Is low vitamin D status in pregnancy associated with adverse outcomes? :a prospective cohort study

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Abstract

Objectives: The relative contributions of vitamin D status to pregnancy complications are not fully understood. We investigated the correlation between vitamin D status and pregnancy outcomes. Design: Prospective analysis of cases Setting: China Population or Sample: A total of 1766 pregnant women admitted to The Eighth Affiliated Hospital, Sun Yat-sen University and Guangdong Women and Children Hospital between January 2019 and December 2020. Methods: This prospective cohort study was performed on women who paid antennal visits during their whole gestation. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured among women before 24 weeks of gestation. Associations between maternal vitamin D status, maternal characteristics, and pregnancy outcomes were assessed. The adjusted odds ratio (OR) for adverse pregnancy outcomes was calculated using the logistic regression analysis. Results: Among all the participants ,192(10.87%), 1023(57.93%) and 551(31.20%) were defined as vitamin D sufficiency, insufficiency, and deficiency, respectively. There was no significant difference in vitamin D between pregnant women with adverse pregnancy outcomes and those without adverse pregnancy outcome. Neither vitamin D deficiency nor insufficiency was associated with adverse pregnancy outcomes compared with vitamin D sufficiency. Risks of adverse outcomes were as follows: GDM (OR=0.72 95%CI 0.46-1.14; OR=0.86 95%CI 0.57-1.30), SGA (OR=1.38 95%CI 0.73-2.60; OR=1.28 95%CI 0.70-2.34), early preterm delivery (OR=0.59 95%CI 0.13-2.70; OR=0.84 95%CI 0.23-3.00), PE (OR=3.44 95%CI 0.43-27.52; OR=2.40 95%CI 0.31-18.50), and postpartum hemorrhage (OR=0.58 95%CI 0.33-1.03; OR=0.81 95%CI 0.49-1.35). Conclusions: Low vitamin D status may not be associated with adverse pregnancy outcomes. Vitamin D screening in all pregnant women seems not reasonable.

Is low vitamin D status in pregnancy associated with adverse outcomes? :a prospective cohort study

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Running title:Low Vitamin D Status and Pregnancy Outcomes

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Keywords: Vitamin D;gestational diabetes mellitus; small for gestational age; preterm delivery; 25-hydroxyvitamin D; pregnancy

Tweetable abstract: A prospective analysis describes the correlation between serum 25-hydroxyvitamin D during pregnancy and pregnancy outcomes.

【Introduction】

Vitamin D is an essential nutritional factor, which has received increasing attention in recent years, due to its primary role in bone remodeling, calcium homeostasis, and muscle functioning[1].During pregnancy, vitamin D plays an important role in maternal metabolism and embryogenesis, especially fetal skeletal development and calcium homeostasis[2]. Vitamin D deficiency means that the serum levels of vitamin D are inadequate to support the daily body needs[3]. Numerous clinical studies have reported that large proportions of global populations are vitamin D "deficiency ", including pregnant women[1, 4, 5].Some researches have also concluded many adverse effects of maternal vitamin D deficiency[6-8]. Animal experiments showed that vitamin D deficiency during pregnancy could lead to reproductive dysfunction and neurobehavioral developmental disorders in adult offspring[9].

Vitamin D level is commonly assessed by the measurement of 25-hydroxyvitamin D[25(OH)D] level, which is considered the best marker of vitamin D status. According to the recommendation and consensus of the Committee of the Institute of Medicine (IOM, USA), most experts agree to define vitamin D insufficiency as 25(OH)D between 30-49.9nmol/L, and 25(OH)D levels of <30nmol/L are considered to be indicative of vitamin D deficiency[10]. This array of values is for everyone: child or adult, pregnant or not,because vitamin D metabolism is markedly different during pregnancy compared to non-pregnancy, significant changes in calcium and vitamin D metabolism occur during pregnancy to meet the needs of growing fetuses[11]. Unfortunately, it is unclear whether the recommended 25(OH)D levels discussed above are suitable for pregnant women. In fact, vitamin D insufficiency and deficiency are very common in pregnant women and the newborns population, almost one in three newborns or one in five pregnant women were found below 25nmol/L[7]. However, it is still controversial whether vitamin D "deficiency" or "insufficiency" as defined by the IOM criteria is really related to adverse pregnant outcomes.

In this prospective study of two tertiary hospitals in South China, our aim was to investigate the association between vitamin D status before 24 gestational weeks and adverse pregnancy outcomes that were mainly reported recent years[12] [gestational diabetes mellitus (GDM), small for gestational age (SGA), early preterm delivery (preterm delivery before 34 weeks), preeclampsia (PE), and postpartum hemorrhage].

