Research Paper

Association of Maternal Serum 25-hydroxyvitamin D Concentrations in Second Trimester with Delivery Mode in A Chinese Population

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Abstract

**Objective:** To determine the maternal serum 25-hydroxyvitamin D [25(OH)D] concentrations in a Chinese population and investigate its associations with subsequent delivery mode by studying 1924 unrelated pregnant women.

**Methods:** The serum 25(OH)D concentrations was measured by enzymelinked immunosorbent assay (ELISA). Simultaneously, maternal information and subsequent delivery mode were collected. Logistic regression analysis was performed to assess the associations between 25(OH)D concentrations and caesarean section.

**Results:** The median (IQR) serum concentration of 25(OH)D for the total subjects was 43.4 (35.2-56.9) nmol/L. Among them, 1225 (63.7%) women were in the status of 25(OH)D deficiency (< 50.0 nmol/L). The 25(OH)D concentrations showed significant variation by body mass index (BMI), parity and season of sampling. Women with caesarean section was older, and with higher BMI and rate of abnormal pregnancy history, suggesting advanced age, obesity and abnormal pregnancy history may be the risk factors for the subsequent caesarean section. Compared with 25(OH)D from 50.0 to 74.9 nmol/L, women with low 25(OH)D concentrations (< 50.0 nmol/L) was not significantly associated with caesarean section. Only in the subgroup of the women without abnormal pregnancy history, higher 25(OH)D (> 75.0 nmol/L) concentrations could significantly decrease the risk of caesarean section.

**Conclusion:** Vitamin D deficiency is a quite serious problem in Chinese pregnant women. There is no evidence that the maternal serum 25(OH)D concentrations is associated with increased risk of caesarean section.

Key words: 25(OH)D; Vitamin D deficiency; Caesarean section.

Introduction

In recent years, a large number of people in different areas were in status of vitamin D deficiency or insufficiency, which has been a globally and gradually serious problem [1]. Vitamin D is a lipid soluble vitamin indispensable to human body. The main function of active vitamin D is to increase the intestinal absorption of calcium, regulate the function of bone cells, affect bone metabolism, and to maintain bone health at all ages [2, 3]. An increasing number of studies have shown that vitamin D deficiency in...
serum during pregnancy are closely related to a series of adverse pregnancy outcomes, including gestational diabetes, preeclampsia, preterm birth, intrauterine growth restriction, and so on [4-6]. Despite lack of vitamin D has indeed affected human health, how to define lack of vitamin D is still an academic controversy [7, 8]. 25-Hydroxyvitamin D [25(OH)D] is the storage form of vitamin D, which is an ideal indicator of vitamin D levels [9]. Most scholars defined vitamin D deficiency as serum 25(OH)D concentrations < 50.0 nmol/L (20.0 ng/mL), and defined vitamin D insufficiency as serum 25(OH)D concentrations < 75.0 nmol/L (30.0 ng/mL) [10]. But it is not clear that the proposed 25(OH)D concentrations are suitable for pregnant women.

With the rapid development of the technique and method of cesarean section, cesarean section has been one of the most commonly used surgical procedures, which is an effective rescue measure to solve the dystocia and some obstetric syndrome of pregnant women [11]. So in many regions, the application of cesarean section has increased substantially over recent decades. However, its disadvantages are also prominent. The pregnant women are prone to bleeding, infection, organ adhesion, and prone to be affected with some other short or long-term complications, whereas the newborns are prone to temporary tachypnea, pathological jaundice, and so on [12, 13]. An observational study from Boston shown that the cesarean section rate in pregnant women with serum 25(OH)D < 37.5 nmol/L was over 4 times more than women with normal 25(OH)D concentrations [14]. However, Bowyer et al. had come to a different conclusion that there is no correlation between vitamin D levels during pregnancy and delivery mode [15]. Currently, there are few studies on the relationship between the level of maternal vitamin D and the mode of delivery. In this study, we measured the serum 25(OH)D concentrations in 1924 pregnant women in second trimester to describe the current situation of vitamin D deficiency in Chinese pregnant women, and to evaluate the relationship between vitamin D levels and delivery mode.

Materials and Methods

This study was approved by the ethics committee of Nanjing Medical University, and the experimental methods were performed strictly in accordance with the approved guidelines.

