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Vitamin D and Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus (GDM) complicates 7–14% of pregnancies in the United States. Vitamin D deficiency also is common in pregnancy. Emerging evidence suggests that Vitamin D administration can improve insulin sensitivity and glucose tolerance, but whether vitamin D supplementation can prevent GDM is unknown. Observational studies provide conflicting evidence as to whether low serum 25-hydroxyvitmain D (25(OH)D) levels are associated with GDM. Two recent systematic reviews concluded that vitamin D deficiency is associated with a higher risk of GDM. However, these reviews are limited by the observational and diverse nature of the included studies. Of greatest concern is the inability to understand how important confounding variables such as race/ethnicity and adiposity might affect the association. Randomized controlled trial data remain limited but are critical to understanding whether supplementation with vitamin D beyond what is contained in routine prenatal vitamins will prevent GDM or improve glucose tolerance for women with GDM.

Keywords

Vitamin D; 25-hydroxyvitamin D; pregnancy; gestational diabetes mellitus; GDM; gestational diabetes

Introduction

Immense interest persists in vitamin D and its potential effects on several pregnancy outcomes including fetal growth, hypertensive disorders and gestational diabetes mellitus (GDM). Two factors make vitamin D intriguing to perinatal investigators studying GDM. First, vitamin D has been shown to improve pancreatic exocrine function and insulin sensitivity in animal models. Second, vitamin D status, like most micronutrients, is easily modified by dietary supplementation. If shown to prevent or improve outcomes of

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Compliance with Ethics Guidelines
Conflict of Interest
Heather H. Burris and Carlos A. Camargo, Jr. declare that they have no conflict of interest.

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pregnancies complicated by GDM, vitamin D intake could be titrated to achieve optimal serum 25-hydroxyvitamin D (25(OH)D) levels.

To date, the literature does not support routine high-dose vitamin D supplementation during pregnancy for either the prevention or the treatment of GDM. In this review, we will briefly describe the metabolic functions of vitamin D and the epidemiology of GDM. We will present the most recent observational studies linking vitamin D to GDM, including results from systematic reviews and meta-analyses, and results from the few interventional trials to date. We will highlight the challenges faced when reading these diverse studies and propose a future research agenda to investigate whether GDM or its complications could be either prevented or mitigated by optimal vitamin D status.

Vitamin D

Vitamin D, also known as calciferol, includes two major, functionally identical forms, vitamin D2 (ergocalciferol) which is synthesized and added to foods and supplements, and vitamin D3 (cholecalciferol) which is present in animal-based foods and made by human skin through a sunlight-induced conversion of 7-dehydrocholesterol [1]. Both forms are prohormones, and inactive until hydroxylated twice: first in the liver to form 25-hydroxyvitamin D (25[OH]D), and then again in the kidney to form the biologically active hormone, calcitriol (1,25-dihydroxyvitamin D). The major circulating form of vitamin D is 25(OH)D which is bound in plasma to vitamin D binding protein (DBP) and albumin, and is the best available marker of overall vitamin D status. Calcitriol synthesis in the kidney is tightly regulated by parathyroid hormone. Calcitriol regulates gene expression by affecting gene transcription through interaction with a nuclear vitamin D receptor (VDR). The traditional role of calcitriol is to regulate serum calcium and phosphate homeostasis and thus maintain bone health.

However, VDRs are found in tissues that are not directly involved in calcium or phosphate metabolism suggesting that calcitriol might have functions beyond its traditional role in bone health [1]. Vitamin D-responsive elements (VDRE) are present in several human genes involved in cell differentiation and proliferation and thus vitamin D has been studied as a potential therapeutic or preventative candidate for cancer [2] and autoimmune diseases including type 1 diabetes mellitus [3]. In rodent models, calcitriol has been shown to have effects on the synthesis, secretion and actions of insulin [4, 5], leading to several human observational and interventional studies of vitamin D and type 2 diabetes mellitus, a few of which have shown a potential benefit of vitamin D supplementation or optimal 25(OH)D levels on type 2 diabetes [6]. Such studies have prompted a growing number of studies on the relationship between vitamin D status and GDM.

