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RESEARCH ARTICLE

# Association of Vitamin D and Glucose Tolerance and Adverse Pregnancy Outcomes in Pregnant Women

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## Abstract

**Background and Objective:** Vitamin D is linked to glucose metabolism, but its role in gestational diabetes is unclear. This study seeks to determine the effect of vitamin D status on glucose tolerance test results and adverse pregnancy outcomes in pregnant women.

**Methods:** A *post hoc* analysis of two vitamin D supplementation studies with a total of 546 pregnant women was conducted. Vitamin D status (25(OH)D) was determined by radioimmunoassay. Serum glucose concentrations were evaluated by a 2-step diagnostic screening for gestational diabetes with a cutoff for an abnormal 1-hour screen of 139 mg/dL and 2 abnormal values on a 3-hour oral glucose tolerance test. Adverse outcomes analyzed were preterm birth (<37 weeks), birth weight <1500 grams, macrosomia/large for gestational age (LGA), need for NICU admission, and non-repeat Caesarian section.

**Results:** Vitamin D deficiency (<20 ng/mL or 50nmol/L) and insufficiency (<30 ng/mL or 75 nmol/L) were associated with glucose tolerance test results >139 mg/dL when controlling for BMI >30 and ethnicity ($p<0.0001$). A screening glucose tolerance test result of >139 mg/dL was also significantly associated with non-repeat Cesarean section deliveries ($p=0.0308$).

**Discussion:** Vitamin D deficiency and insufficiency were associated with an increased risk of failing a screening glucose tolerance test during pregnancy, suggesting that vitamin D deficiency is a risk factor for glucose intolerance and potentially gestational diabetes.

**Keywords:** Gestational diabetes; Vitamin D; Glucose tolerance; Pregnancy

## Introduction

Vitamin D has traditionally been recognized as a key regulator of calcium and phosphorus metabolism, but recent studies suggest that the functions of vitamin D are broad and complex. One area of recent interest in vitamin D research is the effect of vitamin D on insulin resistance. There has been consistent evidence of a correlation between vitamin D deficiency and type 2 diabetes, suggesting hypovitaminosis D is a risk factor for dysfunctional glucose metabolism [1]. Furthermore, the vitamin D receptor has been found in tissues linked with the development of type 2 diabetes [2], including insulin secreting pancreatic B cells, multiple cells of the immune system [3], and the human insulin receptor gene [4].

There is similar evidence supporting an association between vitamin D deficiency and gestational diabetes, although the data are more sparse and controversial. Pregnancy is characterized by significant changes in glucose metabolism. In a normal pregnancy, insulin sensitivity begins to fall at the end of the first trimester and can be reduced by up to 56% by the end of the third trimester [5] as plasma concentrations of pregnancy-related hormones increase. Normally, the pancreatic β cell responds with increased production of insulin in order to maintain euglycemia; if cells collectively fail to respond adequately, gestational diabetes can develop [6]. In their cross-sectional study of 741 pregnant women, Maghbooli et al found that the prevalence of severe vitamin D deficiency (defined as a total circulating 25-hydroxyvitamin D [25(OH) D] concentration <5 ng/mL or <12.5 nmol/L) in patients with gestational diabetes was higher than in normal pregnancies, suggesting a positive correlation between 25(OH)D concentration with insulin sensitivity during pregnancy [7]. Similarly, Zhang et al found in a nested case control study of 953 women that vitamin D deficiency (defined as a total circulating 25(OH) D concentration <20ng/mL or <50 nmol/L) was associated with a 2.7-fold increased risk of gestational diabetes, and furthermore, that for every 5 ng/mL decrease in 25(OH) D concentration, there was a 1.3-fold increase in gestational diabetes risk [8]. In contrast, a study by Pleskacova et al examining midgestational and early postpartum vitamin D status in pregnant women with and

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without gestational diabetes found no significant association between vitamin D status and gestational diabetes, although the prevalence of vitamin D deficiency (defined as <20 ng/mL or <50 nmol/L) was very high among both control and gestational diabetes groups (93% and 95%, respectively) [9], limiting the ability to discern differences on the basis of vitamin D status.

