Original Paper

Association of Maternal Serum 25-Hydroxyvitamin D Concentrations with Risk of Gestational Anemia

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Key Words

Vitamin D • 25(OH)D • Anemia

Abstract

Background/Aims: Vitamin D deficiency has been shown to be associated with a greater prevalence of anemia in various healthy and diseased populations by a great deal of observational studies. However, less work has been done to explore this association in pregnant women. The aim of this study was to evaluate the association between maternal serum 25-hydroxyvitamin D [25(OH)D] concentrations and risk of gestational anemia in a large, nested case-control study. **Methods:** The serum 25(OH)D concentrations were measured by enzyme immunoassay in 775 pregnant women affected with anemia and 1550 controls. Logistic regression analysis was conducted to assess the association of 25(OH)D concentrations with risk of gestational anemia. **Results:** We found the 25(OH)D concentrations were significantly lower in women affected with anemia than in controls. Logistic regression analyses showed that women with 25(OH)D concentrations < 25.0 nmol/L, from 25.0 to 37.4 nmol/L and from 37.5 to 49.9 nmol/L all had increased risk of anemia when compared with women with concentrations from 50.0 to 74.9 nmol/L. And the risk of anemia was significantly increased with the decreasing concentrations of the serum 25(OH)D in a dose-dependent manner (P for trend = 0.012). For women with concentrations < 50.0 nmol/L, they had an 80% increase in anemia risk (95% CI = 1.45-2.25) after adjustment for confounders. We also observed a nonlinear relationship between the serum 25(OH)D and anemia, with a threshold for 25(OH)D of 50.0 nmol/L existed for anemia. **Conclusion:** Maternal serum 25(OH)D < 50.0 nmol/L may be a risk factor for gestational anemia, and it should be monitored for the high-risk pregnant women.

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Introduction

Anemia is characterized by a decrease in concentration of red blood cells or haemoglobin, resulting in impaired oxygen transport throughout the body, which is a major global health concern. About 1.62 billion people are anemic in the world, and anemia is more prevalent in pregnant women. An estimated 50% of pregnant women have anemia in developing countries, compared with 12%-25% in developed countries [1]. Gestational anemia has been associated with an increased risk of intrauterine growth restriction, premature birth, low birth weight, postnatal depression, and maternal morbidity and mortality [2, 3]. It is known that a wide variety of causes could induce anemia, such as iron deficiency, malabsorption, hemolysis, chronic disease or a combination of these [4, 5]. In recent years, an association between anemia and vitamin D has emerged.

Vitamin D deficiency is also an important issue in public health as it is implicated in a wide range of physiological processes beyond bone metabolism. The deficiency of vitamin D is widespread among the general population and is highly prevalent in pregnant women [6-10]. Vitamin D deficiency has been shown to be associated with lower hemoglobin (Hgb) levels and a greater prevalence of anemia in various healthy and diseased populations by a great deal of observational studies [11-15]. Furthermore, retrospective cohort studies in adults with chronic kidney disease have demonstrated that vitamin D supplementation may improve anemia management [16]. However, less work has been done to explore this association in pregnant women.

25-hydroxyvitamin D [25(OH)D], a main indicator of vitamin D status, is used to define vitamin D deficiency in most studies. In our previous large cohort study, we found women with 25(OH)D < 50.0 nmol/L had increased risk of gestational anemia in both univariate and multivariate logistic regression analysis, when compared with women with 25(OH)D concentrations from 50.0 to 74.9 nmol/L [17]. To further evaluate the relationship of maternal vitamin D deficiency and risk of gestational anemia, we performed a nested case-control study in 1:2 ratio, including 775 pregnant women affected with anemia and 1550 controls. Furthermore, we evaluated the threshold of 25(OH)D concentrations for gestational anemia.

Materials and Methods

This study was approved by the institutional review board of Nanjing Maternity and Child Health Care Institute, and the methods were carried out in accordance with the approved guidelines. This trial is registered at ClinicalTrials.gov with clinical trial identifier number NCT02236221.

