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

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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 ($r = -.38$, $-.27$, $-.2$, $-.11$, $-.11$, $-.33$ 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 ($r = .154$, $.103$,

$P < .01$). Compared with the control group, the incidences of pre-eclampsia [4.8% (9/185) vs 1.25% (3/240), $P = .03$], gestational diabetes mellitus [19.45% (36/185) vs 12.08% (29/240), $P = .04$] and premature rupture of membranes [15.68% (29/185) vs 5.42% (13/240), $P < .01$] were higher in the vitamin D deficiency group.

Conclusion: Vitamin D deficiency during pregnancy is associated with maternal glucose and lipid metabolism and pregnancy outcomes. Therefore, it is worth recommending to maintain **vitamin D status** at an optimal level in pregnant women to prevent metabolic disorders and pregnancy complications.

KEYWORDS

glycolipid metabolism, pregnancy outcomes, Vitamin D

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 cut-off of the OGTT is 5.1, 10.0 and 8.5 mmol/L at fasting, 1 hour and

TABLE 1 Maternal characteristics of study subjects

Variables	Vitamin D deficiency	Control	*P*
N	185	240	
Ages (y)	29.34 ± 4.41	28.53 ± 4.42	.06
Specimen collection gestation (w)	25.81 ± 1.20	25.75 ± 1.28	.63
Gestational age of delivery (w)	39.17 ± 1.35	39.18 ± 1.29	.91
Birthweight (g)	3332.70 ± 439.72	3357.79 ± 422.02	.55
Prepregnancy BMI (kg/m^2)	22.55 ± 3.17	22.36 ± 2.80	.52

Abbreviations: BMI, body mass index; n, normally distributed data are presented as mean ± SD.

2 hours postprandial, respectively.[16] 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.[17] PROM is the rupture of membranes during pregnancy before 37 weeks' gestation.[18] Preterm birth is defined as birth occurring at less than 37 weeks' gestation.[19]

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) × fasting glucose (mmol/L)]/ 22.5, HOMA-S = 22.5/ [fasting insulin (mU/L) × fasting glucose (mmol/L)], and HOMA-B = [20 × fasting insulin (mU/L)]/ [fasting glucose (mmol/L)-3.5].[20]

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 ± 1.20 weeks of gestation in the vitamin D deficiency group and at 25.75 ± 1.28 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 ± 1.29) 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/

TABLE 2 Maternal biochemical markers of study subjects

Maternal characteristics and biochemistry	Vitamin D deficiency	Control	*P*
Fasting plasma glucose (mmol/l)	4.67 (4.37, 5.14)	4.38 (4.13, 4.56)	<.01*
1-h OGTT plasma glucose (mmol/l)	8.98 ± 1.55	7.26 ± 1.43	<.01#
2-h OGTT plasma glucose (mmol/l)	7.79 ± 1.53	6.29 ± 1.02	<.01#
Fasting insulin (mU/L)	8.72 ± 3.52	6.72 ± 3.20	<.01#
HOMA-IR	1.83 ± 0.78	1.31 ± 0.66	<.01#
HOMA-β	146.75 (105.58, 237.76)	154.81 (109.28, 229.56)	.57*
HOMA-S	0.54 (0.43, 0.75)	0.66 (0.54, 0.99)	<.01*
Cholesterol (mmol/L)	5.60 (4.63, 6.53)	5.36 (4.79, 5.91)	.09*
HDL-C (mmol/L)	1.51 (1.35, 1.71)	1.52 (1.44, 1.72)	.19*
LDL-C (mmol/L)	3.45 (2.65, 4.48)	3.12 (3.61, 3.74)	<.01*
Triglycerides (mmol/L)	2.77 (2.22, 3.67)	2.56 (1.94, 3.44)	.02*

Abbreviations: HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-S, homeostatic model assessment of insulin sensitivity; HOMA-β, homeostatic model assessment of β-cell function; LDL-C, low-density lipoprotein; n. normally distributed data are presented as mean ± SD.

