The Relationship Between Maternal and Fetal Vitamin D, Insulin Resistance, and Fetal Growth

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Abstract

Evidence for a role of vitamin D in maintaining normal glucose homeostasis is inconclusive. We sought to clarify the relationship between maternal and fetal insulin resistance and vitamin D status. This is a prospective cohort study of 60 caucasian pregnant women. Concentrations of 25-hydroxyvitamin D (25-OHD), glucose, insulin, and leptin were measured in early pregnancy and at 28 weeks. Ultrasound at 34 weeks assessed fetal anthropometry including abdominal wall width, a marker of fetal adiposity. At delivery birth weight was recorded and fetal 25-OHD, glucose, C-peptide, and leptin measured in cord blood. Insulin resistance was calculated using the Homeostasis Model Assessment (HOMA) equation. We found that those with lower 25-OHD in early pregnancy had higher HOMA indices at 28 weeks, ($r = -.32$, $P = .02$). No significant relationship existed between maternal or fetal leptin and 25-OHD, or between maternal or fetal 25-OHD and fetal anthropometry or birth weight. The incidence of vitamin D deficiency was high at each time point (15%-45%). These findings lend support to routine antenatal supplementation with vitamin D in at risk populations.

Keywords

vitamin D, fetal adiposity, maternal BMI, glucose, insulin resistance

Introduction

Vitamin D deficiency is an increasing public health concern.¹ Though most commonly associated with rickets in childhood or osteomalacia in later adult life,² over the last few decades it has become increasingly apparent that a lack of vitamin D has potential health consequences that reach far beyond disordered calcium regulation and bone mineralization.³ Vitamin D receptors are distributed in a variety of tissues throughout the body.⁴ Hypovitaminosis D in adulthood has been linked to hypertension,⁵ cardiovascular disease,⁶ malignancies,^{7,8} and even mortality⁹; whereas during pregnancy, adverse outcomes such as preeclampsia, low birth weight, and an increased incidence of autoimmune diseases have all been linked to low vitamin D status,¹⁰ but the evidence is still inconsistent and inconclusive.¹¹ There is much debate regarding optimal antenatal vitamin D levels, but the recent Institute of Medicine (IOM) report suggested that serum 25-hydroxyvitamin D (25-OHD) concentrations of above 50 nmol/L be classified as sufficient, and concentrations of <30 nmol/L be considered at high risk of deficiency.¹¹

More recently attention has been focused on a possible role for vitamin D in maintaining normal glucose homeostasis in pregnancy. Vitamin D deficiency has been found to be

associated with pancreatic β cell dysfunction and insulin resistance in nonpregnant diabetic and nondiabetic populations.^{12,13} Moreover, it has been shown that insulin secretion is impaired in the vitamin D-deficient pancreas, and it is improved by dietary vitamin D repletion.¹⁴⁻¹⁶ These effects appear to be independent of circulating calcium concentrations.¹⁷

The prevalence of hypovitaminosis D is particularly high in pregnant populations.¹⁸⁻²⁰ The developing fetus is entirely dependent upon the maternal pool of calcium and, as such, there are growing concerns about the implications of vitamin D deficiency in pregnancy and beyond. Glucose is the main energy substrate for intrauterine growth.²¹ Disruption of normal glucose homeostasis in pregnancy predisposes to fetal macrosomia, and in particular, the excess deposition of

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subcutaneous fat.²² Maternal weight is increasing in the developed world and is intrinsically linked to glucose metabolism. Increased maternal BMI in pregnancy confers an increased risk of delivering a macrosomic infant²³ and has also been associated with a higher predisposition to vitamin D deficiency in a number of studies.²⁴ Fetal macrosomia is not only associated with an increased risk of adverse obstetric outcomes such as traumatic birth injury, perineal trauma, and an increase in operative delivery rates,^{25,26} but perhaps more importantly increased birth weight has been linked to childhood obesity²⁷ with its inherent implications for later adult health.

Leptin is an adipokine involved in the regulation of body weight through appetite suppression and the stimulation of energy expenditure.²⁸ Leptin appears to play a role in a number of processes associated with pathological fetal growth, most notably maternal diabetes,²⁹ and interestingly has been proposed as a biomarker for fetal adiposity by a number of authors.³⁰

The relationship between maternal adiposity, maternal vitamin D status, glucose homeostasis, and fetal growth is likely to be complex. Our objective was to clarify this relationship in a prospective, longitudinal study examining maternal and fetal vitamin D status, glucose, insulin resistance, leptin, and both maternal and fetal adiposity in a cohort of healthy women at risk of glucose intolerance and fetal macrosomia during pregnancy.

