The relationship between maternal vitamin D deficiency and glycolipid metabolism and adverse pregnancy outcome

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Funding information
Natural Science Foundation of Zhejiang Province, Grant/Award Number: LY13H040010 and LQ18H040002

Abstract
Objective: Maternal vitamin D deficiency is associated with glucose and lipid metabolism in the mother and offspring. Meanwhile, it can also lead to adverse pregnancy outcomes. The aim of this case-control study was to document maternal, umbilical arterial glucose and lipid metabolic levels and correlations in pregnancies with or without vitamin D deficiency, while also investigating adverse pregnancy outcomes.

Design/Participants/Measurements: A total of 425 pregnant women who received antenatal care and delivered at Wenzhou People’s Hospital were enrolled. According to their serum 25-hydroxyvitamin D [25(OH)D] level, the pregnant women were divided into the vitamin D deficiency group [25(OH)D < 20 ng/mL, 185 participants] and the control group [25(OH)D ≥ 20 ng/mL, 240 participants]. Maternal blood samples were collected at 24-28 weeks of gestation and delivery for 75-g oral glucose tolerance test (OGTT), and measurements of glucose and lipid metabolite levels and 25(OH)D levels. Umbilical arterial samples were collected during delivery (33.57-41.43 gestational weeks).

Results: Compared with control participants, vitamin D deficiency women had significantly higher concentrations of fasting blood-glucose (P < .01), 1-h OGTT plasma glucose (P < .01), 2-h OGTT plasma glucose (P < .01), insulin (P < .01), HOMA-IR (P < .01), LDL (P < .01) and triglycerides (P < .02) and lower concentrations of HOMA-S (P < .01). Compared with the control group, vitamin D deficiency women had higher concentrations of triglycerides (P < .01) and lower concentrations of HDL-C (P < .01) and HOMA-β (P = .01) in infant umbilical arterial blood. Pearson’s correlation analysis demonstrated that the maternal 25(OH)D level was negatively correlated with maternal plasma glucose, insulin, LDL-C, cholesterol, triglyceride and HOMA-IR (r = -.38, -.27, -.2, -.11, -.33 and .11; P < .01, <.01, <.01, <.05, <.05 and <.01, respectively), while there was a positive correlation between maternal serum 25(OH)D and HOMA-S (r = .11, P < .05). The triglyceride level in the umbilical artery was negatively correlated with maternal serum 25(OH)D concentration (r = -.286, P < .01), while the HDL-C and HOMA-β in umbilical artery were positively related (r = .154, .103, .013).
1 | INTRODUCTION

Vitamin D, one of the steroid hormones, is synthesized in the skin from exposure to sunlight.\(^1\) Although vitamin D itself is devoid of any biological activity, its derivative, 1,25 dihydroxy vitamin D, exhibits diverse biological activities. Vitamin D is an essential biological factor for calcium and bone metabolism, and it plays several nonclassical roles in the human body, such as ameliorating oxidative stress, reducing the risk of metabolic syndrome, improving the immune system and preventing insulin resistance.\(^2,3\) Serum 25-hydroxyvitamin D [25(OH)D] has a relatively long half-life of approximately 13-15 days and is considered a useful marker of vitamin D status.\(^4,5\) There is no absolute consensus as to what a normal range for 25(OH)D should be. Previous studies have demonstrated that a circulating 25(OH)D concentration of 20 ng/mL is adequate to meet human physiological requirements.\(^4,6\) So vitamin D deficiency is defined as a 25(OH)D level < 20 ng/mL.\(^5,6\) Vitamin D deficiency is present in more than half of pregnant women and newborns worldwide.\(^7\)

Although most pregnant women in China supplement their diet with multivitamins during pregnancy, vitamin D deficiency remains a common problem in China.\(^8\) Recently, more attention has been focused on the role of Vitamin D during pregnancy. It has been reported that vitamin D deficiency during pregnancy is associated with insulin resistance, gestational diabetes mellitus (GDM) and abnormalities of the foetal immune system.\(^9,10\) Several observational studies have indicated that vitamin D deficiency may be a high-risk factor for GDM.\(^11\) However, randomized controlled trials have found no differences in incidence of GDM between women in the control group and women in the vitamin D supplement group.\(^12\) Although the relationship between maternal glucose and lipid metabolism and vitamin D has been widely studied, the impact of vitamin D deficiency on foetal glucose and lipid metabolism is poorly investigated. Some studies have suggested that some of the damages caused by vitamin D deficiency occur in utero while the foetus is still in development.\(^13\) Therefore, our study aimed to measure the level of 25(OH)D in maternal and infant umbilical cord sera and to investigate their potential association with glucose and lipid metabolism and pregnancy outcome.