While research remains to be done on the conclusive role of vitamin D in gestational diabetes, it is quite clear that gestational diabetes is associated with substantial adverse pregnancy outcomes. Maternal insulin resistance is linked to a number of pregnancy complications, including Large for Gestational Age (LGA) infants. Graves et al in their study of 2,305 pregnant women found that both obesity and gestational diabetes added individually to the risk of LGA birth, and a single abnormal glucose tolerance test during pregnancy significantly contributed to LGA birth while treated gestational diabetes did not [10]. Similarly, the HAPO study of 23,316 pregnant women in nine countries found a strong association between maternal glucose concentrations below criteria for gestational diabetes. Both were associated with increased birth weight and cord-blood serum C peptide concentrations [11], and their results prompted revision of criteria for gestational diabetes diagnosis. In a multicenter randomized trial, Landon et al found that intervention in the form of dietary advice and glucose monitoring was associated with a reduction in the incidence of fetal overgrowth, shoulder dystocia, Cesarean section, and preeclampsia in women with mild gestational diabetes (defined as an abnormal result on two or three timed measurements of a 3-hour Oral Glucose Tolerance Test [OGTT] but fasting glucose concentration <95 mg/dl) [12]. Another study with a similar intervention found significantly reduced rates of serious perinatal complications (infant death, shoulder dystocia, bone fracture, and nerve palsy) [13]. A recent meta-analysis on current opinion regarding vitamin D and pregnancy outcomes concluded that there are associations between low concentrations of maternal circulating 25(OH)D during pregnancy and adverse pregnancy outcomes, including preeclampsia, gestation diabetes, postpartum depression, preterm birth, and small for gestation age infants [14].

The ratio of Paraythroid Hormone to vitamin D [PTH/25(OH) D] has recently been described as having a negative association with insulin resistance in obese women (*). We also examined this relationship in the current study [15].

Given that gestational diabetes affects 2-9% of pregnancies [13] and the strong association of gestational diabetes with serious maternal and fetal complications, further investigation into the association between vitamin D and insulin resistance during pregnancy is warranted. Using a combined dataset from two sequential vitamin D pregnancy supplementation studies, the first objective of this study was to determine if there was a correlation between 25(OH) D and serum glucose concentrations from a single screening one-hour glucose tolerance test in pregnant women. The second objective was to determine if there was a correlation between glucose concentration and adverse outcomes during pregnancy. We hypothesized that blood glucose concentrations would be inversely correlated with 25 (OH) D concentrations, and that increased glucose serum concentrations would be associated with increased risk of adverse pregnancy outcomes.

## Study Population and Methods

### Subjects

Figure 1 shows the enrollment and analysis of 546 pregnant women from two pregnancy studies used for this post hoc analysis – the National Institute of Child Health and Development (NICHD) vitamin D supplementation trial, conducted between 2004-2009 at the Medical University of South Carolina and sponsored by the NIH (NIH R01 HD043921, UL1 RR029882, HR# 10,727), and the Kellogg

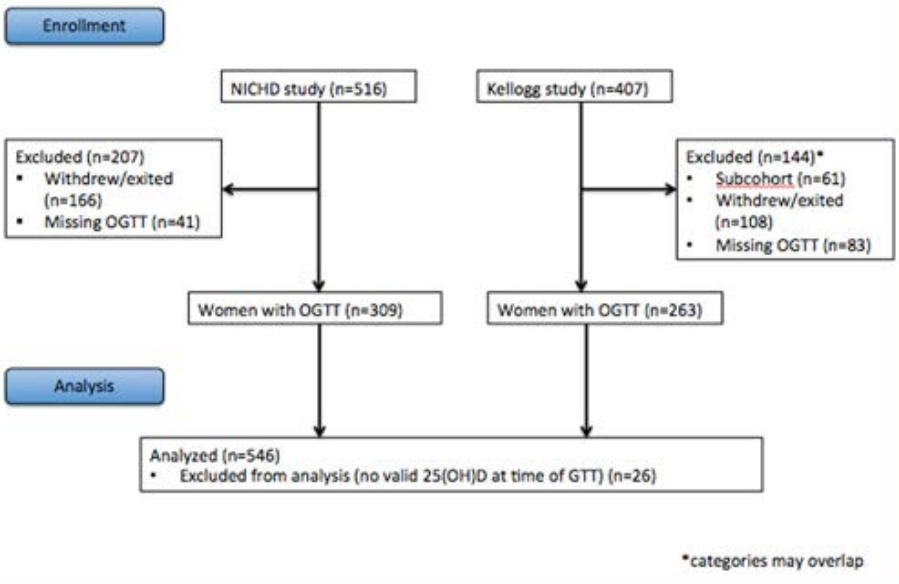


**Figure 1:** Subject demographics.

Pregnancy Study conducted between 2012-2016 at the Medical University of South Carolina sponsored by the W. K. Kellogg Foundation (FDA IND #66,346; HR #20570, UL1 TR0000062). Briefly, The NICHD and Kellogg vitamin D supplementation trials were double blind; placebo controlled, and randomized vitamin D supplementation trials during pregnancy. The baseline 25(OH)D concentration was taken at the first visit. For the NICHD trial supplementation was started between weeks 12 and 16 of pregnancy, and for the Kellogg trial, supplementation was started between 10-14 weeks of gestation. Methods and exclusion criteria are previously published [2].