Study subjects

The pregnant women of this study were recruited from March 2012 to February 2015 in Obstetrics and Gynecology Hospital Affiliated to Nanjing Medical University (between 31 and 32 degrees north latitude), and the related information were collected through questionnaires and conventional electronic medical records. The exclusion criteria included loss of basic information, medical abortion, multiple pregnancy, and the use of assisted reproductive technology or 25(OH)D concentrations beyond the assay detection limit. Each pregnant woman was collected 5ml peripheral blood after completing the questionnaire, and the serum was separated by centrifugation at the Nanjing Maternal and Child Health Institute (NMCHI). Then the samples were stored in chronological order in the 100-hole boxes at -80°C. Using the random number table, the 100-hole boxes were randomly selected from the total population. All cesarean section samples in one box were defined as the case group, and the others were defined as the control group. In the end, 1924 pregnant women agreed to participate in the study and signed informed consents.

Vitamin D measurement

After serum sample thawed, 25(OH)D concentrations was determined by using an euzymelinked immunosorbent assay (ELISA) (25-hydroxy vitamin D Kit, IDS Ltd, Boldon, UK). The inter- and intra-assay coefficients of variation were 4.6% and 5.3%, respectively. And the reported analytic sensitivity of the assay was from 6.8 to 380 nmol/L. For the measurement of serum 25(OH)D, the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method is generally considered to be the best way, however, in our study, the enzyme immunoassay was used. Although the immunoassay may result in a little negative biases and misclassification of participants for vitamin D sufficiency when compared with the LC-MS/MS assay, it is more readily available and require small volume sampling, ideal for testing. All the samples were tested by trained researchers who were not aware of the source of the samples. The commonly used cutoff values for 25(OH)D status were 25, 37.5, 50 and 75 nmol/L [16].

Data source

After the investigators (epidemiology professionals) were trained qualified, a unified designed and pre-investigated questionnaire was used to collected related information. The questionnaire included demographic data, menarche age, menstrual cycle, previously diagnosed hypertension (chronic or pregnancy) or diabetes (pre-gestational or gestational), family history of hypertension or diabetes, history of uterine fibroids, adverse pregnancy history, and so on. The
information of subsequent delivery mode (cesarean section or vaginal delivery) was obtained from routine electronic medical record.

**Statistical analysis**

All the investigation data and experimental data were examined and verified. The EpiData 3.02 software was used to input data and establish the database. Percentiles were used to describe the distribution of 25(OH)D concentrations in the total pregnant women population and its subgroups. Kruskal-Wallis or Mann-Whitney test was used to analyze the difference of the distribution of 25(OH)D concentrations in each subgroup. Student’s t-test, χ² test or Mann-Whitney test were used to compare the demographic characteristics and the distribution of 25(OH)D (< 25, 25-37.4, 37.5-49.9, 50-74.9, > 75nmol/L) between cesarean section and spontaneous delivery group, and univariate and multivariate logistic regression analysis were performed to evaluate the crude and adjusted association between 25(OH)D concentrations and delivery mode by computing odds ratios (ORs) and 95% confidence interval (CIs). The adjustment factors including maternal age, intrapartum body mass index (BMI), birthplace, parity, menarche age, menstrual cycle, abnormal pregnancy history, sampling season, previously diagnosed hypertension or diabetes, family history of hypertension or diabetes, and history of uterine fibroids. All the above statistical analyses were performed with SPSS 18.0 software, and P ≤ 0.05 for a two-sided test was considered statistically significant.