2 | MATERIALS AND METHODS

2.1 Study subjects and exclusion criteria

The study protocol was designed in accordance with the tenets of the Declaration of Helsinki. This retrospective study was approved by our institutional review board, and informed consent was obtained from all the 425 pregnant women enrolled from January 2017 to December 2018. The pregnant women were divided into the vitamin D deficiency group (25(OH)D < 20 ng/mL, 185 participants) and the control group (25(OH)D ≥ 20 ng/mL, 240 participants). Women were invited to participate in the study when registering for antenatal care and delivery in the People’s Hospital of Wenzhou (where there are approximately 21,000 deliveries annually). A total of 2350 pregnant women agreed to participate in the study and provided blood samples, but 1925 pregnant women were excluded from the study because they had any of the following conditions: multiple pregnancies, chronic nephritis, hypertension, acute infection, parathyroid disease, polycystic ovary syndrome, metabolic diseases and incomplete clinical records. The 425 pregnant women with full medical records including their clinical information (age, gestational age, BMI and results of blood tests) were enrolled in this study. Adverse pregnancy outcome includes pre-eclampsia, GDM, foetal growth restriction (FGR), premature rupture of membranes (PROM) and premature delivery. Pre-eclampsia is a multisystem disorder of pregnancy, which is characterized by new-onset hypertension (systolic and diastolic blood pressure of ≥140 and 90 mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of ≥300 mg in a 24-hours urine collection, or a dipstick of ≥2+) that develop after 20 weeks of gestation in previously normotensive women.\(^14,15\) A one-step 75-g two-hour fasting oral glucose tolerance test has been recently used for the diagnosis of GDM during pregnancy at 24 to 28 weeks; the diagnostic cutoff of the OGTT is 5.1, 10.0 and 8.5 mmol/L at fasting, 1 hour and
2 hours postprandial, respectively. Foetal growth restriction refers to a foetus with an estimated foetal weight <10th percentile on ultrasound that, because of a pathologic process, has not attained its biologically determined growth potential. PROM is the rupture of membranes during pregnancy before 37 weeks’ gestation. Preterm birth is defined as birth occurring at less than 37 weeks’ gestation.

### 2.2 Sample and data collection

Maternal blood samples were collected from women in the second trimester of pregnancy (gestational week 24-28) and delivery. In addition, umbilical cord blood samples (umbilical artery) were taken within five minutes of delivery, immediately after clamping the umbilical cord while the placenta was in the uterus. Maternal and umbilical cord blood samples were for analysis of serum 25(OH)D, OGTT and analysis of parameters associated with glucose and lipid metabolism (delivery) including fasting blood-glucose (mmol/L), fasting insulin (INS, mU/L), cholesterol (CHO, mmol/L), triglycerides (mmol/L), high-density lipoprotein-cholesterol (HDL-C, mmol/L), low-density lipoprotein-cholesterol (LDL-C, mmol/L), homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of insulin resistance-β(HOMA-β) and homeostatic model assessment insulin of sensitivity (HOMA-S). HOMA was used to estimate insulin resistance, insulin sensitivity and β-cell function. They were calculated by the following equations: HOMA-IR = [fasting insulin (mU/L) x fasting glucose (mmol/L)]/ 22.5, HOMA-S = 22.5/ [fasting insulin (mU/L) x fasting glucose (mmol/L)], and HOMA-B = [20 x fasting insulin (mU/L)]/ [fasting glucose (mmol/L)-3.5].