In the current analysis, all subjects from both studies who had a glucose tolerance test at 28 weeks of gestation were considered. There were minor differences in study populations that did not affect estimates of the current study, including more Caucasian and older women in the Kellogg study and more Hispanic women in the NICHD study.

All subjects with preexisting type 1 or 2 diabetes were excluded. In addition, subjects from the Kellogg study that were in a sub cohort of medical conditions including diabetes, HIV/AIDS, hypertension, and morbid obesity (BMI >49) were excluded. From the combined total of 572 included women, 26 were then excluded from analysis because they did not have a serum 25(OH)D concentration drawn within 30 days of their OGTT. This parameter was based on the 15-25 day half-life of 25(OH)D [16] and insured that serum 25(OH)D concentration measured would be similar to the 25(OH)D concentration on the day of the OGTT.

**Measurements**

In both the NICHD and the Kellogg vitamin D supplementation trials, screening for gestational diabetes was performed according to criteria endorsed by the American College of Obstetricians and Gynecologists [17]. Women underwent glucose tolerance testing at 28 weeks' gestation and those whose serum glucose concentration exceeded 139 mg/dL at one hour after a 50g oral glucose load were given a fasting 3-hour oral glucose tolerance test with a glucose load of 100g. Criteria for gestational diabetes mellitus (GDM) were met if two or more of the following values were reached or exceeded: (1) Fasting: 95 mg/dL, (2) 1 hr: 180 mg/dL, (3) 2 hr: 155 mg/dL, (4) 3 hr: 140 mg/dL.

Maternal blood samples were taken at baseline and then monthly study visits in each trial to assess total circulating 25(OH)D concentration. Blood samples for one-hour glucose tolerance tests were obtained in the clinic, courier-sent to Clinical Chemistry, MUSC, and run in a CLIA-certified laboratory; results were reported in a secure, electronic database. While maternal blood samples were taken at baseline and then monthly study visits in each trial to assess total circulating 25OHD concentration, only the values within 30 days of the OGTT were analyzed as the indicator of vitamin D status at the time of the OGTT, reflecting the 2-to-3-week half-life of 25(OH)D and serving as the vitamin D status indicator surrounding the timing of the OGTT. As secondary indicator of vitamin D status, an averaged 25(OH)D concentration was calculated for each subject using 25(OH)D concentration at baseline and subsequent monthly 25(OH)D concentrations to visit 4, the time at which the OGTT was conducted, and is referred to as the average 25(OH)D concentration.

Total circulating 25(OH)D concentration was measured as total 25(OH)D (including both $D_2$ and $D_3$) using a rapid, direct RIA developed in the Hollis laboratory and manufactured by Diasorin Corporation (Stillwater, MN, USA). Blood samples for 25(OH)D concentration were obtained in the clinic, transported by study coordinator to laboratory of PI, spun and processed in timely fashion (plasma was stored at -80 until extracted for assay of 25(OH)D). Internal control standards were run with each assay to control for intra-assay variation, which was <10% throughout the study. Vitamin D deficiency was defined as a total circulating 25(OH)D concentration <20ng/mL (50 nmol/L) and vitamin D insufficiency was defined as a total circulating 25(OH)D concentration <30ng/mL (75 nmol/L), both according to the US Endocrine Society guidelines [18].

Adverse pregnancy outcomes measured were: preterm birth (<37 weeks), birth weight <1500 grams, macrosomia/Large for Gestational Age (LGA), need for NICU admission, and non-repeat Cesarean section.

Parathyroid Hormone (PTH) levels were measured in both the NICHD and the Kellogg study at visit 4. We examined intact PTH vs. blood glucose values as continuous variables as well as dichotomized as failed or not failed glucose tolerance test (>139 mg/dL or ≤ 139 mg/dL). We then examined the ratio of PTH/25(OH)D vs. blood glucose values again either as a continuous variable or dichotomized by glucose tolerance test result.

**Power and Sample Size Calculations**

In terms of the power of each contributing study, a two group $c^2$ test with a 0.050 two-sided significance level had 57% power to detect the difference between a proportion of 0.129 (women with 25(OH)D > 50 nmol/L and glucose tolerance > 139 mg/dL) and a proportion of 0.233 (women with 25(OH)D < 50 nmol/L) for an odds ratio of 2.056 when the sample sizes were 481 and 60, respectively (a total sample size of 541). Similarly, a two group $c^2$ test with a 0.050 two-sided significance level had 67% power to detect the difference between a proportion of 0.115 (women with 25(OH)D > 75 nmol/L and glucose tolerance > 139 mg/dL) and a proportion of 0.193 (women with 25(OH)D < 75 nmol/L and glucose tolerance > 139 mg/dL) for an odds ratio of 1.841 when the sample sizes were 365 and 176, respectively (a total sample size of 541).