【Materials and methods】

Study population

We conducted a prospective cohort study in the Department of Obstetrics of The Eighth Affiliated Hospital, Sun Yat-sen University and Guangdong Women and Children Hospital between January 2019 and December 2020. The study design was approved by the local Ethical and Research Committees of the two hospitals. Pregnant women were recruited before 24 weeks of gestation. For most women, the expected delivery date was based on the last menstrual period date, while for a small proportion, this estimate was updated following an ultrasound scan. Those pregnant women would not be enrolled if they had any of the following exclusion criteria: multiple pregnancy, ischemic heart disease, stroke, peripheral vascular disease, diagnosis of diabetes or/and hypertension before the current pregnancy. In addition, the individuals who had a normal diet were selected; vegetarians and malnourished were excluded. Every participant gave full and informed consent to participate in the study. Initially, 1924 women were enrolled in the study. Figure 1 showed the filtering and processing flow chart of the study population. 9 women dropped out midway, 139 women were subsequently excluded because they were discovered to have exclusion criteria or had no blood sample to measure serum 25(OH) D concentrations, 2 women were excluded for implausible information, 8 women did not consent to use of outcome data. Finally, there are 1766 women with available data for analysis. Personal medical histories were self-identified by the participants.

Vitamin D assessment

All women participated in the study provided blood samples before 24 weeks of gestation to measure their 25(OH)D concentrations. Information was recorded on gestational age. A 200 μL blood sample was collected for each participant and placed directly into a 0.5 mL microtube after collection. Within 10 min of collection, samples were centrifuged at 3500 rpm for 15 min at 4 °C, and serum samples were taken after centrifugation and stored at -80 °C until assayed. Serum 25(OH)D concentration of each participant was measure using liquid chromatography tandem mass spectrometry (LC-MS/MS, Mass spectrometer SCIEX4500MD) by the central laboratory of Guangzhou Golden Mile center.

Adverse pregnancy outcomes

All women were under carefully medical surveillance. Once complications occurred, they would receive treatments and the pregnancy outcomes would be followed up until after delivery. The adverse pregnancy outcomes were described as follows: PE was defined as new onset of hypertension (systolic blood pressure [?] 140mmHg, diastolic blood pressure [?]90mmHg on at least two measurements 4 hours apart in a previously normotensive woman), with one of the following at or after 20 weeks of gestation:1. Proteinuria (primarily defined as a

protein concentration of [?]0.3g in 24 hours; i.e. [?]30 mg/mol protein: creatinine ratio; or[?]2 + dipstick);2. Evidence of other maternal organ dysfunction; liver involvement with or without right upper quadrant or epigastric abdominal pain, neurological complications; or hematological complications; or 3.uteroplacental dysfunction[13]. GDM was diagnosed after all women underwent a 75-g oral glucose tolerance test between 24 and 28 weeks of pregnancy, we also applied IADPSG criteria (one or more fasting, 1-h, or 2-h plasma glucose concentrations equal to or greater than threshold values of 5.1, 10.0, or 8.5 mmol/L, respectively) to diagnose GDM[14]. Early Preterm delivery, defined by a gestational age before 34 weeks. A newborn was considered SGA when was smaller than the estimated 10^{th} percentile for the baby's gender and gestational age[15]. Postpartum hemorrhage was defined as blood loss [?]500ml after vaginal delivery or [?]1000ml after cesarean delivery[16].

Statistical analysis

The data on continuous variables with normal distribution were presented as means and standard deviations (SD). The concentration of 25(OH)D was described as a continuous variable and categorized following the standard of the Committee of the IOM (sufficient: [?]50nmol/L; insufficiency:30-49.9nmol/L; deficiency:<30nmol/L). According to the scientific literature and biological plausibility, we selected co-variables as possible confounders of the association between vitamin D concentrations and adverse pregnancy outcomes we studied, including maternal age and parity, since these were hypothesized to be strongly related to vitamin D status[17].Association between 25(OH)D levels and adverse pregnancy outcomes was assessed by logistic regressions including these potential confounders. Logistic regression was also used to estimate adjusted odds ratios (OR) for adverse pregnancy outcomes during the groups. All of the OR were presented with 95% confidence intervals (CIs). SPSS (version 22.0; IBM Corp, Armonk, NY) was used for all of the calculations. In addition, Women with one or more of the adverse pregnancy outcomes were defined as "women with adverse pregnancy outcome group", and the others were defined as "women without adverse pregnancy outcome group". The figure 2 was done using Graphpad Prism Version 9.00 software. Plot the frequency distribution of vitamin D concentrations as a statistical graph, followed by a Gaussian fit.