Participants and study design

We carried out a nested case-control study based on a cohort of 4718 women [17]. The women who had participated in second- and third-trimester pregnancy complications screening at Obstetrics and Gynecology Hospital Affiliated to Nanjing Medical University, between March 2012 and February 2015, were included. Fasting venous blood was drawn for routine multi-index detecting, and serum aliquot was stored at -80°C. Maternal information for serum samples were derived from the laboratory databases and the information about anemia were obtained via electronic medical record collection and information extraction. The extracted variables included maternal age (in year), birthplace (Jiangsu province or other provinces), intrapartum body mass index (BMI) (kg/m²), parity (nulliparae or multiparae), menarche age (in year), menstrual cycle (21-35 days, 36 days or irregularity), abnormal pregnancy history (no or yes), sampling trimester (second or third), and sampling season [Northern Hemisphere: spring (March to May), summer (June to August), autumn (September to November) and winter (December to February)]. The pregnancy women with previously diagnosed diabetes (pregestational or gestational) or hypertension (chronic or pregnancy), kidney disease, uterine fibroids, multiple gestation or any other significant preexisting chronic medical disease were excluded.

From the total cohort of 4718 women, 775 pregnant women affected with anemia (hemoglobin < 100 g/L) and had met all above inclusion and exclusion criteria. These cases were matched by maternal age and

birthplace, in 1:2 ratio, to a random computer-generated referent group of 1550 controls (hemoglobin ≥ 100 g/L) using the same inclusion and exclusion criteria.

Vitamin D measurement

Maternal serum 25(OH)D concentrations was measured by using an *in vitro* diagnostic enzyme immunoassay kit OTEIA 25-Hydroxy Vitamin D (Immunodiagnostic Systems, Boldon, United Kingdom) according to the manufacturer's instructions. The reported analytic sensitivity of the immunoassay was 6.8-380 nmol/L. Commonly used cutoffs to define 25(OH)D status were assigned at 25.0, 37.5, 50.0 and 75.0 nmol/L [17].

Statistical analysis

Differences of maternal characteristics and 25(OH)D serum concentrations between pregnant women affected with anemia and controls were calculated by the Student's *t*-test (for continuous variables), χ^2 test (for categorical variables) and Mann-Whitney test (for 25(OH)D concentrations). The relationship between 25(OH)D concentrations and the risk of gestational anemia was explored by the smoothing plot. Logistic regression analysis were performed to assess the crude and adjusted association between 25(OH)D concentrations (< 25.0, 25.0-37.4, 37.5-49.9, < 50.0, > 75.0 nmol/L vs. 50.0-74.9 nmol/L) and anemia risk by computing odds ratios (OR) and their 95% confidence intervals (CIs). In the multivariate regression analysis, maternal age, birthplace, intrapartum BMI, parity, menarche age, menstrual cycle, abnormal pregnancy history, sampling trimester and sampling season were taken into account. The χ^2 -based Q test was applied to test the heterogeneity of associations between subgroups. All the above statistical analyses were performed with R software (version 2.13.0), and $P \leq 0.05$ in a two-sided test was considered statistically significant.

Results

We successfully analyzed serum 25(OH)D concentrations from all 2325 samples (775 pregnant women affected with anemia and 1550 controls). The selected characteristics of the 2325 women are summarized in Table 1. There were no significant differences in the distribution of maternal age, birthplace, intrapartum BMI, parity, menarche age, menstrual cycle, abnormal pregnancy history, sampling trimester and sampling season between the two matched groups (all $P > 0.05$). Maternal serum 25(OH)D concentrations was significantly lower in women affected with anemia [Median (IQR), women affected with

Table 1. Maternal characteristics and serum 25(OH)D concentration between cases and controls