### 2.3 Laboratory analysis

The serum levels of FBG, INS, CHO, TG, HDL-C and LDL-C were measured using respective assay kits. The Glucose Biochemical Kit was purchased from Applygen (E1010, China), and insulin, TG, and HDL-C ELISA kits were from Bioswamp (RA20092, RA20187, RA20667, USA). Chemiluminescence immunoassay was used to determine the level of 25(OH)D. The serum 25(OH)D kit was purchased from Abbott (ISR 61723, USA). The serum samples harvested after centrifugation for 5 minutes were used for examination of related indexes. Serum biomarker levels were measured using an automated analyser (1681130-4B, Bio-Rad, USA).

### 2.4 Statistical analysis

SPSS 21.0 (IBM, USA) was used to analyse the descriptive statistics. Median (25-75th) values were for quantitative variables with non-normal distribution and mean ± standard values for quantitative variables with normal distribution. Comparison of quantitative variables between the two groups was performed using independent-sample Student’s t test or Mann-Whitney U test when appropriate. Single variable analyses were evaluated using chi-square tests. Chi-square tests or Fisher’s exact tests were applied to determine the statistical differences between the groups of women in terms of the categorical variables. Pearson’s correlation coefficients were used to analyse the relationship between 25(OH)D and other biochemical markers of maternal and umbilical cord blood. A threshold probability value of P < .05 was used in this study.

### 3 RESULTS

#### 3.1 Study population

Table 1 shows the clinical characteristics of the pregnant women in our study. A total of 425 women were enrolled in the study, 185 were in the vitamin D deficiency group, and 240 were in the control group. Blood tests were conducted at 25.81±2.80 weeks of gestation in the vitamin D deficiency group and at 25.75±1.29 weeks of gestation in the control group. No statistical differences were observed between the vitamin D deficiency group and the control group in terms of maternal age (29.34±4.41 vs 28.53±4.42), prepregnancy BMI (22.55±3.17 vs 22.36±2.80), gestational week (39.17±1.35 vs 39.18±1.32) and birthweight (3332.70±439.72 vs 3357.79±422.02), P > .05.

#### 3.2 Maternal demographics and biochemical markers

Table 2 shows the maternal biochemical markers of the two groups based on the vitamin D deficiency threshold of <20 ng/mL vs ≥20 ng/mL.
Compared with the concentration values in control participants, the concentration measurements of the following were higher in women with vitamin D deficiency: fasting blood-glucose [4.67 (4.37, 5.14) vs 4.38 (4.13, 4.56) mmol/L, \( P < .01 \)], 1-h OGTT plasma glucose (8.98 ± 1.55 vs 7.26 ± 1.43 mmol/L, \( P < .01 \)), 2-h OGTT plasma glucose (7.79 ± 1.53 vs 6.29 ± 1.02 mmol/L, \( P < .01 \)), fasting insulin (8.72 ± 3.52 vs 6.72 ± 3.20 mU/L, \( P < .01 \)), HOMA-IR (1.83 ± 0.78 vs 1.31 ± 0.66, \( P < .01 \)), HOMA-β (146.75 (105.58, 237.76) vs 154.81 (109.28, 229.56) mmol/L, \( P = .57 \)), HDL-C (1.13 (0.89, 1.27) vs 1.25 (0.94, 1.56), \( P < .01 \)), LDL-C (1.60 (1.12, 2.03) vs 1.61 (1.10, 2.30), \( P = .81 \)), HOMA-S (0.47 (0.37, 0.58) vs 0.43 (0.37, 0.55), \( P = .35 \)), and triglycerides (2.77 (2.22, 3.67) vs 2.56 (1.94, 3.44) mmol/L, \( P = .02 \)). However, the HOMA-S in the vitamin D deficiency group was lower than in the control group [0.54 (0.43, 0.75) vs 0.66 (0.54, 0.99) mmol/L, \( P < .01 \)]. No statistically significant differences were observed in HOMA-β [146.75 (105.58, 237.76) vs 154.81 (109.28, 229.56) mmol/L, \( P = .57 \)], CHO [5.60 (4.63, 6.53) vs 5.36 (4.79, 5.91), \( P = .09 \)] and HDL-C [1.51 (1.35, 1.71) vs 1.52 (1.44, 1.72), \( P = .19 \)] between the two groups.

