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Maternal early pregnancy vitamin D status in relation to low birth weight and small-for-gestational-age offspring

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ABSTRACT

Maternal vitamin D deficiency is an independent risk factor for fetal growth. We examined the associations between maternal vitamin D status (defined by 25-hydroxyvitamin D [25(OH)D]) at the first prenatal visit and measures of newborn and placental weight, in a large China cohort of singleton, term, live births. From July 2015 to June 2016, women delivering singleton, term, live births with 25(OH)D measured at a first prenatal visit (N = 747). Birth weight, placental weight, the placental to fetal weight ratio, and small for gestational age (SGA) were measured. The relationship between levels of 25(OH)D and SGA were evaluated using univariate and multivariate regression analysis. Vitamin D deficiency was defined as 25(OH)D less than 20 ng/ml.

In those women, 76.9% (95%CI: 74%–78%) were defined as vitamin D deficiency. Incidence of SGA was also high (13.3%; 95%CI: 10.8%–15.7%). We found a nonlinear relation between 25(OH)D and birth weight as well as head circumference ($P < 0.01$). Birth weight and head circumference increased by 69 [95%CI: 38–122] g and 0.31 (0.22–0.40) cm, respectively, per 1 ng/ml increase in maternal 25(OH)D up to 20 ng/ml and then leveled off thereafter. The SGA distribution across the 25(OH)D quartiles ranged between 3.7% (fourth quartile) to 24.1% (first quartile). For each 1 unit decrease of plasma concentration of 25(OH)D, the unadjusted and adjusted risk of SGA increased by 19% (odds ratio 1.19 [95% CI 1.13–1.25], $P < 0.001$) and 9% (1.08 [1.03–1.16], $P = 0.009$), respectively. In a multivariate model using the vitamin D deficiency vs. other together with the clinical variables, the adjusted risk of SGA increased by 205% (odds ratio 3.05 [95% CI 2.24–4.40], $P = 0.001$). Maternal vitamin D insufficiency is common during pregnancy and is independently associated with low birth weight and high risk of SGA in term infants.

1. Introduction

Maternal vitamin D deficiency has been a significant issue in China [1] and across the globe [2–4], due to lack of sunlight exposure and inadequate intake [5]. Maternal vitamin D deficiency could be applied as an indicator for the risk of preeclampsia [6] and gestational diabetes mellitus [GDM, 7]. Furthermore, as we know, maternal vitamin D insufficiency would be relevant to many other issues, such as lower childhood bone mass [8], rickets [9]. It may make further effects on mental disorder [10,11], respiratory and metabolic disease [12,13].

Interestingly, there is mixed evidence in observational studies [14–17] connecting vitamin D to fetal growth. Tian et al. [18] suggested that maternal serum concentrations of 25(OH)D in early and mid-pregnancy were positively associated with birth weight/gestational age among non-Hispanic Black male and female infants and non-Hispanic White male infants. However, another study found that maternal vitamin D status in pregnancy did not influence infant birth outcomes, postnatal growth and adiposity outcomes [19]. Methodologies and quality of studies widely differ, with late pregnancy vitamin D assessment and small sample size seeming to contribute to null findings.

Periconceptional nutritional status may be important in setting the fetal growth trajectory, and, like other exposures, vitamin D status would make early effects on later fetal growth [5]. In a post-hoc analysis, Wagner et al. [20] suggested that achieving a 25(OH)D serum concentration ≥40 ng/ml significantly decreased the risk of preterm birth compared to ≤20 ng/ml. In another study, Wagner et al. [21] reported that a serum concentration of 40 ng/ml in the 3rd trimester was associated with a 47% reduction in preterm births. Similarly, Chen et al. [22] reported that maternal vitamin D deficiency would make effects on infants in a Chinese population and it observed increased risk of small for gestational age (SGA) and low birth weight (LBW). Thus, we hypothesized that maternal vitamin D status at the first prenatal

Abbreviations: 25(OH)D, 25 hydroxyvitamin D; SGA, small for gestational age; OR, odds ratio; LBW, low birth weight; BMI, body mass index; CV, coefficient of variation; CI, confidence intervals; ROC, receiver operating characteristic curves; AUC, area under the curve

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visit would associated with newborn weight and SGA. We aimed to explore the associations between maternal vitamin D status (represented with25-hydroxyvitamin D [25(OH)D]) at the first prenatal visit and index of newborn, as well as weight of placental. The study was performed with a large Chinese single-center cohort of term and live births.