Gestational Diabetes Mellitus (GDM)

The increasing rates of overweight and obesity in the general population are undoubtedly contributing to the ongoing rise in the prevalence of GDM [7], which now complicates approximately 7–14% of pregnancies in the United States [8, 9]. GDM places both mothers and their infants at risk for adverse health consequences [10]. Women with GDM are more likely to undergo cesarean section and later develop type 2 diabetes mellitus. Infants of diabetic mothers are more likely to have congenital anomalies, macrosomia, birth trauma, respiratory distress syndrome, jaundice and hypoglycemia. While several GDM risk factors have been identified [11] – including advanced maternal age, obesity, family history of diabetes and ethnicity [12] – how these risk factors predispose women to GDM remains an active area of scientific inquiry [13]. In recent years, vitamin D deficiency has been increasingly recognized as one potential contributor [14]. While epidemiologic studies have shown a fairly consistent link between vitamin D deficiency and a higher risk of type 2

diabetes [6, 15], and obesity is strongly associated with both GDM [16, 17] and vitamin D deficiency [2, 18, 19], it remains unclear whether vitamin D deficiency contributes to a mother's risk of developing GDM.

Observational studies of vitamin D and GDM

Several, but not all, observational studies have found an association between low 25(OH)D level and increased risk of GDM. In a matched, case-control study of 54 Iranian women with GDM and 11 normoglycemic controls, Soheilykhah et al. found that maternal 25(OH)D concentrations at 24–28 weeks of gestation were significantly lower in women with GDM [20]. They noted that 83% of GDM women had 25(OH)D levels <50 nmol/L (a cutoff often used to define vitamin D deficiency [21–24]) vs. 71% of controls. Clifton-Bligh and colleague studied 264 women in Australia and found that among the 32% with GDM, 25(OH)D levels were significantly lower compared to normoglycemic women [25]. In another study of Iranian women at high risk for vitamin D deficiency, Hossein-Nezhad and colleagues found that 29% of 741 women had 25(OH)D levels <15 nmol/L and the prevalence of GDM in this subgroup was higher compared to women with 25(OH)D levels ≥35 nmol/L [26]. Likewise, Zhang et al. found in a nested case-control study in the United States (Washington) of 57 cases of GDM, that maternal 25(OH)D levels at 16 weeks' gestation were 20% lower among women who later developed GDM [27].

However, other studies have not detected a statistically significant association between 25(OH)D level and GDM. Farrant et al studied 559 pregnant women in India and found no association between second trimester 25(OH)D levels and GDM [28]. Likewise, Makgoba and colleagues studied 90 cases of GDM and 158 controls in the United Kingdom and reported no association between first trimester blood samples and subsequent development of GDM [29]. Baker and colleagues conducted a nested case-control study in the United States (North Carolina) using routine first trimester serum aneuploidy screening blood samples, and in their comparison of 60 women who later developed GDM and 120 controls who did not, the investigators found no association between 25(OH)D level and the odds of GDM.

In addition to skin pigmentation and sun exposure, adiposity and diet can be important determinants of vitamin D status. Physical activity can contribute to sun exposure and reduced adiposity, as well as potentially a decreased risk of GDM. Because none of the above studies adjusted for physical activity or dietary factors, we analyzed data from a pregnancy cohort in Massachusetts that included such variables [30]. Among 1314 pregnant women undergoing routine glucose tolerance screening during pregnancy, we found that women with 25(OH)D levels <25 nmol/L (vs. higher) had higher odds of GDM (OR 3.1, 95% CI 1.3, 7.4) but that this association was attenuated by adjustment for prepregnancy body mass index (OR 2.3, 95% CI 0.9, 5.7). Further adjustment for physical activity and dietary intakes of fish and calcium did not substantially change the estimate, which remained elevated but was statistically non-significant (OR 2.2, 95% CI 0.8, 5.5).