Materials and Methods

Study Sample

This was a prospective cohort study with institutional ethical approval of 60 mother and infant pairs who delivered at the National Maternity Hospital, Ireland, from January 2008 to October 2010. The National Maternity Hospital is a tertiary referral institution delivering over 9000 women annually.

Women were recruited at first antenatal consultation at 14.3 $\pm$ 2.3 weeks' gestation. All women were caucasian and secundigravid, having had 1 previous uncomplicated pregnancy delivering an infant weighing greater than 4 kg, and therefore selected as a cohort at risk of glucose intolerance and fetal macrosomia. Women were excluded if they had any underlying medical conditions, if they were less than 18 years of age, if they had previous gestational or preexisting type 1 or type 2 diabetes or if they were unable to give full informed consent. In order to account for known seasonal variation in vitamin D concentrations, 30 of the women were recruited during summer months and 30 during winter months.

Assessments

At the initial visit and at 28 weeks all women had measurement of weight, height, and upper arm circumference; fasting serum glucose, insulin, leptin, and 25-OHD concentrations were measured. Maternal weight was recorded at each antenatal visit and gestational weight gain calculated at 28 and at 34 weeks of

gestation. At delivery, infant birth weight, infant length, and head circumference were recorded, and a cord blood sample for fetal glucose, leptin, C-peptide, and 25-OHD concentrations taken.

Fetal Ultrasound

Fetal biometry was assessed ultrasonographically at 34 weeks' gestation using a Voluson 730 Expert (GE Medical Systems, Germany). Biparietal diameter, head circumference, abdominal circumference, femur length, and anterior abdominal wall width (AAW), a marker of fetal adiposity were recorded. Fetal AAW was measured at the traditional abdominal circumference view, 2 to 3 cm lateral to the cord insertion and included fetal skin and subcutaneous tissue. A total of 3 measurements were obtained and the mean recorded. This measurement has been validated in both diabetic and nondiabetic populations as a marker of fetal adiposity.^{31,32}

Laboratory Methods

Serum 25-OHD concentrations were measured by competitive radioimmunoassay (Immunodiagnostic Systems Limited, Bolton, Tyne & Wear, UK). The coefficients of variation (CV) for the 25OHD assay are as follows: inter-assay CV at a concentration of 29 nmol/L was 6.2% and at a concentration of 106 nmol/L was 7.7%; intra-assay CV at a concentration of 29 nmol/L was 3.0% and at a concentration of 74 nmol/L was 2.7%. In order to ensure a high standard of analysis, we participate in the Vitamin D External Quality Assessment Scheme.³³ Multianalyte profiling was performed on the Luminex Magpix system (Luminex Corporation Austin, USA). Plasma concentrations of leptin, insulin, and C-peptide were determined by the Human Endocrine Panel. Maternal insulin resistance was calculated using the Homeostasis Model Assessment (HOMA) equation³⁴: $\text{HOMA score} = (\text{Fasting insulin } \mu\text{U/mL} \times \text{fasting glucose mmol/L}) / 22.5$. Fetal insulin resistance was assessed with cord blood C-peptide estimation.

Dietary Assessment

Dietary vitamin D intake was assessed using a 3-day food diary, which was completed in 1 to 2 weeks following the first antenatal consultation. Women were requested to record their usual food and beverage intake over 3 consecutive days, including a weekend day. Dietary data were entered and analyzed using Weighed Intake Software Program (WISP; Tinuviel Software, Anglesey, UK). The WISP uses food composition data from sixth edition of McCance and Widdowson's *The Composition of Foods*.³⁵

Statistical Analysis

Data were assessed for normality using Shapiro Wilk and *P-P* plot. Results are expressed as mean $\pm$ standard deviation (SD). Positive and negative correlations were assessed using Pearson correlation coefficient for normally distributed data and

Table 1. Mean 25-OHD Concentrations and Proportions Classified According to IOM Cut Points Within the Cohort in Early Pregnancy, at 28 Weeks of Gestation and in Cord Blood at Delivery.