2. Patients and methods

From July 2015 to June 2016, 747 consecutive women (age ≥ 18 years old) who were admitted to the Obstetrics center of Second Hospital of Xi'an Jiao Tong University, China, were included. Pregnancies were eligible for the study if they met the following criteria: (1) no preexisting diabetes or hypertension; (2) first pregnancy with singleton gestation; (3) term and live births; (4) without alcohol abuse, renal failure, chronic disease or a history of consumption of drugs that interact with vitamin D metabolism. The design and conduct of this study was approved by the ethics committee of Second Hospital of Xi'an Jiao Tong University. The written informs were obtained from all participants before enrollment.

We recorded maternal–pregnancy characteristics (maternal age, body mass index [BMI], ethnicity, smoking status, marital status, education, family's socio-professional category, delivery, vitamin D supplementation, gestational weeks at admission, seasons of women included) at first prenatal visit. The blood sample draw was performed and the samples were classified by seasons. BMI was calculated as the weight in kilograms divided by the height in meters squared. The information was collected, on lifestyle potential relevant to vitamin D level, such as sources of vitamin D from dietary (dairy products and fish) and exposure to sunlight. A questionnaire from Canadian Community Health Survey was applied to collect the specific information on physical activity of participants [23].

For the indexes of infants, both the birth and placental weight were obtained just after childbirth. The head circumference and length were determined within 24 h of childbirth. The placental to fetal weight ratio [24] were calculated as follows: Placental to fetal weight ratio was the calculated as the percentage of placental weight in grams divided by birth weight in grams. SGA was defined as that the birth weight was less than 10% of national birth weight reference under identical situations such as sex and gestational age based on the ultrasound results [25].

Fasting maternal venous blood was sampled at the first prenatal visit. Plasma concentration of 25(OH)D was routinely measured by E601 modular involving the kit according to manufacturer instructions (Roche Diagnostics, Mannheim, Germany). The results were interpreted into the level of 25(OH)D in ng/ml. The 25(OH)D levels are therefore used to classify the vitamin D status into vitamin D deficiency (< 20 ng/ml), vitamin D insufficiency (20–29 ng/ml) and vitamin D sufficiency (≥30 ng/ml) [26].

3. Statistical analysis

The continuous variables were expressed as mean ± SD or percentage. The difference among groups was tested with chi-square or student's unpaired *t*-test. The logistic regression analyses were applied to fit various variables. 95% CI for incidence density was determined with the Poisson distribution. The incidence rate for SGA was also presented according to the baseline 25(OH) D quartiles.

The level of 25(OH)D was determined as a continuous variable. The independent associations between serum 25(OH)D level at first prenatal visit and outcomes of interest were tested with multivariable linear regression, and the association with SGA using multivariable logistic regression. Nonlinear relations were tested using linear spline regression with a knot at the deficiency cut point.

The relationship between levels of vitamin D deficiency and birth weights, head circumference, and placental weight and placental to fetal weight ratio were evaluated using univariate and multivariate regression analysis. The significant indicators and ORs were adjusted with crude models and multivariate models. Multiple variables were included in the multivariate analysis, including maternal age, maternal race, pre-pregnancy BMI, height, smoking (yes/no), planned pregnancy (yes/no), marital status, education, family's socio-professional category, delivery, season, supplementation of vitamin D, physical activity, vitamin D lifestyle score, and infant sex.

The relation of SGA and 25 (OH)D levels was also evaluated using univariate and multivariate regression analysis. In addition, multivariate analysis models were applied to further explore the relation of SGA and 25 (OH)D levels. It aimed to evaluate the adjusted OR with 95% CIs of SGA for quartiles of 25 (OH)D levels. The overall prediction accuracy of 25 (OH)D levels to diagnose SGA was tested with ROC indicated by AUC. All the statistics were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and the ROCR package (version 1.0-2). $P < 0.05$ was defined to be significant.

Table 1
Baseline characteristics of the enrolled women and their newborns (N = 747).

