, 2.92; 95% CI, 1.25, 6.77). In the second and third trimesters, 5.24% of neonates were LBW infants among subjects with vitamin D deficiency (RR, 11.00; 95% CI, 3.41, 35.51) and 1.53% among subjects with vitamin D insufficiency (RR, 3.22; 95% CI, 0.92, 11.36). In addition, 16.05% of neonates were SGA infants among subjects with vitamin D deficiency (RR, 5.06; 95% CI, 3.13, 8.16) and 5.31% among subjects with vitamin D insufficiency (RR, 1.67; 95% CI, 0.98, 2.86). These results suggest that maternal vitamin D deficiency not only at early but also at middle and late gestational stages elevates the risks of SGA and LBW infants.

The mechanism through which vitamin D deficiency during pregnancy elevates the risks of SGA and LBW infants remains obscure. Increasing evidence demonstrates that vitamin D has an anti-inflammatory activity (30, 31). A recent study showed that the vitamin D receptor plays a pivotal role in regulating placental inflammation (2). Indeed, numerous reports found that maternal and placental inflammation was associated with fetal IUGR in rodents (31, 32). An earlier investigation showed that serum IL-8 and TNF-α levels were significantly increased in pre-eclamptic patients with IUGR infants but not in pre-eclamptic patients with normal infants (33). Another study found that there was a strong association between placental inflammation and the incidence of LBW infants in preterm newborns (34). According to a recent report, chronic inflammation including chronic villitis and chronic chorioamnionitis could be detected in placentas

from pregnant women with IUGR infants (35). These results suggest that placental inflammation was also linked with fetal IUGR in humans. Further research is necessary to investigate the association among vitamin D status during pregnancy, placental inflammation, and the risks of SGA and LBW infants.

An earlier human study found a correlation between serum vitamin D and IGF-1 concentration (36). A recent study showed that vitamin D supplementation increases the production of IGF-1 in adults (37). Indeed, numerous reports demonstrated that mutations or targeted deletions of the IGF ligands IGF-1 and IGF-2, as well as the downregulation of IGF-1 signaling pathway, lead to fetal IUGR in humans and rats (38, 39). Further research is necessary to investigate whether maternal vitamin D deficiency causes fetal IUGR through decreasing production of IGF-1 and IGF-2 in animal experiments.

The present study placed emphasis on whether maternal vitamin D deficiency elevated the risk of SGA and LBW in a Chinese population. However, the present study has several limitations. First, only a single sample at different seasons and gestational ages was analyzed. Second, the present study did not clarify the mechanism by which maternal vitamin D deficiency during pregnancy elevated the risks of LBW and SGA infants. The mechanism by which maternal vitamin D deficiency during pregnancy induces LBW and SGA needs to be explored in animal experiments.

In summary, the present study analyzed the association between the maternal serum 25(OH)D level at different gestational stages and the risks of SGA and LBW infants in a Chinese population-based birth cohort study. We observed a positive correlation between maternal serum 25(OH)D level during pregnancy and birth weight in offspring. Our results demonstrate that maternal vitamin D deficiency, not only at the early stage but also middle and late gestational stages, elevates the risks of SGA and LBW infants in a Chinese population. The present study provides important evidence that maternal vitamin D supplementation during pregnancy should be recommended in Chinese populations.

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References

1. **Holick MF.** Resurrection of vitamin D deficiency and rickets. *J Clin Invest*. 2006;116:2062–2072.
2. **Liu NQ, Kaplan AT, Lagishetty V, et al.** Vitamin D and the regulation of placental inflammation. *J Immunol*. 2011;186:5968–5974.
3. **Coussens AK, Wilkinson RJ, Hanifa Y, et al.** Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. *Proc Natl Acad Sci USA*. 2012;109:15449–15454.
4. **Padi SK, Zhang Q, Rustum YM, Morrison C, Guo B.** MicroRNA-627 mediates the epigenetic mechanisms of vitamin D to suppress proliferation of human colorectal cancer cells and growth of xenograft tumors in mice. *Gastroenterology*. 2013;145:437–446.
5. **Zanetti M, Harris SS, Dawson-Hughes B.** Ability of vitamin D to reduce inflammation in adults without acute illness. *Nutr Rev*. 2014;72:95–98.
6. **Holick MF.** Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
7. **Holmes VA, Barnes MS, Alexander HD, McFaul P, Wallace JM.** Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. *Br J Nutr*. 2009;102:876–881.
8. **Bodnar LM, Krohn MA, Simhan HN.** Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J Nutr*. 2009;139:1157–1161.
9. **Ma R, Gu Y, Zhao S, Sun J, Groome LJ, Wang Y.** Expressions of vitamin D metabolic components VDBP, CYP2R1, CYP27B1, CYP24A1, and VDR in placentas from normal and preeclamptic pregnancies. *Am J Physiol Endocrinol Metab*. 2012;303:E928–E935.
10. **Cho GJ, Hong SC, Oh MJ, Kim HJ.** Vitamin D deficiency in gestational diabetes mellitus and the role of the placenta. *Am J Obstet Gynecol*. 2013;209:560.e1–e8.
11. **Javaid MK, Crozier SR, Harvey NC, et al.** Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet*. 2006;367:36–43.
12. **Devereux G, Litonjua AA, Turner SW, et al.** Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr*. 2007;85:853–859.
13. **Brehm JM, Celedón JC, Soto-Quiros ME, et al.** Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179:765–771.
14. **McGrath JJ, Burne TH, Féron F, Mackay-Sim A, Eyles DW.** Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophr Bull*. 2010;36:1073–1078.
15. **Harvey NC, Moon RJ, Sayer AA, et al.** Maternal antenatal vitamin D status and offspring muscle development: findings from the Southampton Women's Survey. *J Clin Endocrinol Metab* 2014;99:330–337.
16. **Saenger P, Czernichow P, Hughes I, Reiter EO.** Small for gestational age: short stature and beyond. *Endocr Rev*. 2007;28:219–251.
17. **Bukowski R, Hansen NI, Willinger M, et al.** Fetal growth and risk of stillbirth: a population-based case-control study. *PLoS Med*. 2014;11:e1001633.
18. **Farrant HJ, Krishnaveni GV, Hill JC, et al.** Vitamin D insufficiency