**Results**

In total, 2318 serum samples were tested for 25(OH)D, of which 2131 (91.9%) pregnant women had detailed health information. We excluded 207 women who had medical abortion or multiple pregnancy, who applied assisted reproductive technology, or who had 25(OH)D concentrations exceeded the assay detection limit. In the end, 1924 pregnant women were included in the study. The percentile distributions of 25(OH)D in the total women and subgroups were shown in Table 1. In the total population, the median (IQR) concentration of 25(OH)D was 43.4 (35.2 - 56.9) nmol/L; 53 pregnant women (2.8%) had concentrations < 25.0 nmol/L; 567 (29.5%) had concentrations from 25.0 to 37.4 nmol/L; 605 pregnant women (31.4%) had concentrations from 37.5 to 49.9 nmol/L; 492 (25.6%) had concentrations from 50.0 to 74.9 nmol/L; 207 pregnant women (10.8%) had concentrations > 75.0 nmol/L. Pregnant women with intrapartum BMI ≥ 30 kg/m² and multipara had lower 25(OH)D concentrations (P = 0.015 and 0.010, respectively), and there was a significant variation of 25(OH)D concentrations by sampling season (P < 0.001). The 25(OH)D concentrations was relatively higher in summer and autumn, and lower in spring and winter, suggesting that vitamin D levels were closely related to sunlight exposure. However, in other subgroups (by maternal age, birthplace, menarche age, menstrual cycle and adverse pregnancy history), no significant differences in the 25(OH)D concentrations were observed (all P > 0.05).

In this study, there were 1883 pregnant women with delivery information, including 1060 cases of spontaneous labor and 823 cases of cesarean section. As shown in table 2, pregnant women with cesarean section were more likely to be older, to have higher intrapartum BMI, and more likely to have an abnormal pregnancy history as compared with controls (all P < 0.05). In addition, pregnant women with cesarean section were less likely to be nullipara with a borderline significance (P = 0.060). These evidences suggested advanced age, obesity, abnormal pregnancy history and multipara may be the risk factors for the subsequent caesarean section. However, there was no significant difference in birthplace, menarche age, menstrual cycle, sampling season, 25(OH)D concentrations and distributions between the cesarean section group and controls (all P > 0.05).

Univariate and multivariate logistic regression analysis showed that there was no association between low 25(OH)D concentrations (< 50.0 nmol/L) and risk of cesarean section, as compared with women with 25(OH)D concentrations from 50.0 to 74.9 nmol/L. And the results of the subgroup analysis were consistent with the results of the total population. While for the higher 25(OH)D concentrations (>75.0 nmol/L), univariate and multivariate logistic regression analysis also suggested no significant association between the 25(OH)D concentrations and risk of cesarean section. Only in the subgroup of the women without abnormal pregnancy history, higher 25(OH)D concentrations (> 75.0 nmol/L) could significantly decrease the risk of caesarean section (OR = 0.65, 95%CI = 0.45 - 0.96). After adjustment for confounding factors, a borderline significant protective effect of higher 25(OH)D concentrations for cesarean section was also observed (OR = 0.70, 95%CI = 0.47-1.05) (Table 3).
**Table 1.** The 25(OH)D concentrations by maternal characteristics