Baseline Characteristics	N (%) or mean(SD)	Range(min-max)
Pregnant women		
Race, Han Chinese	685(91.7)	
Maternal age (yr)	30.6 ± 2.8	22–46
Pre-pregnancy BMI (kg/m^2)	23.3 ± 3.3	17.2–40.8
Smoking at study entry	182(24.4)	
Planned pregnancy	633(84.7)	
Married	667(89.3)	
Education		
High school or less	233(31.2)	
University	514(68.8)	
Family's socio-professional category		
Low	176(23.6)	
Middle	378(50.6)	
High	198(25.8)	
Delivery		
Vaginal delivery	576(77.1)	
Assisted delivery	171(22.9)	
Season of blood sampling		
Winter	187(25.0)	
Spring	194(26.0)	
Summer	182(24.4)	
Fall	184(24.6)	
Vitamin D supplementation, n (%)	598(80.1)	
Physical activity, kcal/kg day(IQR)	1.3(0.7–2.1)	
Vitamin D lifestyle score	2.3 ± 0.7	
Newborns		
Male	385(51.5)	
Gestational age at delivery	39.0 ± 1.5	37–42
Birth weight (g)	3195 ± 632	1638–4432
Head circumference (cm)	34.8 ± 2.9	29–42
Placental weight (g)	421 ± 75	168–824
Placental to fetal weight ratio, (%)[a]	13.2 ± 2.6	7.5–23.3
SGA[b]	99(13.3)	

BMI: Body Mass Index; SGA; small for gestational age.
[a] Placental to fetal ratio = placental weight (grams)/birth weight (grams)/100.
[b] Defined by Alexander 1996 birth weight reference at less than the 10th percentile for males or females [25].

4. Results

Blood from women at first prenatal visit was available for 747 women, and most women were young, married, and Han Chinese (Table 1). The plasma concentration of 25(OH)D was 15.8 ± 5.5 ng/ml, which was expressed as mean ± SD. In those women, 76.9% (95%CI: 74%–78%) were defined as vitamin D deficiency, which was defined as the plasma concentration of 25(OH)D lower than 20 ng/ml. Incidence of SGA was also high as 13.3% (95% CI:10.8%–15.7%).

A bivariate analysis was conducted to compare effects from women with vitamin D deficiency or adequacies. We observed that women with material vitamin D deficiency would lead to lower birth weights and

Table 2
Associations between maternal vitamin D deficiency at admission and measures of infant and placental size.

	Vitamin D[a]		Unadjusted difference			Adjusted difference[b]		
	< 20 ng/ml	≥20 ng/ml	β	95%CI	P	β	95%CI	P
Birth weight (g)	3138(663)	3480(320)	342	245–498	< 0.001	172	85–294	0.003
Head circumference (cm)	34.2(3.78)	37.8(2.84)	36	22–53	< 0.001	24	14–39	0.015
Placental weight (g)	412(24.3)	438(25.5)	26	5–59	0.042	16	3–31	0.21
Placental to fetal weight ratio, (%)[c]	12.9(5.0)	14.1(4.2)	1.2	−0.8 to 2.2	0.10	–		

OR: odds ratio; CI: confidence interval; BMI: Body Mass Index.
[a] The data was presented as mean and standard deviation.
[b] Adjusted for maternal age, maternal race, pre-pregnancy BMI, height, smoking (yes/no), planned pregnancy(yes/no), marital status, education, family's socio-professional category, delivery, season, vitamin D supplementation, physical activity, vitamin D lifestyle score and infant sex.
[c] Placental to fetal ratio = placental weight (grams)/birth weight (grams)/100.