### 3.3 Infant umbilical arterial biochemical markers

Table 3 shows the infant biochemical markers. Serum HDL-C and HOMA-β concentrations of the arterial umbilical blood in the
vitamin D deficiency group were lower than those in the control group $[1.13 (0.89, 1.27) vs 1.25 (0.94, 1.56) \text{mmol/L, } 113.31 \pm 26.68 \text{ vs } 120.11 \pm 28.32; P < .01, P = .01, \text{respectively}].$ The concentration of triglycerides in the infant arterial umbilical blood of the vitamin D deficiency group was higher than that in the control group $[3.12 (2.45, 4.19) vs 2.54 (2.08, 3.24) \text{mmol/L, } P < .01].$ No statistically significant differences were observed in the infant arterial umbilical blood between the vitamin D deficiency group and the control group in terms of infant glucose $[5.17 (5.06, 5.24) \text{ vs } 5.15 (5.05, 5.26) \text{ mmol/L, } P = .67],$ LDL-C $[1.60 (1.12, 2.03) vs 1.61 (1.10, 2.30) \text{ mmol/L, } P = .81],$ insulin $[9.22 (7.35, 11.28) \text{ vs } 10.14 (8.15, 11.49) \text{ mU/L, } P = .18],$ HOMA-IR $[2.13 (1.71, 2.70) vs 2.31 (1.82, 2.70), P = .35]$ and HOMA-S $[0.47 (0.37, 0.58) \text{ vs } 0.43 (0.37, 0.55), P = .35].$

### 3.4 Correlations between maternal biochemical markers and maternal serum 25(OH)D concentrations

Table 4 shows the correlations between the maternal biochemical markers and maternal serum 25(OH)D concentrations represented by Pearson’s correlation coefficients. No obvious association was found between maternal serum 25(OH)D concentration and maternal age, prepregnancy BMI, HDL and HOMA-β ($r = -0.09, -0.05, 0.07$ and $-0.03$, respectively, all $P > .05$). However, there was an inverse correlation between serum 25(OH)D and glucose, insulin, LDL, CHO, triglycerides and HOMA-IR ($r = -0.38, -0.27, -0.2, -0.11, -0.33$ and $-0.11; P < .01, <.01, <.01, <0.05, <0.05$ and $.01$, respectively) and there was a positive correlation between serum 25(OH)D and HOMA-S ($r = 0.11, P < .05$).

### 3.5 Correlations between infant umbilical arterial biochemical markers and maternal serum 25(OH)D concentrations

Table 5 shows the correlations between infant umbilical arterial biochemical markers and maternal serum 25(OH)D concentrations represented by Pearson’s correlation coefficients. The triglyceride level in the umbilical artery was negatively correlated with maternal serum 25(OH)D concentration ($r = -0.286, P < .01$), while HDL-C and HOMA-β in the umbilical artery were positively correlated with maternal serum 25(OH)D concentration ($r = 0.154, 0.103; P < .01, <.05$, respectively). No significant correlation was found between maternal serum 25(OH)D concentration and glucose, INS, LDL-C, HOMA-IR and HOMA-S ($r = -0.081, 0.034, -0.025, 0.015$ and $-0.028$, respectively, all $P > .05$).

### 3.6 Adverse pregnancy outcome

The incidences of GDM $[19.45\% (36/185) \text{ vs } 12.08\% (29/240), P = .04],$ pre-eclampsia $[4.8\% (9/185) \text{ vs } 1.25\% (3/240), P = .03]$ and PROM $[15.68\% (29/185) \text{ vs } 5.42\% (13/240), P < .01]$ in pregnant women with vitamin D deficiency were higher than those in the control group. No significant difference was found in FGR and preterm delivery between the two groups ($\chi^2 = 0.54$ and $2.53$, respectively, both $P > .05$) (Table 6).