## Statistics

Chi-square analyses were used to test for differences in categories of average maternal 25(OH)D concentration from baseline to GTT test and categories of ethnicity, BMI >30, education, previous gestational diabetes, insurance, and GTT >139. Analysis of variance (ANOVA) analyses were used to test for differences in means among categories of maternal

25(OH)D and maternal age. Kruskal-Wallis non-parametric analyses were used to test for differences in medians among categories of maternal 25(OH)D and gravidity and parity. Logistic regression was used to analyze associations of greater incidence of GTT>139 with categories of maternal 25(OH)D concentration, BMI >30, ethnicity, maternal age, season of entry into study, and study site.

For secondary outcome analyses, all regression analyses used logistic regression as the outcomes were dichotomous. Significance for all variables was set at $p<0.05$. All analyses were performed using SAS, 9.4 software (Cary, NC).

## Results

### Patient Characteristics

**Ethnicity/race:** Characteristics of the 546 pregnant women are outlined in Table 1. Overall distribution of 25(OH)D concentrations are shown in Figure 2, separated by self-reported race/ethnicity. Both vitamin D deficiency and insufficiency were significantly associated with differences in self-reported race/ethnicity, such that mothers with 25(OH)D concentration <20ng/mL (<50 nmol/L) or <30 ng/mL (<75 nmol/L) were more likely to be black or Hispanic as opposed to white when compared to those women with 25(OH)D concentration ≥20

**Table 1:** Maternal Sociodemographic and clinical characteristics of pregnancy cohort

| Maternal Characteristic | 25(OH)D <20ng/mL (50nmol/L) | 25(OH)D ≥20 ng/mL (50 nmol/L) | p-value | 25(OH)D <30ng/mL (75nmol/L) | 25(OH)D ≥30ng/mL (75nmol/L) | p-value |
|---|---|---|---|---|---|---|
| **Race/Ethnicity, N (%)** | | | | | | |
| Black | 36 (72%) | 117 (24%) | p<0.0001 | 73 (55%) | 80 (19%) | p<0.0001 |
| Hispanic | 13 (26%) | 196 (39%) | | 44 (33%) | 165 (40%) | |
| Caucasian | 1 (2%) | 183 (37%) | | 16 (12%) | 168 (41%) | |
| BMI >30, N (%) | 26 (58%) | 109 (24%) | p<0.0001 | 55 (46%) | 80 (21%) | p<0.0001 |
| Age (yrs), mean ±SD (range) | 27.18±4.9 (20-41) | 29.5±4.9 (18-42) | p=0.0244 | 27.6±4.7 (20-41) | 29.8±4.9 (18-42) | p=0.0026 |
| Education beyond HS, N (%) | 33 (66%) | 339 (72%) | p=0.3487 | 87 (67%) | 285 (73%) | p=0.1779 |
| Gravidity, median (range) | 2 (1-7) | 2 (1-14) | p=0.5782 | 2 (1-7) | 2 (1-14) | p=0.1850 |
| Parity, median (range) | 1 (0-4) | 4 (0-5) | p=0.1813 | 1 (0-4) | 1 (0-5) | p=0.0286 |
| Prior GDM diagnosis,N (%) | 1 (2%) | 4 (0.8%) | p=0.3825 | 2 (2%) | 3 (0.7%) | p=0.5998 |
| Private insurance, N (%) | 7 (14%) | 199 (40%) | p=0.0003 | 24 (18%) | 182 (44%) | p<0.0001 |