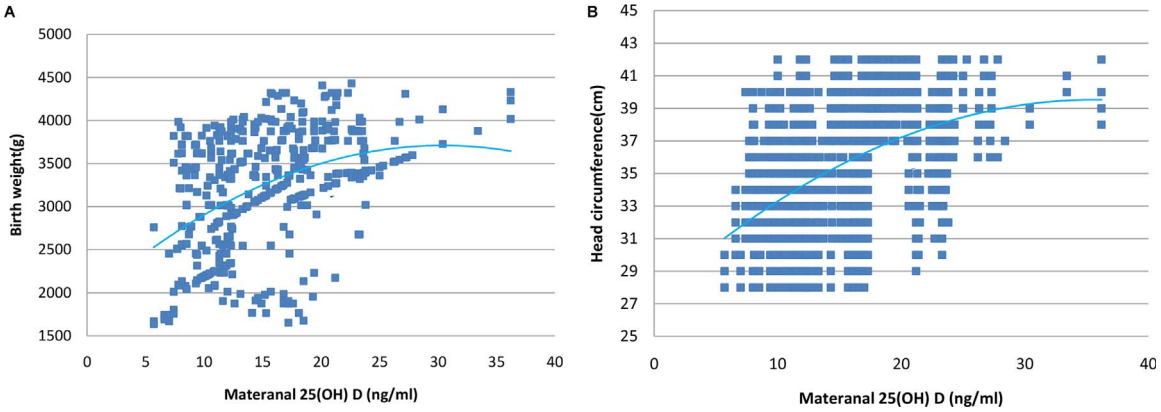

Fig. 1. The association between 25(OH)D and fetal physiological growth. (A) The Nonlinear association between 25(OH)D and birth weight; (B) The Nonlinear association between 25(OH)D and head circumference.

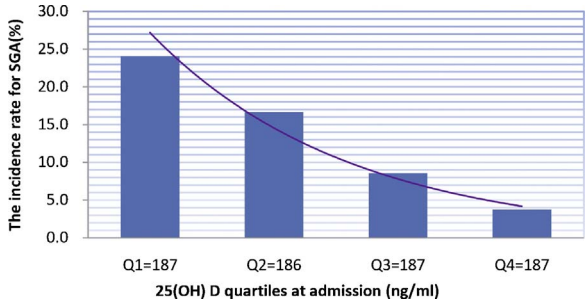

Fig. 2. The incidence rate for SGA according to the baseline 25(OH)D quartiles. Plasma levels of 25(OH)D in Quartile 1 (< 11.4 ng/ml), Quartile 2 (11.4–15.6 ng/ml), Quartile 3 (15.7–19.4 ng/ml), and Quartile 4 (> 19.4 ng/ml). SGA = Small for gestational age; 25(OH)D = 25-Hydroxyvitamin D.

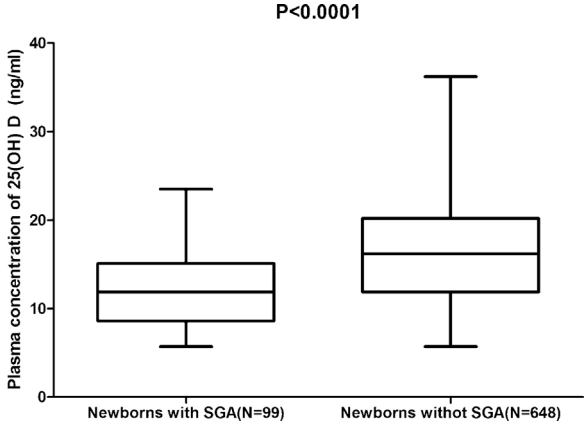

Fig. 3. Plasma levels 25(OH)D in women with newborns with SGA and without SGA. All data are medians and in-terquartile ranges (IQR). *P* values refer to Mann-Whitney *U* tests for differences between groups. SGA = Small for gestational age; 25(OH) D = 25-Hydroxyvitamin D.

head circumference of infants, while there was no different placental weight nor placental to fetal weight ratio (Table 2). After adjustment for maternal age, maternal race, pre-pregnancy BMI, height, smoking (yes/no), planned pregnancy (yes/no), marital status, education, family's socio-professional category, delivery, season, vitamin D supplementation, physical activity, vitamin D lifestyle score, and infant sex, there were still differences in indexes of infants between the women with vitamin D deficiency and remaining women [25(OH)D ≥ 20 ng/ml], including both the birth weight and head circumference (Table 2). We found that the concentration of 25(OH)D was nonlinearly related to the indexes of infants (P < 0.01; Fig. 1). Birth weight and head circumference would be increased by 69 [95%CI: 38–122] g and 0.31 (0.22–40) cm, respectively, per 1 ng/ml increase in plasma concentration of 25(OH)D as high as 20 ng/ml and then leveled off thereafter.