Recent systematic reviews (including meta-analyses) have examined the published literature. Wei and colleagues included 12 studies with 5615 participants and concluded that among women with 25(OH)D levels <50 nmol/L there is a modest increase in odds of GDM (crude OR 1.38, 95% CI 1.12, 1.70) [31] (Figure 1). Similarly, Aghajafari and colleagues concluded that 25(OH)D levels <75 nmol/L were associated with increased odds of GDM (OR 1.49 (95% confidence interval 1.18 to 1.88) based on a meta-analysis of 10 studies [32]. However, the quality of these meta-analyses is limited by the observational nature of the included studies, the mixing of diverse study populations from various regions, and the different laboratory techniques and timing of measurement of serum 25(OH)D level.

However, of greatest concern is the inability to understand how important confounding variables such as race/ethnicity and adiposity might change the effect estimates.

Trials of Vitamin D in Pregnancy

While there are several ongoing randomized controlled trials (RCT) of vitamin D supplementation in pregnancy [33], few are targeted at treatment of GDM and none is testing prevention of GDM. In our search of the scientific literature, we located just one trial of vitamin D supplementation and GDM. Rudnicki and Mølsted-Pedersen enrolled 12 nulliparous women in Denmark with abnormal glucose tolerance tests, defined as two or more serum glucose measurements 3 SD above the mean [34]. Women underwent a fasting, oral glucose tolerance (OGTT) with 75 g of glucose. Each subject continued their normal diets over the following two days after which they underwent a second OGTT. Two hours before this second test, subjects received 2μg/m^2 of 1,25-dihydroxyvitamin D_3 (Etalpha) intravenously. For the next two weeks they received a daily dose of 0.25 μg Etalpha orally and then underwent a third OGTT. Glucose and insulin measurement were obtained before each OGTT and at 30 minute increments for 3 hours afterward. Only IV (not oral) vitamin D administration lowered serum glucose levels compared to baseline, from 5.6 to 4.8 mmol/L ($P<0.01$). Post OGTT insulin levels were significantly lower ($P<0.05$) (compared to baseline) after IV vitamin D administration. With oral administration insulin levels were lower but this difference did not reach statistical significance ($P=0.13$). Nonetheless, lower insulin levels suggest that the mechanism of improved glucose tolerance was not from increased insulin production but potentially increased insulin sensitivity.

In our searches, we did note one other RCT of likely relevance to the relationship between vitamin D and GDM. Soheilykhah and colleagues recently published a data on various vitamin D supplementation regimens and measures of insulin resistance in pregnant, non-diabetic women, [35]. The investigators enrolled 120 pregnant, non-insulin-requiring women in Iran during the women's first trimester of pregnancy and obtained fasting blood glucose, insulin levels and 25(OH)D levels. Women were then randomized to one of three Vitamin D groups: 200 IU daily, 2000 IU daily, or 4000 IU daily. At the end of pregnancy, fasting blood samples were again obtained for blood glucose, insulin and 25(OH)D levels. The authors demonstrated dose-response relationships for two of the three measures. Specifically, in the highest supplemented groups, 25(OH)D levels rose the most and insulin levels rose the least (Table 1). Fasting glucose levels in these non-diabetic women were unchanged. The HOMA-IR (the product of glucose and insulin levels and a measurement of insulin resistance) was lower (better) in the highest supplemented group compared to lowest supplemented group (2.2 vs. 3.0, respectively). Calcium levels were similar across treatment groups. Although this study included non-diabetic women and thus may not be generalizable to women with GDM, it provides compelling evidence that supplementation with high doses of vitamin D may improve insulin sensitivity.