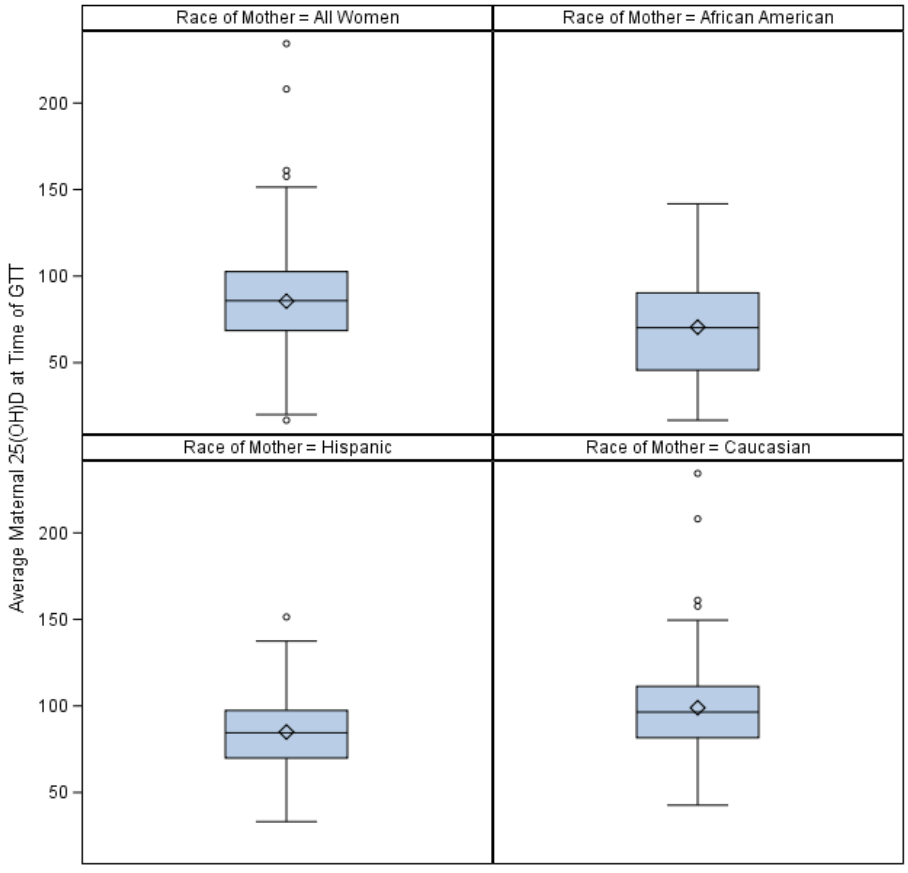


**Figure 2:** Overall distribution of 25(OH)D concentrations at time of glucose tolerance test, presented by ethnicity.

ng/mL (≥50 nmol/l) or ≥30 ng/mL (≥75 nmol/L) (p<0.0001). Regression analysis was subsequently stratified by race and discussed below.

Of note, in this population having private insurance was highly associated with race/ethnicity, so the difference found in insurance status was accounted for by controlling for race/ethnicity in the multivariate analysis.

**Other characteristics:** There was a significant difference in the percentage of women with BMI >30 within both 25(OH)D status comparison groupings; this was also controlled for in further analysis. Age was also included in the model to control for potential differences in vitamin D concentration. Seasonality at the time of blood collection for 25(OH)D analysis was added to the model given its potential effect on vitamin D concentration. Women in the Kellogg study were shown to be more likely to have a failed glucose tolerance test than those women in the NICHD study, so this variable was also added to regression analysis. In the comparison between 25(OH)D concentration <30 ng/mL and ≥30 ng/mL, there was a statistically significant difference in parity but this was also not considered clinically relevant. There were no significant differences found in either comparison group for education beyond high school, gravidity, or prior gestational diabetes diagnosis (analyzed using Fisher's exact test).

**Vitamin D and glucose tolerance:** Total circulating 25(OH)D concentration was not correlated with a standard one-hour screening oral glucose test in the raw data. Given the wide range of variance in both glucose and 25(OH)D concentrations, women were then categorized by clinically relevant vitamin D status, namely whether their vitamin D concentration was deficient, insufficient, or sufficient. As shown in Figure 3, when mothers were categorized by vitamin D deficiency (25(OH)D <20 ng/mL or 50 nmol/L), deficiency was associated with a failed screening one-hour glucose test (GTT >139 mg/dL) (p=0.0331). Vitamin D insufficiency, defined as 25(OH)D <30 ng/mL (<75 nmol/L), showed a trend correlating with a failed glucose tolerance test [(Figure 3); p=0.0873].

**Regression analysis:** Regression analysis was performed including variables identified as possible confounders in patient characteristics-BMI >30, race/ethnicity, age, season, and study (Kellogg vs NICHD). As shown in Table 2,3 women with 25(OH)D <20 ng/mL (<50 nmol/L) were 3.37 times more likely to have a GTT >139 mg/dL (p=0.0023), 95% CI [1.545, 7.363]. Similarly, women with vitamin D insufficiency were 2.57 times more likely to have GTT >139 mg/dL (p=0.0024),