The SGA distribution across the 25(OH)D quartiles ranged between 3.7% (fourth quartile) to 24.1% (first quartile), Fig. 2. The mean plasma concentration of 25(OH)D at first prenatal visit was significantly lower in women in whom SGA later developed compared with those in whom it did not (12.3 [SD: 4.2]ng/ml *vs.* 16.3[5.5]ng/ml; F = 11.146, P < 0.001), Fig. 3. In addition, women who developed SGA were more likely suffered from vitamin D deficiency compared with those in whom it did not (93.9% vs. 74.2%, P < 0.001).

A univariate logistic regression analysis was also performed to characterize the prediction of SGA by 25 (OH)D levels with the odds ratio (OR). For each 1 ng/ml decrease of plasma concentration of 25(OH)D, the unadjusted and adjusted risk of SGA would be increased by 19% (with the OR of 1.19 [95% CI 1.13–1.25], P < 0.001) and 9% (1.09 [1.03–1.16], P = 0.009), respectively (Table 3). In multivariate

Table 3
Associations between maternal serum 25(OH)D at admission and SGA.

25(OH) D, ng/ml	Crude OR (95%CI)	Multivariable-adjusted[a]	P
Decrease per unit	1.19(1.13–1.25)	1.09(1.03–1.16)	0.009
Quartile 1(< 11.4)	6.15(3.85–11.32)	4.15(2.57–6.19)	< 0.001
Quartile 2(11.4–15.6)	3.96(2.33–5.15)	3.02(2.21–4.31)	0.002
Quartile 3(15.6–19.4)	2.35(1.48–3.36)	1.55(0.96–2.07)	0.09
Quartile 4(> 19.4)	Reference	1.00	1.00
Vitamin D deficiency vs. other	3.99(2.30–5.11)	3.05(2.24–4.40)	0.001

OR, odds ratio; CI, confidence interval; 25(OH)D, 25-Hydroxyvitamin D; BMI, body mass index; SGA; small for gestational age.

[a] Adjusted for maternal age, maternal race, pre-pregnancy BMI, height, smoking (yes/no), planned pregnancy (yes/no), marital status, education, family's socio-professional category, delivery, vitamin D supplementation(yes/no), physical activity, vitamin D lifestyle score, season, and infant sex.

models comparing the concentration of 25(OH)D in first (Q1), second and third quartiles against the fourth quartile (Table 3), concentrations of 25(OH)D in Q1 and Q2 were associated with SGA later developed, and increased risk of SGA by 315% (4.15[2.57–6.19]) and 202% (3.02[2.21–4.31]). The independent relationship between 25(OH)D with SGA was confirmed using the likelihood ratio test (P = 0.003). In a multivariate model using the vitamin D deficiency vs. other together with the clinical variables, the adjusted risk of SGA increased by 205% (odds ratio 3.05 [95% CI 2.24–4.40], P = 0.001). From above results, the plasma concentration of 25(OH)D could be treated as a predictor for SGA screening. In addition, the cutoff value was optimized based on the receiver operating characteristic curves (ROC), which was estimated to be 10.6 ng/ml. The sensitivity and specificity was 84.6% and 62.8%, respectively, with the area under curve (AUC) of 0.72 (95%CI, 0.67–0.77).

5. Discussion

In this China pregnancy cohort of singleton infants born at term, maternal vitamin D status at first prenatal visit has made positive effects on both birth weight and head circumference, and it was negatively associated with risk of SGA. This was known as the first study on evaluating concentration of 25(OH)D at first prenatal visit of gestation in relation to the development of SGA and to investigate its clinical utility in Chinese newborns. The group with vitamin D deficiency displayed prognostic information, and the adjusted risk of SGA was increased by 205% (OR = 3.05 [95% CI: 2.24–4.40]) than women without vitamin D deficiency. Targeted lifestyle intervention and more frequent medical interventions should be emphasized to minimize these effects.

There were controversies on the relations of maternal vitamin D status and infant birth weight. A positive association had been suggested in previous two observational studies [14,15]. Similarly, Bowyer et al. [27] found that risk of neonatal vitamin D deficiency would be increased by maternal vitamin D deficiency, as well as the risk of lower birth weight. However, no relation was obtained between maternal vitamin D and birth weight in two other observational studies [28,29]. In addition, in our study, 25(OH) D was found to be positively associated with head circumference in term infants, which was disagreed with the results from two previous studies [30,31], whereas agreed with another study [5]. Contradictory findings may be explained by many factors, including the statistical approaches of 25(OH)D, the number of subjects, and studying different time points in gestation.