| Maternal characteristics | n (%) | 25(OH)D percentiles (nmol/L) | P * |
|--------------------------|-------|-------------------------------|-----|
|                          |       | 5th                          | 10th | 25th | 50th | 75th | 90th | 95th |
| All women                | 1924 (100.0) | 26.6                        | 29.5 | 35.2 | 43.4 | 56.9 | 77.0 | 94.9 |
| Maternal age (year)      |       |                              |      |      |      |      |      |      |
| < 25                     | 92 (4.9) | 25.6                        | 28.9 | 35.6 | 43.7 | 56.4 | 79.6 | 101.5 |
| 25-                      | 915 (48.6) | 26.6                        | 29.2 | 35.0 | 43.0 | 55.7 | 74.4 | 93.0 |
| 30-                      | 731 (38.8) | 26.8                        | 30.0 | 35.9 | 44.2 | 61.0 | 78.1 | 94.8 |
| 35-                      | 124 (6.6) | 25.1                        | 29.6 | 34.3 | 42.9 | 55.4 | 80.9 | 106.3 |
| 40-                      | 21 (1.1)  | 24.8                        | 27.4 | 34.5 | 44.1 | 61.1 | 70.1 | 159.2 |
| Intrapartum BMI (kg/m²)  |       |                              |      |      |      |      |      |      |
| < 25                     | 541 (29.1) | 27.0                        | 30.3 | 35.7 | 44.8 | 59.2 | 80.8 | 97.0 |
| 25-                      | 995 (53.4) | 26.6                        | 29.4 | 35.6 | 43.0 | 57.5 | 77.1 | 93.9 |
| 30-                      | 281 (15.1) | 24.8                        | 27.7 | 34.2 | 40.4 | 52.8 | 69.1 | 93.4 |
| 35-                      | 45 (2.4)  | 25.6                        | 30.2 | 34.6 | 44.7 | 51.6 | 71.7 | 82.5 |
| Birthplace               |       |                              |      |      |      |      |      |      |
| Jiangsu province         | 1819 (96.7) | 26.6                        | 29.5 | 35.4 | 43.5 | 57.1 | 76.9 | 95.0 |
| Other provinces          | 63 (3.3) | 26.0                        | 27.6 | 33.4 | 41.9 | 61.0 | 81.7 | 92.0 |
| Parity                   |       |                              |      |      |      |      |      |      |
| Nullipara                | 1777 (93.4) | 26.7                        | 29.5 | 35.6 | 43.8 | 57.4 | 77.7 | 95.3 |
| Multipara                | 126 (6.6) | 26.0                        | 29.0 | 33.4 | 39.8 | 51.4 | 62.9 | 85.7 |
| Menstrual cycle (day)    |       |                              |      |      |      |      |      |      |
| 21-                      | 1656 (88.0) | 26.5                        | 29.3 | 35.2 | 43.5 | 57.2 | 77.7 | 96.5 |
| 36-                      | 162 (8.6) | 26.6                        | 29.8 | 35.4 | 43.0 | 58.8 | 73.6 | 86.9 |
| Irregularity             | 64 (3.4) | 28.4                        | 30.8 | 36.9 | 43.5 | 52.8 | 66.8 | 79.4 |
| Abnormal pregnancy history |       |                              |      |      |      |      |      |      |
| No                       | 1578 (82.0) | 26.8                        | 29.5 | 35.2 | 43.4 | 56.8 | 77.0 | 95.3 |
| Yes                      | 346 (18.0) | 25.9                        | 29.2 | 35.2 | 43.6 | 57.6 | 76.9 | 91.0 |
| Sampling season          |       |                              |      |      |      |      |      |      |
| Spring                   | 553 (28.7) | 24.7                        | 26.7 | 32.7 | 40.8 | 53.2 | 67.8 | 83.8 |
| Summer                   | 632 (32.8) | 29.7                        | 32.0 | 37.1 | 46.0 | 59.6 | 79.8 | 95.6 |
| Autumn                   | 361 (18.8) | 28.4                        | 30.7 | 36.1 | 44.6 | 61.0 | 93.5 | 106.3 |
| Winter                   | 378 (19.6) | 26.3                        | 28.9 | 35.1 | 42.5 | 56.0 | 69.6 | 88.0 |

* P-values were determined by using the Kruskal-Wallis or Mann-Whitney test. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.

**Table 2.** Maternal characteristics and 25(OH)D serum concentrations between women with natural labor and cesarean section

| Maternal characteristics | Natural labor (n = 1006) | Cesarean section (n = 823) | P * |
|--------------------------|--------------------------|----------------------------|-----|
| Maternal age (years) a   | 28.9 ± 3.0               | 30.2 ± 3.8                 | < 0.001 |
| Intrapartum BMI (kg/m²) b | 26.3 ± 3.1               | 27.9 ± 3.6                 | < 0.001 |
| Birthplace of Jiangsu Province [n (%)] | 1024 (96.6) | 795 (96.7) | 0.894 |
| Nullipara [n (%)]        | 1013 (94.3)              | 764 (92.2)                 | 0.060 |
| Menarche age a           | 13.6 ± 1.1               | 13.6 ± 1.3                 | 0.283 |
| Irregular menstrual cycle [n (%)] | 31 (2.9)   | 33 (4.0)                  | 0.196 |
| Having abnormal pregnancy history [n (%)] | 145 (13.2) | 201 (24.2) | < 0.001 |
| Sampling in summer and autumn [n (%)] | 577 (52.7) | 416 (50.2) | 0.275 |
| 25(OH)D (nmol/L) c       | 43.0 (35.2, 57.4)        | 43.4 (35.3, 56.4)          | 0.950 |
| 25(OH)D [n (%)] < 25.0 nmol/L | 29 (2.6)          | 24 (2.9)                  | 0.542 |
| 25.0-37.4 nmol/L         | 330 (30.1)              | 237 (28.6)                 |       |
| 37.5-49.9 nmol/L         | 338 (30.9)              | 267 (32.2)                 |       |
| 50.0-74.9 nmol/L         | 271 (24.7)              | 221 (26.7)                 |       |
| >75 nmol/L               | 127 (11.6)              | 80 (9.7)                   |       |