【Results】

Maternal characteristics of the study population

Maternal characteristics of the study population and the means of maternal 25(OH)D concentrations before 24 weeks of gestation are showed in table 1. The pregnant women who participated in this study presented mean of 29.53±4.49 years old. Mean 25(OH)D concentrations was 36.85±14.23nmol/L(range from 3-174.3nmol/L). Mean gestational weeks at blood collection was 17.87±3.27 weeks. Among all of the participants, 192(10.87%), 1023(57.93%) and 551(31.20%) were defined as vitamin D sufficiency, insufficiency, and deficiency, respectively. Figure 2 shows the distributions of vitamin D concentrations in all participants, there was no significant difference in serum 25(OH)D concentrations between the adverse pregnancy outcomes group and the non-adverse pregnancy outcomes group (P>0.05). Notably,there were 89.13% pregnant women in low vitamin D status.

Influence of maternal characteristics on gestational serum 25(OH)D concentration

The maternal characteristics that affect the status of vitamin D were analyzed. Compared with young women, serum 25(OH)D concentration was higher in advanced women(39.09+-15.55nmol/L vs 36.46+-13.96nmol/L, P=0.006). While compared with nulliparous, serum 25(OH)D concentration was higher in multiparous(37.78+-13.60nmol/L vs 36.16+-14.65nmol/L,P=0.018).

Correlation between Vitamin D status and adverse pregnancy outcomes concerned:

The five primary outcomes we studied were PE, GDM, early preterm delivery, SGA and postpartum hemorrhage. In the crude model, risks of adverse pregnancy outcomes in vitamin D deficiency or insufficiency were not different form that in vitamin D sufficiency. After the adjustment for potential confounding factors (age and parity), there is no significant difference in outcomes either. (Table 2).

【Discussion】

Low vitamin D status is a global epidemic affecting people of all ages. It has attracted scholars to great interest in recent years. Although vitamin D is important for musculoskeletal health, increasing data suggest that vitamin D may also be important for fertility and pregnancy outcomes[18]. The number of research on the pleiotropic effects of vitamin D in pregnancy and the impact of low vitamin D status on maternal and infant outcomes has been expanding.

The main role of vitamin D during pregnancy is to promote calcium absorption and placental calcium transport. Existing evidence on maternal 25(OH)D concentrations during pregnancy is inconsistent, possibly due to small study samples, lack of adjustment for seasonal, or ethnic variation and cross-sectional design[11].Some studies suggest that women are more likely to suffer from vitamin D deficiency or insufficiency during pregnancy and with a gradual decrease in the total amount of 25(OH)D from the first trimester to term[19] because the change of their hormone and metabolic conditions and the required nutrients increase significantly[20]. A meta-analysis carried out by Papapetrou, P. D.[21] reported no difference in the concentrations of 25(OH)D before, either during or after pregnancy. It's unclear whether low vitamin D status is more frequent in pregnant women when compared to same-aged non-pregnant women. Therefore, pregnancy may not be a cause of low vitamin D status compared to non-pregnancy.

Risk factors associated with low vitamin D status delineated by several studies are: inadequate sun explore, low ambient UVR level, physical inactivity, low dietary vitamin D intake, no or low vitamin D supplementation and medication[22]. Moreover, variations in skin color, social and cultural habits concerning sun seeking behavior, diet, and other factors are evident. However, there is no authoritative criteria for appropriate vitamin D status in pregnancy. Different criteria have been used for diagnosing vitamin D deficiency, but mostly referring to 50nmol/L and 75nmol/L. A high prevalence of vitamin D deficiency up to 62.34% was reported in South China[23]. Recent evidence showed that pregnant women in Shanghai are generally deficient in vitamin D, the result suggest that 72.5% of the participants were vitamin D deficient[24]. At present, the classification standard for the determination of serum 25(OH)D concentration recommended by the IOM is still an indicator commonly used internationally to categorize the vitamin D status in adults. A large number of studies[6, 11, 25, 26]published in recent years emphasize the relationship between low vitamin D status and several adverse pregnancy outcomes such as PE, GDM, preterm birth, etc according to IOM standard. Rostami et al[27] infer the ideal level of vitamin D during pregnancy based on pregnancy outcomes, they recommend a cutoff of 25(OH)D >37.5 nmol/L for the prevention of adverse pregnancy outcomes. In this study, vitamin D levels were measured in Asian pregnant women in South China on a normal diet during pregnancy. In contrast to many conclusions based on White British women and Pakistani women[28], the study found no significant association between low vitamin D status and adverse pregnancy outcomes. The reasons may be as follows: 1) The current vitamin D assessment is based on the upper limit of vitamin D level that satisfies 97.5% of the population to maintain normal bone health, instead of the "cut-off values" based on pregnancy outcomes. 2)The efficiency of vitamin D utilization was variable among people with different skin colors[11],3)Low vitamin D might affect pregnancy in long term after delivery, consequently, women's long-term outcomes and the development of children should be given as much attention as the adverse outcomes associated with vitamin D during pregnancy. These speculations still need to be confirmed by more studies.