*Mann-Whitney U test.

#Independent-sample Student's t test.

TABLE 3 Infant umbilical arterial biochemical markers

Infant arterial umbilical chemistry	Vitamin D deficiency	Control	*P*
N	185	240	
Glucose (mmol/l)	5.17 (5.06, 5.24)	5.15 (5.05, 5.26)	.67*
Triglycerides (mmol/L)	3.12 (2.45, 4.19)	2.54 (2.08, 3.24)	<.01*
HDL-C (mmol/L)	1.13 (0.89, 1.27)	1.25 (0.94, 1.56)	<.01*
LDL-C(mmol/L)	1.60 (1.12, 2.03)	1.61 (1.10, 2.30)	.81*
HOMA-IR	2.13 (1.71, 2.70)	2.31 (1.82, 2.70)	.35*
HOMA-β	113.31 ± 26.68	120.11 ± 28.32	.01#
HOMA-S	0.47 (0.37, 0.58)	0.43 (0.37, 0.55)	.35*
Fasting insulin(mU/L)	9.22 (7.35, 11.28)	10.14 (8.15, 11.49)	.18*

Abbreviations: HDL-C, high-density lipoprotein;HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-S, homeostatic model assessment of insulin sensitivity; HOMA-β, homeostatic model assessment of β-cell function; LDL-C, low-density lipoprotein; n. normally distributed data are presented as mean ± SD.

*Mann-Whitney U test.

#Independent-sample Student's t test.

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, $P < .01$), 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, $P < .01$), LDL-C [3.45 (2.65, 4.48) vs 3.12 (3.61, 3.74) mmol/L, $P < .01$] 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) mmol/L, $P = .09$] and HDL-C [1.51 (1.35, 1.71) vs 1.52 (1.44, 1.72) mmol/L, $P = .19$] 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) mmol/L, 113.31 ± 26.68 vs 120.11 ± 28.32; $P < .01$, $P = .01$, 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) 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) vs 5.15 (5.05, 5.26) mmol/L, $P = .67$], LDL-C [1.60 (1.12, 2.03) vs 1.61 (1.10, 2.30) mmol/L, $P = .81$], insulin [9.22 (7.35, 11.28) vs 10.14 (8.15, 11.49) 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) 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 ($r = -.09$, $-.05$, $.07$ and $-.03$, respectively, all $P > .05$). However, there was an inverse correlation between serum 25(OH)D and glucose, insulin, LDL, CHO, triglycerides and HOMA-IR ($r = -.38$, $-.27$, $-.2$, $-.11$, $-.11$, $-.33$ and $.11$; $P < .01$, $<.01$, $<.01$, $<.05$, $<.05$ and $<.01$, respectively) and there was a positive correlation between serum 25(OH)D and HOMA-S ($r = .11$, $P < .05$).

TABLE 4 Correlations between maternal biochemical markers and maternal serum 25(OH)D concentrations

Variable	*r*	*P*
Ages	−.09	.06
Prepregnancy BMI (kg/m^2)	−.05	.34
Fasting insulin (mU/L)	−.27	<.01
Glucose (mmol/l)	−.38	<.01
Cholesterol (mmol/L)	−.11	.03
Triglycerides (mmol/L)	−.11	.02
HDL-C (mmol/L)	.07	.14
LDL-C (mmol/L)	−.2	<.01
HOMA-IR	−.33	<.01
HOMA-S	.11	.03
HOMA-β	−.03	.49

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-S, homeostatic model assessment of insulin sensitivity; HOMA-β, homeostatic model assessment of β-cell function; LDL-C, low-density lipoprotein.