* Means: SD; † P-values were determined by using t test, χ² test or Mann-Whitney test; ‡ Median (IQR). Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.
Discussion

Pregnancy is a special stage in the life of women. Their hormone levels and metabolic conditions change and the required nutrients increase significantly. So, in this period, women are prone to vitamin D deficiency. The requirement for vitamin D during pregnancy will increase by 4-5 times to meet the needs of fetal bone growth and extra calcium [17]. Therefore, the lack of vitamin D was prevalent in the world. Shand et al. had completed a prospective cohort study of 221 women in early pregnancy, and they found 75% of pregnant women with vitamin D insufficiency, 53% of pregnant women with vitamin D deficiency, and serum vitamin D levels were significantly lower in Asian women than in Caucasians [18]. Schneuer et al. examined serum 25(OH)D in 5109 Australia women in the first trimester. They reported the median 25(OH)D concentrations was 56.4 nmol/L, and the serum 25(OH)D concentrations showed significant variation by parity, smoking, weight, sampling season, country of birth, and socioeconomic status [16]. Recently, in a Belgium nationwide survey, 1311 pregnant women were collected from 55 obstetric clinics, and 74.1% of them were found to be in a status of vitamin D deficiency [19]. At present, the status of vitamin D deficiency in China is also very serious. Song et al. conducted an investigation involving 125 pregnant women in Beijing, and showed 96.8% of pregnant women with vitamin D deficiency, and about half of them with severe lack of vitamin D [25(OH)D] < 25 nmol/L [20]. In our study, only 10.8% of pregnant women were in a status of adequate vitamin D, about 89.2% of pregnant women were in a status of vitamin D deficiency, and 2.8% of the subjects were severely deficient. Thus, the status of serum vitamin D during pregnancy is not optimistic. Since the vitamin D levels
during pregnancy are closely related with a series of adverse pregnancy outcomes, the medical workers and pregnant women should pay enough attention to the vitamin D levels.

The constantly improvement of urbanization and modernization resulted in the air pollution, outdoor activities reduction, and the use of anti-ultraviolet products, all of which could lead to insufficient sunshine [21]. Thus, the rate of vitamin D deficiency was significantly increased, especially in pregnant women. This study showed that the serum 25(OH)D concentrations also have significant variation by sampling seasons. It is relatively high in summer and autumn, and relatively low in spring and winter, which further validated that the vitamin D concentrations was closely associated with the sunlight exposure. In addition, our study found that serum 25(OH)D concentrations were relatively low in pregnant women with intrapartum BMI ≥ 30 kg/m². Vitamin D is lipid soluble vitamin, so it is easy to be absorbed by adipocytes and stored in adipose tissue, which may affect the vitamin D biological effect. Therefore, obesity can also cause blood 25(OH)D concentrations decreased. With the improvement of living standards, the obese population continues to expand, especially for the pregnant women with over-nutrition, which may also lead to vitamin D deficiency in pregnant women.

In this study, the cesarean section rate was relatively high in pregnant women who were older, who have higher intrapartum BMI, or who have an abnormal pregnancy history, suggesting advanced maternal age, high BMI, adverse pregnancy history may be the risk factors of cesarean section. Compared with 25(OH)D from 50.0 to 74.9 nmol/L, women with low 25(OH)D concentrations (< 50.0 nmol/L) was not significantly associated with cesarean section. Only in the subgroup of the women without abnormal pregnancy history, higher 25(OH)D concentrations (> 75.0 nmol/L) could significantly decrease the risk of cesarean section. And after adjusting for confounding factors, a borderline significant protective effect was observed for higher 25(OH)D. In total, the serum 25(OH)D concentrations may not be related with cesarean section. Further studies with large sample size in diverse populations are warranted to validate the association between maternal vitamin D levels and the subsequent delivery mode.

Abbreviations

25(OH)D: 25-Hydroxyvitamin D; ELISA: enzymelinked immunosorbent assay; ORs: odds ratios; CIs: confidence interval; BMI: body mass index.

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Competing Interests

The authors have declared that no competing interest exists.

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