At present, vitamin D screening during pregnancy has been more and more used as a routine antenatal examination, which leads to additional vitamin D supplements distribution to pregnant women with low vitamin D status. In fact, studies on the association of vitamin D and pregnancy outcomes have not reached agreement. A mendelian randomization study found no strong evidence to support an effect of vitamin D status on pregnancy related hypertensive disorders[29]. Observational studies had also not found that low vitamin D levels are associated with postpartum hemorrhage, and showed an inverse relationship between vitamin D status and the occurrence of postpartum hemorrhage which remains unexplained [18, 25]. Agarwal, S et al[2] reviewed plenty observational and interventional studies, and they found that the role of vitamin D in GDM remains inconclusive, this critical review showed that several observational studies reported an inverse

relationship between vitamin D status in early pregnancy and the risk of GDM, conversely, there were also multiple studies failed to determine the role of vitamin D in the prevention of GDM. Large-scale prospective studies are still needed to assess the role of vitamin D in GDM. This prospective study demonstrated that low vitamin D status is not associated with adverse pregnancy outcomes, which was different from other researches[8, 30, 31].In other words, is low vitamin D status in pregnant women really matters, should we give positive medical intervention remains uncertain and requires further confirmation. Most experts agree that broad-based screening of serum 25(OH)D levels in the general population or during pregnancy is unnecessary[32]. In addition, the issue of vitamin D supplementation during pregnancy still needs to be further explored. Some high quality RCT studies have failed to prove that vitamin D supplementation during pregnancy can reduce pregnancy complications and is beneficial to the development of fetus[33-35]. In France and in Belgium, women are not routinely supplemented with vitamin D before pregnancy[17]. A review also questioned whether vitamin D supplementation improved outcomes in osteoporosis prevention[36]. Researches concludes that different populations in different regions have not been unified, neither RCTs nor observational trials have demonstrated that serum vitamin D levels are associated with pregnancy outcomes, nor have vitamin D supplementation improved pregnancy outcomes. This is because, on the one hand, vitamin D "deficiency" or "insufficiency" diagnosed by the IOM criteria is not necessarily applicable to all populations in all regions of the world, and on the other hand, low vitamin D status may not be correlated with most adverse outcomes.

It is important to clarify the meaning of IOM reference values for vitamin D, as they are related to both human health and clinical consideration. In fact, the use of "50nmol/L" and "30nmol/L" as a cut-off value is based on misinterpretation and misapplication of the IOM vitamin D reference values. The IOM developed these reference values, referred to as Dietary Reference Intakes (DRIs), for a range of nutrients. That is, the cause relationship of vitamin D and musculoskeletal health outcomes was used to inform dietary vitamin D requirements. Central to the DRI concept is the biologic reality that the requirements for any nutrient vary from person to person, and are usually normally distributed across the population. However, the exact nutritional requirements of an individual cannot be known. A common misconception is that the RDA functions as a "cut point" and that almost the entire population must have a serum 25(OH)D level above 50nmol/L to achieve good bone health[32]. Note that the values assume minimal to no sun. Vitamin D levels largely depend on exposure to the sun and are influenced by nutritional habits at only a minimal level[11].The reality is that most (about 97.5%) of the population has a requirement of vitamin D 50nmol/L or less[32]. Diagnosis of vitamin D "deficiency" or "insufficiency" itself presents a challenge due to the "diagnostic threshold" of vitamin D status in pregnancy cannot be equated with "nutrient supply". A systematic review and meta-analysis published recent years [33] showed that, neither intermittent nor daily standard doses of vitamin D alone were associated with reduced risk of fracture. Excessive concern about vitamin D "deficiency" or "insufficiency" can adversely affect patient care, including unnecessary vitamin D screening and supplementation, as well as rising health care costs.

Low vitamin D status may not relate to adverse pregnancy outcomes. However, the results bias caused by research samples cannot be ruled out. The etiology of various maternal and infant outcomes is complex and multifactorial, with many confounding factors. Determining the relationship of vitamin D levels during pregnancy requires further evaluation through large, multicenter, randomized controlled clinical trials focusing on specific adverse pregnancy outcomes.

【Conclusion】

Our finding shows that vitamin D "deficiency" and "insufficiency" during pregnancy diagnosed according to the existing "50 nmol/L" and "30nmol/L" are not associated with adverse pregnancy outcomes we concerned. Moreover, there is no larger population study to prove that higher levels of vitamin D in pregnancy can lead to better outcomes.

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Author contributions

JYS wrote the manuscript and researched data, XXY contributed significantly to analyze the data and written the discussion. QL reviewed and edited the manuscript, LW, PPH, HH and XHL collected data, QL and JYW supervised and guided the whole study. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Details of ethics approval

The study was approved by the research ethics committee at the Guangdong Women and Children Hospital (201901031) and the Eighth Affiliated Hospital of Sun Yat-sen University (2020-034-02).

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