### 4 DISCUSSION

Vitamin D deficiency has been identified as a major public health issue across the world. Our study compared maternal, umbilical arterial glucose and lipid metabolic levels and correlations in pregnancies with or without vitamin D deficiency, while also investigating adverse pregnancy outcomes. The results showed that
TABLE 6: Adverse pregnancy outcome

| Variables          | Vitamin D deficiency | Control | χ²    | P     |
|--------------------|----------------------|---------|-------|-------|
| N                  | 185 (43.53%)         | 240 (56.47%) |       |       |
| Pre-eclampsia      | 9 (2.12%)            | 3 (0.71%)   | 4.98  | .03   |
| GDM                | 36 (8.47%)           | 29 (6.82%) | 4.39  | .04   |
| FGR                | 4 (0.94%)            | 2 (0.47%)   | 0.54  | .46   |
| PROM               | 29 (6.82%)           | 13 (3.06%)  | 12.35 | <.01  |
| Premature delivery | 9 (2.12%)            | 5 (1.18%)   | 2.53  | .11   |

Abbreviations: FGR, foetal growth restriction; GDM, gestational diabetes mellitus; PROM, premature rupture of membranes.

Vitamin D deficiency during pregnancy is associated with maternal glucose and lipid metabolism and adverse pregnancy outcomes. According to the published Endocrine Society Practice Guideline, vitamin D deficiency is defined as serum 25(OH)D level < 20 ng/ml. El Koumi MA reported that 42%-72% of pregnant women in the United States, 18%-90% in Europe, 46% in the Eastern Mediterranean, 66%-96% in South-East Asia and 41%-97% in the Western Pacific region suffer from vitamin D deficiency. Limited sun exposure has been a major cause for the vitamin D deficiency pandemic in adults and children. Vitamin D is a fat-soluble steroid that is transported to the liver for hydroxylation to produce the main circulating form of vitamin D, 25(OH)D. A second hydroxylation event generates the active form, 1,25-dihydroxyvitamin D, which occurs mostly in the kidneys. The active 1,25-dihydroxyvitamin D can bind to VDR and participate in a wide range of biological functions. The main physiological function of 1,25-dihydroxyvitamin D is to regulate calcium and phosphorus metabolism, as well as immune response, glycolipid metabolism and inflammatory response. The high prevalence of vitamin D deficiency during pregnancy could be explained as such: (a) daily intake of vitamin D did not keep up with the increasing nutritional demand for pregnant women and foetuses during pregnancy; (b) lifestyle changes and limited outdoor activities during pregnancy that led to reduced sun exposure.

Vitamin D receptors are expressed in a large range of cells, including those involved in the regulation of glucose metabolism. In addition to affecting glucose metabolism, vitamin D also plays a role in the secretion of insulin specifically by promoting insulin sensitivity through stimulating the expression of insulin receptors and increasing glucose transport. Pregnancy induces an insulin-resistant state during which β cells in the pancreas proliferate to secrete more insulin in order to meet the increasing nutritional demands associated with this time period. Maternal serum 25(OH)D concentration has been shown to negatively correlate with fasting glucose and insulin levels during pregnancy. Previous studies found that serum 25(OH)D concentration was lower in GDM participants. With the accumulation of fat mass during pregnancy, vitamin D deficiency could affect lipid metabolism and promote the accumulation of lipids in tissues other than the liver. Consistent with previous reports, in our study, compared with control participants, vitamin D deficiency women had significantly higher concentrations of fasting blood-glucose, 1-h OGTT plasma glucose, 2-h OGTT plasma glucose, insulin, HOMA-IR, LDL-C, and triglycerides, while lower concentration of HOMA-S. Pearson’s correlation analysis demonstrated that maternal 25(OH)D level was negatively correlated with maternal plasma glucose, insulin, LDL, CHO, triglycerides and HOMA-IR. Our findings suggest that maternal vitamin D deficiency during pregnancy may lead to various disorders associated with glucose and lipid metabolism, insulin resistance and hyperlipidemia.