In this study, we found that maternal vitamin D status was negatively related to the SGA risk. Similarly, two first-trimester observational studies found a connection between vitamin D and SGA in term infants [14,16]. Gernand et al. [32] reported that the SGA risk was associated with maternal vitamin D deficiency during 2ndtrimester, for both the group of all women and subgroups of white and nonobese women. These results were also proved with a meta-analysis and the pooled ORs were 1.85(95%CI: 1.52–2.26) [33]. Another meta-analysis also suggested that low maternal vitamin D levels during pregnancy lead to rising risk of preterm birth and SGA [34]. Interestingly, a randomized trial have demonstrated third-trimester vitamin D supplementation could reduce risk of SGA by twice, compared to that of in control group (29% vs. 15%)[35].

Vitamin D deficiency has been generally observed in pregnant women. From the results of this study, we found that more than three quarters women (76.9%) were suffered from vitamin D deficiency. Previous studies had found that the rate of vitamin D deficiency in pregnant women range from 40.7%–82.6% [1,26,36]. In another study, Viljakainen et al. [37] suggested that vitamin D deficiency was observed in 71% of women and 15% of newborns, even if the current Nordic recommendations on vitamin D supplement (10 μg, or 400 IU/d) have been reached in pregnant women. The reported rates of vitamin D deficiency were inconsistent in different studies, while it may be resulted from many factors, including the varied subject samples, determination methods and cutoffs, as well as the assessment times.

The mechanisms attributed to the relations of 25(OH)D level and its effects on fetal growth were interpreted. First, maternal vitamin D deficiency may impede the typical increase in calcium absorption and affect bone metabolism to in turn reduce fetal bone accretion. An observation study suggested that fetal femoral development could be affected by maternal vitamin D insufficiency since 19 weeks during pregnancy [38]. Second, placental and maternal decidual cells express the CYP27B1 enzyme to synthesize the active 1, 25-dihydroxyvitamin D3 and have vitamin D receptors, allowing for numerous potential roles of vitamin D in pregnancy including fetal growth restriction [5]. Third, many human hormones could be regulated by vitamin D and the reverent receptors or derivatives. The glucose and fatty acid metabolism of mother would be affected through these pathways, thus making effects on fetal nutrients supply [39]. Therefore, vitamin D might influence newborn mass through an effect on transplacental glucose and fatty acid transport and accretion of fat and nonskeletal lean mass. Lastly, immune function might be related to fetal growth [40]. Vitamin D may play a pivotal role in normal decidual immune function by promoting innate responses to infection, while simultaneously preventing an over-elaboration of inflammatory adaptive immunity [41].

In this study, the data on various potentially confounding risk factors were also collected. Thus, the independent effects of 25(OH)D on SGA could be evaluated. This study was a well-designed prospective study enabling the prediction and early screening. The levels of 25(OH) D were determined at first visit, while in most of other studies, the levels of 25OHD were determined since second trimester [15,27]. The last strength is the focus on term infants because it is highly problematic to accurately estimate SGA in preterm births. Some limitations should be taken into account. First, the included population was merely women of Han Chinese. Although it would be benefit for data homogeneity, the fact is that the obtained results and conclusions could not be directly extended to other populations. Second, the data of vitamin D supplementation and lifestyle could be biased since it was only a self-reported result. Third, meat is also a source of vitamin D as 25(OH)D [42]. However, it is not included on Food Frequency Questionnaires (FFQs). Lastly, the study was not based on cross-sectional design; as such, we could not determine the impacts from adequate vitamin D supplementation on SGA and could not suggest any causal relationship. In a randomized control trial, the data suggested that risk of pregnant comorbidities could be mitigated by supplementing vitamin D. In addition, the neonatal outcomes also could also be improved [43]. More well-designed and controlled studies should further be performed to explore the specific effects from maternal vitamin D intakes on SGA during pregnancy.

In summary, the data presented here suggests that maternal vitamin D insufficiency was generally observed in pregnant women and it was

independently related to the risks of low birth weight and SGA in term infants. Further studies should attempt to demonstrate the issue of Vitamin D supplementation for minimizing SGA and improving neonatal healthy situations.

Conflict of interest

The authors report no conflict of interest.

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