is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. *Eur J Clin Nutr*. 2009;63:646–652.
19. **Gale CR, Robinson SM, Harvey NC, et al.** Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008;62:68–77.
20. **Bodnar LM, Catov JM, Zmuda JM, et al.** Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *J Nutr*. 2010;140:999–1006.
21. **Gernand AD, Simhan HN, Caritis S, Bodnar LM.** Maternal vitamin D status and small-for-gestational-age offspring in women at high risk for preeclampsia. *Obstet Gynecol*. 2014;123:40–48.
22. **Tao FB, Hao JH, Huang K, et al.** Cohort profile: the China-Anhui birth cohort study. *Int J Epidemiol*. 2013;42:709–721.
23. **Marchant T, Willey B, Katz J, et al.** Neonatal mortality risk associated with preterm birth in East Africa, adjusted by weight for gestational age: individual participant level meta-analysis. *PLoS Med*. 2012;9:e1001292.
24. **Waterhouse M, Tran B, Armstrong BK, et al.** Environmental, personal, and genetic determinants of response to vitamin D supplementation in older adults. *J Clin Endocrinol Metab*. 2014;99:E1332–E1340.
25. **Lawlor DA, Wills AK, Fraser A, Sayers A, Fraser WD, Tobias JH.** Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study. *Lancet*. 2013;381:2176–2183.
26. **Tornhammar P, Ueda P, Hult M, Simila H, Eyles D, Norman M.** Season of birth, neonatal vitamin D status, and cardiovascular disease risk at 35 y of age: a cohort study from Sweden. *Am J Clin Nutr*. 2014;99:472–478.
27. **Andersen LB, Abrahamsen B, Dalgård C, et al.** Parity and tanned white skin as novel predictors of vitamin D status in early pregnancy: a population-based cohort study. *Clin Endocrinol (Oxf)*. 2013;79:333–341.
28. **Schneuer FJ, Roberts CL, Guilbert C, et al.** Effects of maternal serum 25-hydroxyvitamin D concentrations in the first trimester on subsequent pregnancy outcomes in an Australian population. *Am J Clin Nutr*. 2014;99:287–295.
29. **Gernand AD, Simhan HN, Klebanoff MA, Bodnar LM.** Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. *J Clin Endocrinol Metab*. 2013;98:398–404.
30. **Luderer HF, Nazarian RM, Zhu ED, Demay MB.** Ligand-dependent actions of the vitamin D receptor are required for activation of TGF-β signaling during the inflammatory response to cutaneous injury. *Endocrinology*. 2013;154:16–24.
31. **Cotechini T, Komisarenko M, Sperou A, Macdonald-Goodfellow S, Adams MA, Graham CH.** Inflammation in rat pregnancy inhibits spiral artery remodeling leading to fetal growth restriction and features of preeclampsia. *J Exp Med*. 2014;211:165–179.
32. **Xu DX, Chen YH, Wang H, Zhao L, Wang JP, Wei W.** Tumor necrosis factor α partially contributes to lipopolysaccharide-induced intra-uterine fetal growth restriction and skeletal development retardation in mice. *Toxicol Lett*. 2006;163:20–29.
33. **Tosun M, Celik H, Avci B, Yavuz E, Alper T, Malatyalioğlu E.** Maternal and umbilical serum levels of interleukin-6, interleukin-8, and tumor necrosis factor-α in normal pregnancies and in pregnancies complicated by preeclampsia. *J Matern Fetal Neonatal Med*. 2010;23:880–886.
34. **Moscuzza F, Belcari F, Nardini V, et al.** Correlation between placental histopathology and fetal/neonatal outcome: chorioamnionitis and funisitis are associated to intraventricular haemorrage and retinopathy of prematurity in preterm newborns. *Gynecol Endocrinol*. 2011;27:319–323.
35. **Veerbeek JH, Nikkels PG, Torrance HL, et al.** Placental pathology in early intrauterine growth restriction associated with maternal hypertension. *Placenta*. 2014;35:696–701.
36. **Bogazzi F, Rossi G, Lombardi M, et al.** Vitamin D status may contribute to serum insulin-like growth factor I concentrations in healthy subjects. *J Endocrinol Invest*. 2011;34:e200–e203.
37. **Ameri P, Giusti A, Boschetti M, et al.** Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency. *Eur J Endocrinol*. 2013;169:767–772.
38. **Randhawa RS.** The insulin-like growth factor system and fetal growth restriction. *Pediatr Endocrinol Rev*. 2008;6:235–240.
39. **Deng Y, Cao H, Cu F, et al.** Nicotine-induced retardation of chondrogenesis through down-regulation of IGF-1 signaling pathway to inhibit matrix synthesis of growth plate chondrocytes in fetal rats. *Toxicol Appl Pharmacol*. 2013;269:25–33.