Challenges to Analyses of Vitamin D and Health

Studying vitamin D status and health outcomes attracts investigators from a variety of fields because of the widespread actions of vitamin D, the ubiquity of vitamin D receptors in the human body, and the fascinating epidemiology of vitamin D deficiency. Causal or not, vitamin D status tracks with several risk factors for poor health outcomes. Importantly, in the United States, low 25(OH)D levels are most prevalent in African Americans [36] and overweight/obese individuals [2, 18, 19]. Large disparities in health outcomes persist between black and white Americans and much interest persists in investigating the potential contribution of vitamin D deficiency to health outcomes that differ by race, including birth outcomes [37]. However, in the case of GDM, disparities are not exclusive to black-white

differences. Asian and Hispanic women have higher rates of GDM compared to white women [12], with smaller differences in vitamin D status compared to black-white vitamin D disparities [22]. In contrast, obesity is clearly both associated with vitamin D deficiency and with GDM [16, 17]. Whether suboptimal vitamin D status causes an increased risk in GDM remains unknown and may be difficult to tease out from risk factors that may act as effect measure modifiers and confounders. For example, whether vitamin D deficiency affects an obese woman's risk of GDM differently than a lean woman's risk of GDM remains unknown. Based on the very limited human trials of vitamin D supplementation during pregnancy, the vitamin D-induced increase in insulin sensitivity lends biologic plausibility to a threshold phenomenon. Further, regardless of whether optimal vitamin D status can prevent GDM, the limited trial data suggest that exploring an adjunctive role of vitamin D supplementation for women with established GDM may be fruitful. While additional observational studies on the topic are likely, the field needs well-designed RCTs to answer this and other important questions about the relationship between vitamin D and GDM.

Conclusion

The current body of literature examining the association between vitamin D status and GDM is largely comprised of conflicting observational studies. This work recently culminated in two well-done meta-analyses that presented evidence of a modest association between low 25(OH)D level and increased odds of GDM. However, whether vitamin D deficiency contributes to the pathophysiology of the development of GDM remains unknown. To our knowledge, no large randomized trial of various vitamin D doses in women either at high risk for developing GDM or with prior GDM has been published. The only RCTs available are promising but far from definitive, and RCTs are critical to demonstrating a protective effect of optimal vitamin D status with respect to the development or management of GDM.

Current recommendations from the American College of Obstetrics and Gynecology (ACOG) do not recommend routine screening for 25(OH)D level in pregnancy nor vitamin D supplementation beyond what is contained in a prenatal vitamin [38]. However, ACOG suggests that for women at high risk for vitamin D deficiency, screening may considered and if women are found to be deficient then supplementation with 1000–2000 IU is reasonable. ACOG does not specifically list GDM as being associated with vitamin D deficiency, but the scientific literature suggests that women with GDM are at higher risk than normoglycemic women of low 25(OH)D levels even if the causality of the vitamin D deficiency – GDM association is not yet clear. The next challenge for clinician researchers is to determining whether optimal vitamin D status can prevent GDM and whether vitamin D supplementation for diabetic women with vitamin D deficiency improves glucose tolerance, thus improving perinatal outcomes for mothers and their infants.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
GDM	gestational diabetes mellitus
DBP	vitamin D binding protein

VDR	vitamin D receptor
VDRE	vitamin D responsive elements
OGTT	oral glucose tolerance test
RCT	randomized controlled trial
HOMA-IR	homeostatic model assessment of insulin resistance
ACOG	American College of Obstetricians and Gynecologists