	Mean (SD) 25-OHD, nmol/L	≥50 nmol/LN (%)	30-49.9 nmol/LN (%)	<30 nmol/L, N (%)
Early pregnancy ^a	45.7 (22.5)	23 (38%)	20 (33%)	17 (28%)
28 Weeks' gestation	54.4 (33.4)	25 (42%)	26 (43%)	9 (15%)
Cord blood	31.8 (12.5)	5 (8%)	28 (47%)	27 (45%)

Abbreviations: 25-OHD, 25-hydroxyvitamin D; IOM, Institute of Medicine.

^a Early pregnancy = 14.3 ± 2.3 weeks' gestation.**Table 2.** Correlation Between Maternal and Fetal 25-OHD and Maternal and Fetal Insulin Resistance and Leptin.^a

	Early Pregnancy HOMA Index	28-Week HOMA Index	Cord Blood C-Peptide	Early Pregnancy Leptin	28-Week Leptin	Cord Blood Leptin
Early pregnancy 25-OHD	.13	.19	-.14	-.22	-.14	-.11
28-week 25-OHD	-.32 ^b	-.25	-.08	-.01	.03	-.01
Cord blood 25-OHD	.08	.05	-.08	-.04	.02	-.15

Abbreviations: HOMA Index = Homeostasis Model Assessment Equation.²⁵ (HOMA index = (Fasting insulin μU/mL × fasting glucose mmol/L)/ 22.5); 25-OHD, 25-hydroxyvitamin D.^a Correlation coefficient = Spearman rho for nonparametric data.^b $P < .05$.

Spearman rho for nonparametric data. Comparison of means within groups of patients was accomplished with the independent samples *t* test. Further analysis was performed by dividing the cohort into 2 equal-sized groups based on 25-OHD concentrations at each time point of greater than or less than the median for the group (namely 41.0 nmol/L in early pregnancy, 45.7 nmol/L at 28 weeks, and 30.8 nmol/L in cord blood). Statistical significance was set at $P < .05$. Statistical analysis was performed using SPSS Windows version 18.0 (SPSS, Chicago, Illinois).

Results

The mean 25-OHD concentration was 45.7 ± 22.5 nmol/L in early pregnancy, 54.4 ± 33.4 nmol/L at 28 weeks of gestation, and 31.8 ± 12.5 nmol/L in cord blood at delivery. According to IOM, using a probabilities approach to 25-OHD cut points, a value <30 nmol/L indicates high risk of deficiency, and a value >50 indicates adequacy in the majority.²⁹ In our study 25-OHD values >50 nmol/L was noted in 38% in early pregnancy, 42% at 28 weeks, and 8% at birth. Values <30 nmol/L were noted in 28% in early pregnancy, 15% at 28 weeks, and 45% at birth (Table 1). Within the cohort, 37 women were taking prenatal vitamin supplementation, which included vitamin D. The mean dietary intake of vitamin D as assessed by the 3-day food diary in early pregnancy was low, at just 2.78 ± 1.8 μgm. The mean dietary intake including supplements was 7.78 ± 4.8 μgm.

No significant association was identified between maternal 25-OHD at any time point for maternal weight, height, BMI, or upper arm circumference in early pregnancy.

Similarly there was no association found between maternal 25-OHD and upper arm circumference at 28 weeks of gestation and gestational weight gain at 28 or 34 weeks of gestation. No significant association was identified between maternal or fetal 25-OHD and fetal weight or adiposity (AAW) at 34 weeks of gestation, nor between maternal or fetal 25-OHD and neonatal anthropometry.

There was a significant association between maternal 25-OHD at 28 weeks of gestation and maternal insulin resistance in early pregnancy (Table 2). Those with lower 25-OHD in early pregnancy had higher HOMA indices at 28 weeks ($r = -.32$, $P = .02$). Those with lower 25-OHD at 28 weeks also had higher HOMA indices at 28 weeks, though this trend was not statistically significant ($r = -.25$, $P = .08$).

Maternal leptin correlated with maternal BMI ($r = .31$, $P = .02$ in early pregnancy) and arm circumference ($r = .37$, $P = .007$ in early pregnancy, $r = .37$, $P = .007$ at 28 weeks; Table 3). Maternal leptin at each time point correlated with the estimated fetal weight at 34 weeks of gestation ($r = .38$, $P = .005$ in early pregnancy and $r = .33$, $P = .017$ at 28 weeks). Maternal early pregnancy leptin was also related to birth weight ($r = .36$, $P = .008$). There was no association between fetal leptin and maternal or infant size (Table 3). No significant correlation was noted between maternal or fetal 25-OHD at any time point and maternal or fetal leptin.