TABLE 5 Correlations between infant umbilical arterial biochemical markers and maternal serum 25(OH)D concentration

Variable	*r*	*P*
Fasting insulin (mU/L)	.034	.49
Glucose (mmol/L)	−.081	.1
Triglycerides (mmol/L)	−.286	<.01
HDL-C (mmol/L)	.154	<.01
LDL-C (mmol/L)	−.025	.61
HOMA-IR	.015	.75
HOMA-S	−.028	.56
HOMA-β	.103	.03

Abbreviations: HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-S, homeostatic model assessment of insulin sensitivity; HOMA-β, homeostatic model assessment of β-cell function; LDL-C, low-density lipoprotein.

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 ($r = -.286$, $P < .01$), while HDL-C and HOMA-β in the umbilical artery were positively correlated with maternal serum 25(OH)D concentration ($r = .154$, $.103$; $P < .01$, $<.05$, respectively). No significant correlation was found between maternal serum 25(OH)D concentration and glucose, INS, LDL-C, HOMA-IR and HOMA-S ($r = -.081$, $.034$, $-.025$, $.015$ and $-.028$, respectively, all $P > .05$).

3.6 | Adverse pregnancy outcome

The incidences of GDM [19.45% (36/185) vs 12.08% (29/240), $P = .04$], pre-eclampsia [4.8% (9/185) vs 1.25% (3/240), $P = .03$] and PROM [15.68% (29/185) 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	χ^2	*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.[5-7] 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.[21] Limited sun exposure has been a major cause for the vitamin D deficiency pandemic in adults and children.[22,23] Vitamin D is a fat-soluble secosteroid 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.[24,25] 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[26-28] [26-28]. 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 foetus 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,[29,30] specifically by promoting insulin sensitivity through stimulating the expression of insulin receptors and increasing glucose transport.[30] 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.[31,32] Maternal serum 25(OH)D concentration has been shown to negatively correlate with fasting glucose and insulin levels during pregnancy.[33] Previous studies found that serum 25(OH)D concentration was lower in GDM participants.[34,35] 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.[36] Consistent with previous reports,[36,37] 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 (r = −.38, −.27, −.2, −.11, −.11, −.33 and .11; P < .01, <.01, <.01, <.05, <.05 and <.01, respectively), while a positive correlation was observed between serum 25(OH)D and HOMA-S (r = .11, P < .05). Therefore, we infer that 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.[38] Foetuses with vitamin D deficiency are at excessive risk of FGR, obesity, insulin resistance, hypocalcaemia and other orthopaedic complications.[39] 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.[40,41] Maternal vitamin D deficiency is also associated with lower bone mineral concentration and impaired glucose homeostasis in newborn infants.[42-44] Intra-uterine exposure to low 25(OH)D concentrations is associated with lower muscle mass and higher insulin resistance in children.[45] 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.[46] 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.[47,48] 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 (r = −.286, P < .05), while HDL and HOMA-β in infant umbilical arterial blood were positively correlated with maternal serum 25(OH)D concentration (r = .154 and .103; P < .01 and <.05, respectively). 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.[9,49] 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.[50] 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.[40] 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.

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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. HYC, HPZ, YJ and ZQH executed the study. HYC, HXX and QQD analysed and involved in interpretation of data. HYC and JQZ drafted the article. HYC 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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REFERENCES