**Table 2:** Odds ratio estimates from models predicting OGTT>139 mg/dL from vitamin D deficiency

| Effect | Point Estimate | 95% Confidence Limits |
|---|---|---|
| 25(OH)D <20 ng/mL (50 nmol/L) | 3.373 | 1.545-7.363 |
| BMI >30 | 1.848 | 1.036-3.296 |
| Black | 1.139 | 0.533-2.431 |
| Hispanic | 1.377 | 0.712-2.663 |
| Age | 1.019 | 1.019-1.131 |
| Season | 1.157 | 0.690-1.942 |
| Study (Kellogg) | 1.97 | 1.145-3.391 |

**Table 3:** Odds ratio estimates from models predicting OGTT>139 mg/dL from vitamin D insufficiency.

| Effect | Point Estimate | 95% Confidence Limits |
|---|---|---|
| 25(OH)D <30 ng/mL (75 nmol/L) | 2.566 | 1.395-4.722 |
| BMI >30 | 1.797 | 1.005-3.214 |
| Black | 1.117 | 0.524-2.380 |
| Hispanic | 1.332 | 0.685-2.591 |
| Age | 1.08 | 1.025-1.138 |
| Season | 1.117 | 0.524-2.380 |
| Study (Kellogg) | 2.032 | 1.180-3.499 |

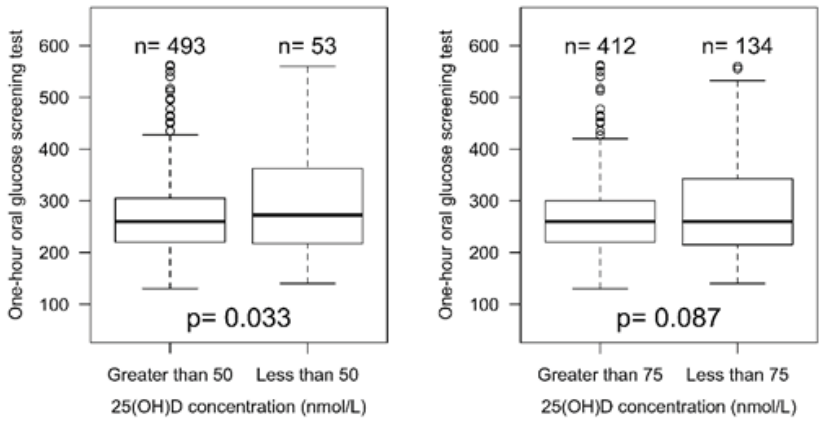


**Figure 3:** One-hour glucose tolerance test (mg/dL) results by 25(OH)D status. a) Box plot of maternal vitamin D deficiency versus all others (insufficiency and sufficiency) as defined by the US Endocrine Society (deficiency being <20 ng/ml [50 nmol/L]) plotted against the one-hour glucose tolerance test result (mg/dL) at 28 weeks' gestation. b) A similar box plot compares vitamin D insufficiency and sufficiency (defined by the US Endocrine Society as 25(OH)D concentration <30 ng/ml [75nmol/L]) plotted against one-hour glucose tolerance test results.

95% CI [1.395, 4.722]. BMI >30 was also associated with a failed screening one-hour glucose test in both vitamin D deficient and insufficient group (p= 0.0374 and p=0.0480, respectively). Race was not significant in either group, nor was season. Age showed a slight association, in that older women were roughly 1.1 times more likely to have GTT >139 in both groups (p=0.0079 and p=0.0041). When the calculated average 25(OH)D concentration from baseline to visit 4 (to the time of the GTT) was used in the model for the cutpoints <50 nmol/L and <75 nmol/L, vitamin D status remained an independent predictor of abnormal OGTT (p=0.03 and p<0.05, respectively). Site of study was significant, and women in the Kellogg study were approximately 2 times as likely in both groups to fail the glucose tolerance test (p=0.0144 and p=0.0105). Overall, vitamin D status remained the most predictive independent factor for a failed glucose tolerance test.

Regression analysis was repeated with discreet categorization of vitamin D groups, such that deficient women (<50 nmol/L) were compared to insufficient only (50-74 nmol/L) and sufficient (>70nmol/L). Deficient women did not differ from insufficient women in glucose tolerance (p=0.1875) but both groups were more likely to fail than sufficient women (p=0.0305).

Regression was additionally stratified by race to elucidate any potential trends. African American women with vitamin D deficiency were 2.67 times more likely to have an abnormal GTT than African American women who were not deficient (p=0.0480). BMI >30, age, season, and study site were not associated, leaving vitamin D status as the only predictive factor for a failed GTT. This was also the case in African American women who were vitamin D insufficient; they were 3.16 times more likely to fail GTT (p=0.0244) with no other significant predictors found. Vitamin D deficient Hispanic women were 4.5 times more likely to fail (p=0.0456) and were also very significantly affected by study site; deficient Hispanic women in the Kellogg study were 7.9 times more likely to fail than their NICHD counterparts (p=0.0005). Similar trends were seen with insufficiency. Because there were not enough vitamin D deficient Caucasian women for analysis, that analysis was precluded; however, with insufficient Caucasian women, vitamin D status was the only significant predictive factor (4.88 times more likely to fail GGT, p=0.0456).