Maternal characteristics	Gestational anemia (n = 775)	Controls (n = 1550)	P ^b
Maternal age (years) ^a	28.9 $\pm$ 3.5	29.0 $\pm$ 3.2	0.661
Birthplace of Jiangsu province [n (%)]	737 (95.1)	1485 (95.8)	0.433
Intrapartum BMI (kg/m ²) ^a	26.9 $\pm$ 3.1	26.9 $\pm$ 3.2	0.667
Nulliparae [n (%)]	720 (92.9)	1438 (92.8)	0.910
Menarche age (years) ^a	13.7 $\pm$ 1.2	13.7 $\pm$ 1.2	0.222
Long (36 ~) or irregular menstrual cycle [n (%)]	66 (8.5)	171 (11.0)	0.059
Having abnormal pregnancy history [n (%)]	109 (14.1)	228 (14.7)	0.677
Sampling in second trimester [n (%)]	289 (37.3)	612 (39.5)	0.306
Sampling season [n (%)]			0.888
Spring	196 (25.3)	386 (24.9)	
Summer	245 (31.6)	511 (33.0)	
Autumn	173 (22.3)	348 (22.5)	
Winter	161 (20.8)	305 (19.7)	
25(OH)D (nmol/L) ^c	39.9 (33.4, 51.4)	44.3 (35.8, 58.9)	< 0.001
25(OH)D [n (%)]			< 0.001
< 25.0 nmol/L	27 (3.5)	31 (2.0)	
25.0-37.4 nmol/L	278 (35.9)	443 (28.6)	
37.5-49.9 nmol/L	259 (33.4)	468 (30.2)	
50.0-74.9 nmol/L	141 (18.2)	425 (27.4)	
>75 nmol/L	70 (9.0)	183 (11.8)	

^a Mean $\pm$ SD; ^b $P < 0.05$ (chi-square test, *t* test, or Mann-Whitney test as appropriate); ^c Median (IQR); 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.

Fig. 1. The relationship between maternal 25(OH)D and gestational anemia. A nonlinear relationship between the serum 25(OH)D and gestational anemia was observed. (A) For women in the second trimester; (B) For women in the third trimester; (C) For all the women. 25(OH)D, 25-hydroxyvitamin D.

Fig. 2. The crude and adjusted odds ratios (OR) of maternal 25(OH)D concentrations for gestational anemia.

anemia vs. controls: 39.9 [33.4, 51.4] vs. 44.3 [35.8, 58.9] nmol/L, $P < 0.001$]. Among women affected with anemia, 72.8% of women had serum concentrations < 50.0 nmol/L compared with 60.8% of women in the controls (Table 1). As shown in Fig. 1, there was a nonlinear relationship between the serum 25(OH)D and anemia, with a threshold for 25(OH)D of 50.0 nmol/L existed for anemia. When the 25(OH)D concentrations reached 50.0 nmol/L, the prevalence of gestational anemia plateaued.

Logistic regression analyses showed that women with 25(OH)D concentrations < 25.0 nmol/L, from 25.0 to 37.4 nmol/L and from 37.5 to 49.9 nmol/L all had increased risk of gestational anemia when compared with women with concentrations from 50.0 to 74.9 nmol/L (Table 2. and Fig. 2). And the risk of gestational anemia was significantly increased with the decreasing concentrations of the serum 25(OH)D in a dose-dependent manner (P for trend = 0.012). For women with concentrations < 50.0 nmol/L, they had an 80% increase in anemia risk (95% CI = 1.45-2.25) after adjustment for confounders (Table 2). The association of the 25(OH)D concentrations with risk of gestational anemia were also evaluated by stratifying on maternal age, intrapartum BMI, parity, menarche age, menstrual cycle, abnormal pregnancy history, sampling trimester and sampling season (Table 2). Similar association strengths were shown between most subgroups ($P > 0.05$ for heterogeneity test).

Discussion

In this large nested case-control study conducted on gestational anemia, we found maternal serum 25(OH)D concentrations was significantly lower in women affected with

anemia. For women with concentrations < 50.0 nmol/L, they had an 80% increase in anemia risk, when compared with women with 25(OH)D from 50.0 to 74.9 nmol/L. We also observed a threshold for 25(OH)D of 50.0 nmol/L existed for gestational anemia. Further studies are warranted to validate and extend our findings. In general, our results suggested that maternal serum 25(OH)D < 50.0 nmol/L may be a risk factor for anemia, and it should be monitored for the high-risk pregnant women.