1. Schuster I. Cytochromes P450 are essential players in the vitamin D signaling system[J]. *Biochim Biophys Acta*. 2011;1814(1):186-199.
2. Jo EK. Innate immunity to mycobacteria: vitamin D and autophagy[J]. *Cell Microbiol*. 2010;12(8):1026-1035.
3. Autier P, Boniol M, Pizot C, et al. Vitamin D status and ill health: a systematic review[J]. *Lancet Diabetes Endocrinol*. 2014;2(1):76-89.
4. Rosen CJ, Abrams SA, Aloia JF, et al. IOM committee members respond to endocrine society vitamin D guideline [J]. *J Clin Endocrinol Metab*. 2012;97(4):1146-1152.
5. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. *Ann Epidemiol*. 2009;19(2):73-78.
6. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency [J]. *Lancet*. 1998;351(9105):805-806.
7. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline[J]. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.
8. Zhang C, Qiu C, Hu FB, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus[J]. *PLoS One*. 2008;3(11):e3753.
9. Kaushal M, Magon N. Vitamin D in pregnancy: a metabolic outlook[J]. *Indian J Endocrinol Metab*. 2013;17(1):76-82.
10. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention[J]. *Rev Endocr Metab Disord*. 2017;18(2):153-165.
11. Triunfo S, Lanzone A, Lindqvist PG. Low maternal circulating levels of vitamin D as potential determinant in the development of gestational diabetes mellitus[J]. *J Endocrinol Invest*. 2017;40(10):1049-1059.
12. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials[J]. *Fertil Steril*. 2015;103(5):1278-1288.e4.
13. Wagner CL, Hollis BW. The implications of vitamin D status during pregnancy on mother and her developing child[J]. *Front Endocrinol*. 2018;9:500.
14. Monte S. Biochemical markers for prediction of preclampsia: review of the literature [J]. *J Prenat Med*. 2011;5(3):69-77.
15. Mol BWJ, Roberts CT, Thangaratinam S, et al. Pre-eclampsia [J]. *Lancet*. 2016;387(10022):999-1011.
16. Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus [J]. *Am Fam Physician*. 2015;91(7):460-467.
17. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol [J]. *Fetal Diagn Ther*. 2014;36(2):86-98.
18. Medina TM, Ashley Hill D. Preterm premature rupture of membranes: diagnosis and management [J]. *Am Fam Physician*. 2006;73(4):659-664.
19. Gotsch F, Gotsch F, Romero R, et al. The preterm parturition syndrome and its implications for understanding the biology, risk