Of the total 546 women analyzed, 34 went on to be formally diagnosed with gestational diabetes (6.2%). The mean 25(OH) D concentration of the women formally diagnosed with gestational diabetes was 37.3 ng/mL (93.3 nmol/L) vs. 40.5 ng/mL (101.2 nmol/L) in those women not diagnosed with gestational diabetes (p= 0.3021).

**Adverse outcomes:** A one-hour screening glucose tolerance test result of >139 mg/dL was significantly associated with non-repeat Cesarean section deliveries (p=0.0308). In this cohort, an abnormal glucose tolerance test was not associated with large for gestational age (LGA) births, need for NICU admission, birth weight <1500 grams, or preterm birth (Table 4).

**Table 4:** Incidence of adverse outcomes by OGTT result (pass or fail).

| Adverse outcome | OGTT ≤139 mg/dL | OGTT >139 mg/dL | p-value |
|---|---|---|---|
| Preterm birth (<37 weeks) | 33 (7%) | 5 (7%) | p=0.1937 |
| Birthweight <1500 grams | 4 (1%) | 1 (1%) | p=0.5241 |
| NICU admission | 43 (9%) | 6 (8%) | p=0.1698 |
| Large for gestational age | 21 (5%) | 6 (9%) | p=0.2397 |
| Non-Elective Cesarean section | 133 (41%) | 25 (60%) | p=0.0308 |

**Parathyroid Hormone to vitamin D ratio [PTH/25(OH)D]:** Glucose values and intact PTH were positively correlated as continuous variables, such that as glucose levels rose, so did PTH levels (r=0.11, p=0.035). PTH was similarly correlated to a failed glucose tolerance test. The ratio of PTH/25(OH)D was also positively correlated to fasting glucose level (r=0.11, p=0.031) and to a failed glucose tolerance test.

## Discussion

Previous studies have described the relationship between glucose metabolism and vitamin D, but most studies have focused on diabetic, nonpregnant patients. Studies that exist on the association between 25(OH)D concentrations and hyperglycemia during pregnancy are limited and contradictory [5, 19, 20]. This study identifies a relationship between clinically relevant vitamin D status (deficiency and insufficiency) and serum blood glucose from a single screening test in pregnant women.

As mentioned, total circulating 25(OH)D concentration was not correlated with a standard one-hour screening oral glucose test overall in the raw data. This was likely due to the wide range of variance in both glucose and 25(OH)D values, and separating women into categories defined by accepted standards of vitamin D status (deficient, insufficient, and sufficient) bore statistically significant differences in screening glucose tolerance. The main finding of this study was that vitamin D deficiency (total circulating 25(OH)D concentration <20 ng/mL or <50 nmol/L) and insufficiency (25(OH)D concentration <30 ng/mL or <75 nmol/L) were both related to a failed screening one-hour glucose test in pregnant women above all other factors analyzed. A 25(OH)D concentration of <20ng/mL (<50 nmol/L) was associated with a 3.37-fold greater risk for a failed glucose screening test, which was consistent with data from Zhang et al's study of 953 women where the authors found that 25(OH)D <20ng/mL (<50 nmol/L) was associated with a 2.57-fold increased risk of gestational diabetes (8). Our data are also consistent with that of Burris et al., who found an inverse linear relationship with glucose concentrations obtained during a 50-g, 1-hour glucose load screening test and second trimester 25(OH)D status [21]. Similarly, Maghbooli et al. found a significant correlation between vitamin D and insulin resistance and fasting glucose (7). Additionally, Burris et al determined through review of the scientific literature that women with GDM are at higher risk than normoglycemic

women of having low 25(OH)D concentrations even if the mechanism behind vitamin D and gestational diabetes remains unclear [22].

Several important trends were also found regarding race/ethnicity in the context of vitamin D and glucose tolerance testing. Vitamin D deficiency or insufficiency was the single most predictive factor for a failed glucose tolerance test across all African American and Hispanic women, as well as in insufficient Caucasian women. Vitamin D concentration was more predictive in all groups than BMI >30, age, season, or study. This could represent a population of increased nutritional need and special attention should be paid in future studies to address this disparity. We hypothesize that the higher likelihood of all women (and especially Hispanic women) in the Kellogg study to have a failed glucose tolerance test is a measure of time, since this study was done almost 10 years after NICHD and therefore could be capturing higher rates of gestational diabetes in the general population. This study's findings add to the existing body of literature that supports an association between vitamin D deficiency/insufficiency and impaired glucose tolerance, but further randomized clinical trials are needed to specifically determine if vitamin D supplementation can prevent gestational diabetes (20).