A comparison of maternal and fetal insulin resistance and leptin between those with 25-OHD concentrations greater than or less than the median for each time point was made (Table 4). Those with 25-OHD concentrations greater than the median at 28 weeks of gestation had significantly lower HOMA indices in early pregnancy than those who did not

Table 3. Correlation Between Maternal and Fetal Leptin and Maternal, Fetal, and Infant Size.^{a,b}

		BMI in Early Pregnancy	Arm Circumference in Early Pregnancy	Estimated Fetal Weight at 34 Weeks	Birth Weight
Early pregnancy leptin	Correlation coefficient	.31	.37	.38	.36
	P value	.02	.007	.005	.008
28-week leptin	Correlation coefficient	.26	.37	.33	.23
	P value	.06	.007	.017	.08
Cord leptin	Correlation coefficient	.14	.21	.24	.15
	P value	.3	.1	.1	.2

Abbreviations: BMI, body mass index.

^a Correlation coefficient = Spearman rho for nonparametric data.^b $P < .05$ considered significant.**Table 4.** Comparison of Mean Maternal and Fetal Insulin Resistance and Leptin in Those With 25-OHD Concentrations Above and Below the Median at Each Time Point.

		Early Pregnancy HOMA Index	28-Week HOMA Index	Cord blood C-Peptide, pg/mL	Early Pregnancy Leptin, pg/mL	28-week Leptin, pg/mL	Cord Blood Leptin, pg/mL
Early pregnancy 25-OHD ^a	Less than median	1.56 (1.7)	2.36 (3.2)	396.4 (361)	17 179 (9737)	19 456 (12 425)	260 401 (18 882)
	Greater than median	1.87 (1.9)	2.42 (1.5)	400.6 (391)	14 541 (10 191)	16 962 (10 617)	24 320 (19 292)
	P Value	.5	.9	.9	.3	.4	0.7
28 Weeks 25-OHD ^b	Less than median	2.24 ^d (2.1)	3.05 (3.1)	411.05 (375)	16 152 (9799)	19 415 (12 951)	24 916 (18 618)
	Greater than median	1.1 ^d (1.9)	1.72 (1.7)	385.53 (378)	15 811 (10 269)	17 179 (10 201)	25 441 (19 656)
	P value	.02	.07	.8	.9	.4	.9
Cord blood 25-OHD ^c	Less than median	1.35 (1.5)	2.61 (3.1)	465.18 (368)	16 443 (9390)	17 164 (11 739)	29 207 (20 936)
	Greater than median	2.1 (1.9)	2.15 (1.9)	329.24 (372)	15 543 (10 596)	19 430 (11 454)	20 950 (15 900)
	P Value	.1	.5	.1	.7	.4	.1

Abbreviations: HOMA = Homeostasis Model Assessment; 25-OHD, 25-hydroxyvitamin D.

^a Median 25-OHD in early pregnancy = 41.0 nmol/L.^b Median 25-OHD at 28 weeks = 45.7 nmol/L.^c Median 25-OHD in cord blood = 30.8 nmol/L.^d $P < 0.05$ considered significant.

(1.1 ± 1.9 vs 2.2 ± 2.1 , $P = .02$). Those with 25-OHD concentrations of greater than the median at 28 weeks of gestation also had lower HOMA indices at 28 weeks, though this was not statistically significant (1.7 ± 1.7 vs 3.1 ± 3.1 , $P = .07$).

Discussion

These results in a cohort of 60 women, with assessment of 25-OHD at multiple time points in pregnancy, confirm the complexity of the relationship between maternal and fetal glucose homeostasis, adiposity, and vitamin D status in pregnancy. Our findings confirm the high prevalence of hypovitaminosis D in pregnant populations, particularly those living in countries at high latitudes. According to IOM cut points for 25-OHD, 28% were at risk for deficiency at outset, reducing to 15% at 28 weeks but up to 45% at birth.³⁶ Our cohort of women was caucasian and living in Dublin, which is located at latitude 53° North. It is established that vitamin D status varies with the season in young adults and in the elderly individuals and is known to be lower during the winter in Europe than in both North America and Scandinavia; additionally oral vitamin D intake is known to be lower in Europe than in both North America and Scandinavia.³⁷

We did not identify any significant relationship between 25-OHD and either maternal or fetal weight or adiposity;

however, a relationship between maternal 25-OHD and insulin resistance was found. Those with lower 25-OHD in early pregnancy had significantly higher HOMA indices at 28 weeks, and those with lower 25-OHD at 28 weeks also had higher HOMA indices at 28 weeks though this trend was not statistically significant.