assessment, diagnosis, treatment and prevention of preterm birth [J]. *J Matern Fetal Neonatal Med*. 2009;22(S2):5-23.
20. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program[J]. *Diabetes Care*. 1998;21(12):2191-2192.
21. El Koumi MA, Ali YF, Abd El Rahman RN. Impact of maternal vitamin D status during pregnancy on neonatal vitamin D status[J]. *Turk J Pediatr*. 2013;55(4):371-377.
22. Wacker M, Holick MF. Sunlight and Vitamin D: a global perspective for health[J]. *Dermatoendocrinology*. 2013;5(1):51-108.
23. Holick MF. Biological effects of sunlight, ultraviolet radiation, visible light, infrared radiation and vitamin D for health[J]. *Anticancer Res*. 2016;36(3):1345-1356.
24. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective[J]. *Mayo Clin Proc*. 2013;88(7):720-755.
25. Haussler MR, Haussler CA, Bartik L, et al. Vitamin D receptor: molecular signaling and actions of nutritional ligands in disease prevention[J]. *Nutr Rev*. 2008;66(10 Suppl 2):S98-S112.
26. Challa AS, Makariou SE, Siomou EC. The relation of vitamin D status with metabolic syndrome in childhood and adolescence: an update[J]. *J Pediatr Endocrinol Metab*. 2015;28(11–12):1235-1245.
27. Mitri J, Nelson J, Ruthazer R, et al. Plasma 25-hydroxyvitamin D and risk of metabolic syndrome: an ancillary analysis in the Diabetes Prevention Program[J]. *Eur J Clin Nutr*. 2014;68(3):376-383.
28. Jamka M, Woźniewicz M, Jeszka J, et al. The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis[J]. *Sci Rep*. 2015;5:16142.
29. Chiu K, Chu A, Go V, et al. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction[J]. *Am J Clin Nutr*. 2004;79(5):820-825.
30. Palomer X, González-Clemente JM, Blanco-Vaca F, et al. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus[J]. *Diabetes Obes Metab*. 2008;10(3):185-197.
31. Gurol A, Okten-Kursun A, Kasapoglu P, et al. The synergistic effect of ω3 and Vit D3 on glycemia and TNF-α in islet transplantation[J]. *Cell Mol Biol*. 2016;79(5):90-98.
32. Van Assche FA, Holemans K, Aerts L. Long-term consequences for offspring of diabetes during pregnancy. *Br Med Bull*. 2001;60(1):173-182.
33. Maghbooli Z, Hossein-nezhad A, Karimi F, et al. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy[J]. *Diabetes Metab Res Rev*. 2008;24(1):27-32.
34. McManus R, Summers K, de Vrijer B, et al. Umbilical Arterial and Umbilical Venous 25-hydroxyvitamin D and adipocytokine concentrations in pregnancies with and without gestational diabetes [J]. *Clin Endocrinol*. 2014;80(5):635-641.
35. Arnold DL, Enquobahrie DA, Qiu C, et al. Early pregnancy maternal vitamin D concentrations and risk of gestational diabetes mellitus [J]. *Paediatr Perinat Epidemiol*. 2015;29(3):200-210.
36. Savastano S, Barrea L, Savanelli MC, et al. Low vitamin D status and obesity: Role of nutritionist [J]. *Rev Endocr Metab Disord*. 2017;18(2):215-225.
37. Soheilykhah S, Mojibian M, Rashidi M, et al. Maternal vitamin D status in gestational diabetes mellitus[J]. *Nutr Clin Pract*. 2010;25(5):524-527.
38. Barker DJ, Osmond C. Diet and coronary heart disease in England and Wales during and after the second world war[J]. *J Epidemiol Community Health*. 1986;40(1):37-44.
39. Elsori DH, Hammoud MS. Vitamin D deficiency in mothers, neonates and children. *J Steroid Biochem Mol Biol*. 2018;175:195-199.
40. Zhou J, Su L, Liu M, et al. Associations between 25-hydroxyvitamin D levels and pregnancy outcomes: a prospective observational study in southern China[J]. *Eur J Clin Nutr*. 2014;68(8):925-930.
41. Camargo CA, Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D Levels and Risk of Respiratory Infection, Wheezing, and Asthma[J]. *Pediatrics*. 2011;127(1):e180-e187.
42. Yang J, Tamura R, Uusitalo U, et al. Vitamin D and probiotics supplement use in young children with genetic risk for type 1 diabetes. *Eur J Clin Nutr*. 2017;71(12):1449-1454.
43. Mannion C, Gray Donald K, Koski K. Association of low intake of milk and vitamin D during pregnancy with decreased birth weight[J]. *CMAJ*. 2006;174(9):1273-1277.
44. Weiss S, Litonjua A. Childhood asthma is a fat-soluble vitamin deficiency disease[J]. *Clin Exp Allergy*. 2008;68(8):385-387.
45. Krishnaveni GV, Veena SR, Winder NR, et al. Maternal vitamin D status during pregnancy and body composition and cardiovascular risk markers in Indian children: the Mysore Parthenon study [J]. *Am J Clin Nutr*. 2011;93(3):628-635.
46. Huisjes HJ, Aarnoudse JG. Arterial or venous umbilical pH as a measure of neonatal morbidity? [J]. *Early Hum Dev*. 1979;3(2):155-161.
47. Wojcik-Baszko D, Charkiewicz K, Laudanski P. Role of dyslipidemia in preeclampsia-a review of lipidomic analysis of blood, placenta, syncytiotrophoblast microvesicles and umbilical cord artery from women with preeclampsia [J]. *Prostaglandins Other Lipid Mediat*. 2018;139:19-23.
48. Bae JY, Seong WJ. Umbilical arterial N-terminal pro-B-type natriuretic peptide levels in preeclampsia, fetal growth restriction, preterm birth and fetal distress [J]. *Clin Exp Obstet Gynecol*. 2016;43(3):393-396.
49. Kraemer F, Ginsberg H. Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease[J]. *Diabetes Care*. 2014;37(5):1178-1181.
50. Baker AM, Haeri S, Camargo CA, et al. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia[J]. *J Clin Endocrinol Metab*. 2010;95(11):5105-5109.

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