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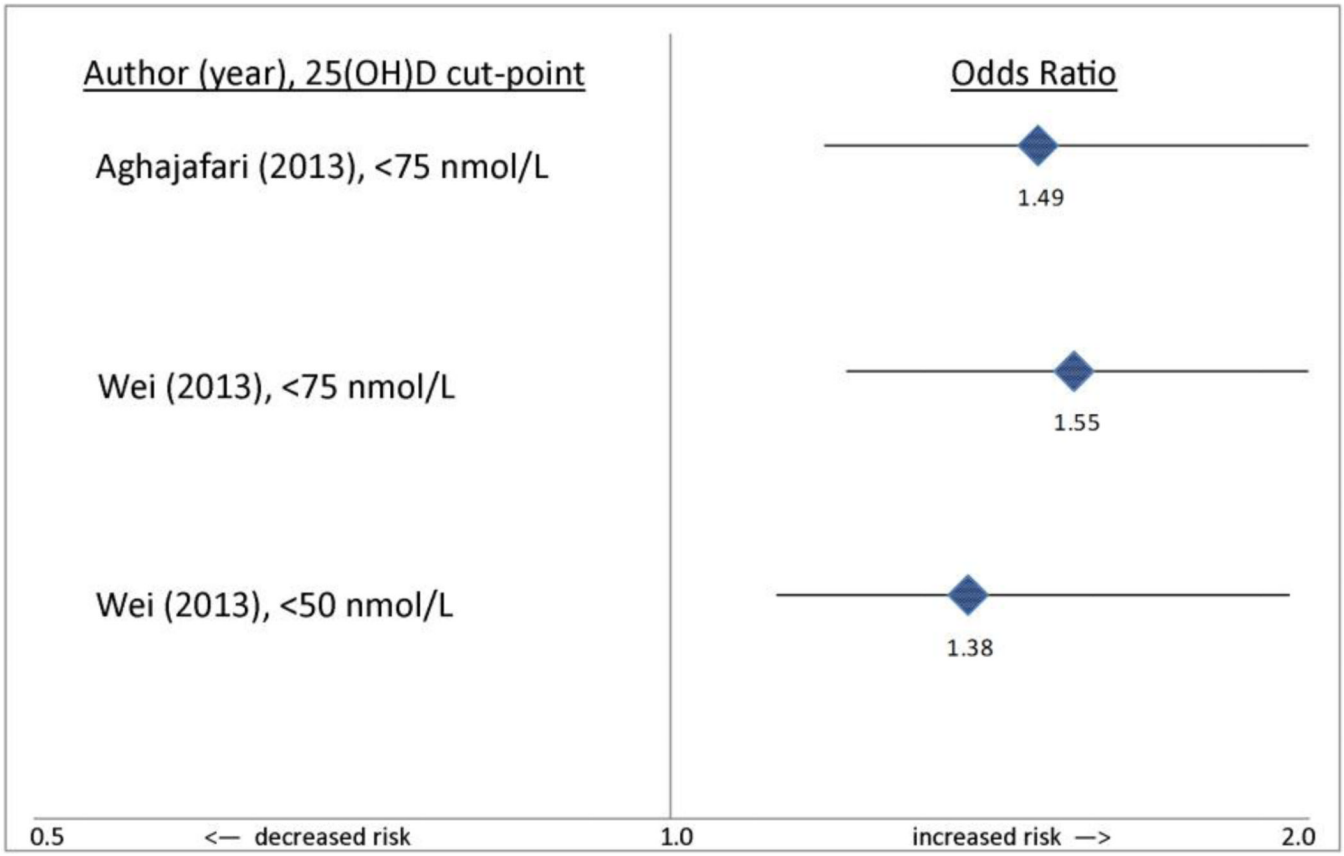

Figure 1.
Associations between 25-hydroxyvitamin D levels and odds of gestational diabetes mellitus, results from two systematic reviews/meta-analyses [31, 32]. (Created from odds ratio (95% confidence interval) published by Wei and colleagues [39] and Aghajafari and colleagues[32]; 25(OH)D denotes 25-hydroxyvitamin D.)

Table 1

First trimester and end of pregnancy plasma markers of vitamin D status and insulin resistance before and after daily oral vitamin D supplementation of 200 IU, 2000 IU, and 4000 IU

	200 IU/day n=35	2000 IU/day n=38	4000 IU/day n=40	*P*
25(OH)D level ng/ml				
Before	8.3	7.3	7.3	0.95
After	17.7	27.2	34.1	0.001
Insulin (IU/ml)				
Before	8.3	7.4	8.0	0.52
After	15.3	12.2	11.6	0.009
HOMA-IR				
Before	1.6	1.4	1.5	0.74
After	3.0	2.4	2.2	0.01
Fasting blood sugar (mg/dl)				
Before	76.6	78.8	78.0	0.23
After	77.6	79.0	76.0	0.04
Calcium				
Before	9.7	9.7	9.6	0.28
After	9.4	9.5	9.2	0.04

Results from a trial in Iran of 113 women by Soheilykhah and colleagues [35].

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HOMA-IR, homeostatic model assessment of insulin resistance.