Our results are in line with recent studies suggesting a strong association of low 25(OH)D with anemia risk in various healthy and diseased populations [11-15]. In a meta-analysis including seven studies involving 5183 participants, the outcomes showed that vitamin D deficiency increased the risk of developing anemia [18]. Bener et al. and Thomas et al. both reported that maternal vitamin D deficiency in pregnancy was significantly associated with elevated risk for anemia [19, 20]. There are several possible mechanisms to explain the relationship between vitamin D deficiency and anemia. Calcitriol, the active form of vitamin D, could up-regulate the expression of the erythropoietin receptor on erythroid progenitor cells, and may have a proliferative effect on erythroid burst forming units, which is synergistic with erythropoietin. There are data to show vitamin D deficiency result-

Table 2. The associations between 25(OH)D serum concentrations and gestational anemia and stratified analyses on the associations

Gestational anemia (n = 775)	Univariate				Multivariate			
	< 25.0	25.0-37.4	50.0-74.9	> 75.0	< 25.0	25.0-37.4	50.0-74.9	> 75.0
All women	2.63 (1.52-4.55)	1.89 (1.48-2.41)	1.0 (ref)	1.15 (0.83-1.61)	2.63 (1.50-4.60)	1.88 (1.47-2.40)	1.0 (ref)	1.14 (0.82-1.60)
Maternal age (year)								
< 30	1.90 (0.94-3.83)	1.71 (1.25-2.34)	1.0 (ref)	1.23 (0.79-1.91)	1.79 (0.88-3.65)	1.65 (1.20-2.27)	1.0 (ref)	1.21 (0.78-1.89)
30~	4.45 (1.79-11.08)	2.17 (1.48-3.20)	1.0 (ref)	1.06 (0.64-1.78)	5.06 (1.98-12.89)	2.31 (1.56-3.43)	1.0 (ref)	1.03 (0.61-1.73)
Intrapartum BMI (kg/m ²)								
< 30	2.53 (1.36-4.70)	1.78 (1.37-2.31)	1.0 (ref)	0.99 (0.69-1.43)	2.44 (1.30-4.58)	1.75 (1.34-2.27)	1.0 (ref)	0.98 (0.67-1.41)
30~	3.38 (1.00-11.37)	2.73 (1.41-5.29)	1.0 (ref)	2.76 (1.16-6.56)	4.78 (1.31-17.37)	3.01 (1.52-5.95)	1.0 (ref)	2.72 (1.13-6.59)
Parity								
Nulliparae	2.86 (1.59-5.12)	1.81 (1.41-2.33)	1.0 (ref)	1.12 (0.79-1.59)	2.80 (1.55-5.05)	1.78 (1.38-2.29)	1.0 (ref)	1.12 (0.79-1.59)
Multiparae	1.47 (0.24-8.85)	3.51 (1.37-8.99)	1.0 (ref)	1.67 (0.46-6.05)	2.74 (0.38-19.58)	5.23 (1.82-15.01)	1.0 (ref)	3.16 (0.76-13.12)
Menarche age (year)								
< 13	3.04 (0.41-22.85)	1.66 (0.89-3.09)	1.0 (ref)	0.48 (0.17-1.36)	3.86 (0.46-32.19)	1.90 (0.99-3.64)	1.0 (ref)	0.48 (0.16-1.38)
13~	2.55 (1.30-5.00)	1.98 (1.47-2.67)	1.0 (ref)	1.30 (0.87-1.95)	2.52 (1.27-4.99)	1.96 (1.45-2.65)	1.0 (ref)	1.29 (0.86-1.93)
15~	2.73 (0.90-8.24)	1.77 (1.01-3.09)	1.0 (ref)	1.27 (0.58-2.77)	2.61 (0.82-8.32)	1.77 (0.98-3.17)	1.0 (ref)	1.36 (0.61-3.04)
Menstrual cycle (day)								
21~	2.99 (1.65-5.42)	1.90 (1.48-2.45)	1.0 (ref)	1.05 (0.74-1.48)	2.90 (1.58-5.29)	1.89 (1.46-2.44)	1.0 (ref)	1.05 (0.74-1.50)
36~ or irregularity	1.40 (0.25-7.76)	1.87 (0.80-4.36)	1.0 (ref)	3.43 (1.05-11.18)	1.60 (0.27-9.46)	1.74 (0.73-4.14)	1.0 (ref)	3.09 (0.90-10.61)
Abnormal pregnancy history								
No	2.18 (1.21-3.92)	1.92 (1.47-2.50)	1.0 (ref)	1.11 (0.77-1.60)	2.15 (1.18-3.91)	1.90 (1.45-2.48)	1.0 (ref)	1.10 (0.76-1.59)
Yes	16.20 (1.81-145.24)	1.65 (0.88-3.07)	1.0 (ref)	1.43 (0.62-3.30)	15.61 (1.68-144.79)	1.68 (0.89-3.19)	1.0 (ref)	1.47 (0.62-3.50)
Sampling trimester								
Second	3.37 (1.40-8.13)	1.95 (1.29-2.93)	1.0 (ref)	1.60 (0.94-2.74)	3.08 (1.26-7.52)	1.90 (1.26-2.87)	1.0 (ref)	1.67 (0.97-2.87)
Third	2.26 (1.11-4.57)	1.86 (1.37-2.51)	1.0 (ref)	0.94 (0.61-1.45)	2.36 (1.15-4.86)	1.87 (1.38-2.55)	1.0 (ref)	0.93 (0.60-1.44)
Sampling season								
Spring/Winter	2.52 (1.30-4.91)	2.19 (1.51-3.17)	1.0 (ref)	1.21 (0.67-2.17)	2.83 (1.43-5.60)	2.26 (1.55-3.29)	1.0 (ref)	1.18 (0.65-2.12)
Summer/Autumn	4.40 (1.40-13.81)	1.71 (1.24-2.36)	1.0 (ref)	1.10 (0.73-1.65)	4.50 (1.42-14.21)	1.67 (1.20-2.32)	1.0 (ref)	1.09 (0.72-1.65)