In this study, an association between a failed screening one-hour glucose tolerance test and the need for a non-repeat Cesarean section delivery was found. These data are consistent with the findings of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which showed that each 1-SD increase in glucose concentration (measured using the International Association of the Diabetes and Pregnancy Study Groups 75-g oral glucose tolerance test) was associated with an increase of 8 to 11% in the odds of Cesarean section delivery [11]. Loy et al also found a trend between 25(OH) D inadequacy and higher likelihood of emergency Cesarean section in Chinese and Indian women in the Growing Up in Singapore Toward Healthy Outcomes (GUSTO) study (Odds Ratio (OR) = 1.39, 95% CI = 0.95, 2.05) [23]. Furthermore, several studies found a reduction of Cesarean section births when mothers were treated for gestational diabetes using dietary intervention, glucose monitoring, and insulin therapy (12, 13). Our study did not find an association between a failed screening one-hour glucose tolerance test and Large for Gestational Age (LGA) births, need for NICU admission, birth weight <1500 grams, or preterm birth. This is largely inconsistent with current literature and is likely due to the small number of adverse outcomes experienced by the women in the study.

Similar to Stanley et al's findings, this study found a positive correlation between PTH and PTH/25(OH)D with insulin sensitivity (15), where women with lower 25(OH)D, a higher PTH or PTH/25-OHD ratio were more likely to have a higher faster blood glucose and to fail their screening glucose test in pregnancy. This adds to new literature suggesting that PTH and vitamin D may be important markers for insulin resistance not only in obesity but in pregnancy as well.

This study was limited by its cross-sectional design, as we measured 25(OH)D concentration on the same day (or within 30 days) of the blood glucose measure. Given that the half-life of 25(OH)D is approximately three weeks, this timeframe allowed for an accurate assessment of correlation between vitamin D status and blood glucose concentration but was simply one time point. When average 25(OH)D was added to the model in place of the one timepoint, however, the association of vitamin D status and abnormal GTT persisted. Another limitation was the relatively low number of women with vitamin D deficiency, which makes estimation uncertain. The association between failed glucose tolerance testing and vitamin D status could also potentially be explained in part by maternal diet (regardless of BMI) and differing levels of exercise, which were unable to be compared in this study due to different measures used in each contributing study.

Another important limitation of this study and others is that there is little consensus on criteria for both vitamin D deficiency and gestational diabetes. The US Institute of Medicine concluded in 2011 that 25(OH)D concentrations >20ng/mL (>50 nmol/L) are sufficient for 97.5% of the population [3], while the US Endocrine Society sets the optimal concentration at >30 ng/mL (>75 nmol/L) [24], and emerging evidence suggests that concentrations of at least 40 ng/mL are required during pregnancy to optimize concentrations of the active metabolite $1,25(OH)_2D$ [25]. Given the controversy surrounding what constitutes vitamin D deficiency, we opted to use the US Endocrine Society standards for both deficiency and insufficiency; however, standards continue to differ among studies.

Similarly, criteria for gestational diabetes screening vary widely, making comparison of studies difficult. This study used standards of screening endorsed by the American College of Obstetricians and Gynecologists, which are based on non-pregnancy values associated with the risk of the mother developing diabetes later in life and thus could be less sensitive than recently released IADSPG standards, which are based on 1.75 fold increased risk of adverse pregnancy outcomes [26].

Both a strength and weakness of this study was that we included only the screening OGTT that all women received at 28 weeks' gestation as we were not powered to include analysis of the 3-hour OGTT that women who failed the screening would go on to have. Finding an association between a single glucose screening test and vitamin D insufficiency early in pregnancy speaks to the strength of the association and could be a cost-effective way to screen for patients with impaired glucose tolerance that may also be vitamin D deficient. However, the lack of association found between a failed screening test and most adverse outcomes suggests a single screening is not specific enough to capture the relationship of insulin resistance with adverse pregnancy outcomes. Future studies should include randomized controlled trials investigating the role of vitamin D deficiency in pregnancy as a risk factor for impaired glucose metabolism.

## Conclusion

Based on our findings, vitamin D status appears to play a role in glucose homeostasis in pregnant women. Our findings add to the literature supporting vitamin D deficiency (and insufficiency) as a risk factor for insulin resistance and raise the question of whether treating vitamin D deficient women during pregnancy could contribute to lowered rates of gestational diabetes. Further studies powered to examine this objective are warranted.

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