Foetal vitamin D level is mainly dependent on maternal concentration, and maternal vitamin D deficiency may lead to adverse outcomes in offspring. The established doctrine of the “Barker Hypothesis” described that diseases that manifest in adulthood actually began during the perinatal period. Foetuses with vitamin D deficiency are at excessive risk of FGR, obesity, insulin resistance, hypocalcaemia and other orthopaedic complications. It has been reported that maternal vitamin D deficiency is closely associated with infant heart failure, acute lower respiratory tract infection, increased risk of childhood wheezing and type 1 diabetes. Maternal vitamin D deficiency is also associated with lower bone mineral concentration and impaired glucose homeostasis in newborn infants. Intra-uterine exposure to low 25(OH)D concentrations is associated with lower muscle mass and higher insulin resistance in children. Our study evaluated the effects of vitamin D deficiency on maternal and foetal glucose and lipid metabolism and found that maternal vitamin D deficiency was associated with glucose and lipid metabolism not only in adults, but also in offspring. Maternal blood comes in contact with the placenta first and then to foetal via umbilical vein; foetal blood comes in contact with umbilical arteries first and then to maternal blood via the placenta. Therefore, umbilical arterial samples may more closely reflect infant metabolic concentrations than umbilical venous samples. Accordingly, umbilical artery biochemical indicators have been used to reflect adverse pregnancy outcomes. We found that 25(OH)D-deficient pregnant women had significantly higher concentrations of triglycerides and lower concentrations of HDL and HOMA-β in infant umbilical arterial blood compared with control participants. Furthermore, triglyceride levels in infant umbilical arterial blood were negatively correlated with maternal serum 25(OH)D concentration, while HDL and HOMA-β in infant umbilical arterial blood were positively correlated with maternal serum 25(OH)D concentration. Our findings suggest that 25(OH)D-deficient offspring possess abnormal metabolic concentrations when they are in utero, which may be correlated with maternal transfer, placental issues and foetal metabolism. In addition, in our study, we found that there was no significant correlation between foetal umbilical glucose and insulin levels and maternal
25(OH)D levels. It is speculated that the protective effect of maternal 25(OH)D on the glucose metabolism of the offspring has not been absolutely shown in the foetal period.

Glucose and lipid metabolism disorder is an important factor in metabolic syndromes such as GDM and pre-eclampsia, and insulin resistance is the main mechanism of metabolic syndrome. Normal concentration of vitamin D in pregnant women can protect the growth of foetal bone and nervous system and reduce the risk of pregnancy complications including FGR, gestational diabetes and pre-eclampsia. Studies have shown that occurrence of pre-eclampsia is higher in pregnant women from vitamin D deficiency group than controls and that serum concentration of vitamin D is closely related to gestational diabetes and preterm delivery. Our study specifically evaluated the changes in glucose and lipid metabolism that are potentially related to vitamin D deficiency during pregnancy. We found that the incidences of pre-eclampsia, gestational diabetes and PROM in the vitamin D deficiency group were higher than those in the control group (P < .05), which is consistent with the results reported in previous studies.

There were some limitations in our study. First, a single measurement of serum 25(OH)D level is not likely to provide a holistic, integrated assessment of maternal vitamin D status during pregnancy. Second, our sample size is small, and large prospective and multicentre investigations are needed to further confirm the effect of vitamin D deficiency on maternal and foetal outcome.

5 | CONCLUSION

In conclusion, vitamin D deficiency is prevalent among pregnant women. Lower levels of 25(OH)D during pregnancy were associated with maternal and foetal glucose and lipid metabolism, as well as other pregnancy complications. Therefore, it is recommended that pregnant women should be informed about the importance of maintaining adequate vitamin D status during pregnancy, especially those at the greatest risk of vitamin D deficiency.

ACKNOWLEDGEMENTS

We appreciate the patients for their participation in this study. This work was supported by the Natural Science Foundation of Zhejiang Province under Grant Nos. LY13H040010 and LQ18H040002.

CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest in this work.

AUTHORS’ CONTRIBUTIONS

HYC and JQZ conceived and designed the study. HYG, HPZ, YJ and ZQH executed the study. HYG, HXX and QQD analysed and involved in interpretation of data. HYG and JQZ drafted the article. HYG and JQZ made final approval of the version to be published.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethic committee of Wenzhou People’s Hospital. Informed consent was obtained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Chen H-Y, Zhang H-P, Yang J, et al. The relationship between maternal vitamin D deficiency and glycolipid metabolism and adverse pregnancy outcome. Clin Endocrinol (Oxf). 2020;93:713–720. https://doi.org/10.1111/cen.14298