All values are ORs (95% CIs). Values were determined by using logistic regression. Adjusted values were adjusted for maternal age, birthplace, intrapartum BMI, parity, menarche age, menstrual cycle, abnormal pregnancy history, sampling trimester or sampling season (excluded the stratified factor in each stratum). 25(OH)D, 25-hydroxyvitamin D.

ing in decreased calcitriol production in the bone marrow may limit erythropoiesis [21-23]. Calcitriol also play an important role in the immune function regulation by suppressing the pro-inflammatory cytokines expression [24]. This immunomodulatory effect may be central to its role in preventing anemia. Perlstein et al. found a strong association between vitamin D deficiency and anemia of inflammation compared with both subjects with other anemia subtypes and non-anemic subjects [14]. Besides, hepcidin, a systemic iron-regulatory hormone, was shown to be regulated by iron requirements of erythroid precursors for hemoglobin synthesis, and may be associated with anemia [25, 26]. Vitamin D deficiency may up-regulate hepcidin, thus promote the decrease of hemoglobin and contribute to anemia [27]. Further studies to deeply explore the possible mechanisms are still warranted.

In this study, the prospective data collection, a relatively large sample size, random sampling and blinded analysis, and statistical adjustment provided sufficient statistical power and convincing data. There are also some limitations to this study. This is a cross-sectional study, and thus it is not possible to determine a causal relationship between vitamin D deficiency and anemia. And we did not have data on iron deficiency, Hgb levels, plasma erythropoietin and reticulocyte count, so we could not analyze the relation among vitamin D and these markers. As our subjects were Chinese pregnant women, it is not clear whether we can extend our results to the other populations. Further prospective studies considering above potential confounders and incorporating diverse populations with long-term effects are warranted, which would have important implications for public health policy. Despite all this, our study has provided robust epidemiological evidence that low serum 25(OH)D in pregnant women was significantly associated with increased risk of gestational anemia. The findings suggested that vitamin D supplements in pregnancy should be encouraged to prevent gestational anemia.

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J.W and X.G designed the study. Y.Y, Z.C, Y.D, Q.H, X.W, L.Z, P.X, L.Y and X.W collected the data. J.W, C.J and X.G conducted the statistical analysis and interpretation. Y.Y and Z.C wrote the report. J.W and X.G revised the report. All the authors reviewed the report and approved the final version.

Disclosure Statement

The authors declare no conflict of interest.

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