Data in the literature to date regarding the relationship between vitamin D and glucose metabolism are conflicting. Poor vitamin D status has been implicated in the pathogenesis of type 1 diabetes for some time,³⁸ but more recently evidence is emerging for a role in insulin resistance and type 2 diabetes.^{12,13} The data relating to gestational diabetes (GDM) and fetal growth are less clear. In 2008, Zhang et al performed a nested case-control study of 57 women with GDM and 114 without from a prospective cohort of 953 women.³⁹ The authors found that among women who developed GDM, maternal plasma 25-OHD concentrations at an average of 16 weeks of gestation were significantly lower than controls and concluded that maternal vitamin D deficiency in early pregnancy is associated with a significantly elevated risk of GDM. They also reported an inverse association between maternal BMI and 25-OHD concentrations, though no comment on maternal or fetal adiposity, or infant birth weight was made. In contrast, Farrant et al in 2009 found no association between maternal hypovitaminosis D

at 30 weeks of gestation and the incidence of gestational diabetes, impaired fetal growth, or cord insulin resistance in a large cohort of Indian mothers.⁴⁰ Interpretation of these studies is limited by the heterogeneity of the populations studied and difficulty in determining relationships based on a single 25-OHD level at one time point and the pregnancy outcome.

Our study is strengthened by the assessment of 25-OHD concentrations and markers of insulin resistance at multiple time points and also by the addition of data on maternal, and particularly fetal adiposity, which, to our knowledge, has not been previously examined. Infant birth weight is a complex interplay of environmental and genetic factors, the addition of a marker of fetal adiposity is useful in determining whether a baby is constitutionally large or has been exposed to excess substrate delivery secondary to disruption of the normal glucose–insulin–leptin axis.⁴¹

Though we did note a relationship between maternal insulin resistance and 25-OHD, we did not establish an association with either maternal or fetal leptin levels; larger studies are now needed to elucidate whether a relationship between vitamin D and leptin exists.

Our study has some limitations worthy of consideration. Our cohort is just 60 women, but all had analyses at multiple time points in pregnancy and had additional ultrasonographic and neonatal assessments, which previous studies have overlooked. Our study had strict inclusion criteria: all our study participants were caucasian, living in a climate of limited sun exposure, and secundigravid having previously delivered a macrosomic infant. They are not, therefore, a representative sample of all pregnant women and it could be argued that these strict inclusion criteria limited the potential to identify a relationship between 25-OHD and birth weight. They were, however, specifically identified as a group likely to be at risk of both impaired glucose tolerance and fetal macrosomia and therefore potentially be the target of any future intervention trials of vitamin D supplementation to maintain normal glucose homeostasis and fetal growth in pregnancy.

These findings add to the growing body of evidence supporting routine antenatal supplementation with vitamin D in deficient populations. There remains, however, a significant lack of data in the literature regarding optimal antenatal dosing. The IOM specified that the intake needed to meet the requirements of 97.5% of pregnant women was 600 IU/d in those with minimal sunlight exposure.^{36,42} Using a probabilistic distribution approach and a simulated dose response, they identified a serum 25-OHD level of 50 nmol/L as being equivalent to the recommended daily allowance.¹¹ The Endocrine Society Clinical Practice Guideline suggests⁴³ that pregnant and lactating women require at least 600 IU/d of vitamin D and comment that at least 1500 to 2000 IU/d of vitamin D may be needed to maintain a blood level of 25(OH)D above 30 nmol/L. Further, larger randomized studies are necessary before the optimum dose of antenatal supplementation can be clarified.

In conclusion, our findings have confirmed that the relationship between maternal vitamin D, glucose homeostasis, and fetal growth is complex. Further interrogation of the relationship between vitamin D and insulin resistance is required and consideration given to a randomized control trial of vitamin D supplementation in women at risk of gestational diabetes.

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Declaration of Conflicting Interests

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