Vitamin D deficiency in early pregnancy is associated with increased cardiometabolic risk and gestational diabetes

Aya Mousa¹, Sally K Abell^{1,2}, Soulmaz Shoraeke^{1,2}, Cheryce L Harrison¹, Danielle Hiam³, Alba Moreno-Asso³, Nigel K Stepto³, Robert Scragg⁴, Helena J Teede^{1,2}, Barbora de Courten^{1,2}

¹ Monash Centre for Health Research & Implementation, Monash University, Melbourne, Australia; ² Diabetes and Vascular Unit, Monash Health, Melbourne, Australia; ³ Institute of Sport, Exercise and Active Living, Victoria University, Melbourne, Australia; ⁴ School of Population Health, University of Auckland, New Zealand.
Correspondence to Barbora de Courten: barbora.decourten@monash.edu

Background

- Vitamin D deficiency is prevalent worldwide, including in women of reproductive age.
- Low vitamin D has been linked to cardiometabolic risk during pregnancy and adverse pregnancy outcomes.
- Chronic low-grade inflammation has been proposed as a potential mechanism.

Aims

- To investigate relationships between maternal vitamin D level, glucose homeostasis, cardiovascular risk, and inflammation in pregnancy, as well as pregnancy outcomes.
- To examine whether relationships between vitamin D level and cardiometabolic risk and pregnancy outcomes may be mediated by underlying chronic low-grade inflammation.

Hypothesis

We hypothesized that there is an inverse relationship between vitamin D level and glucose intolerance, dyslipidemia, and adverse pregnancy outcomes, and that these relationships are mediated by increased inflammation.

Study population

- 102 pregnant women:
- Age >18 years (31.9 ± 4.5 years);
 - BMI 25 - 45 kg/m²;
 - High risk for Gestational Diabetes Mellitus (GDM) (score >3 on risk prediction tool)¹;
 - No type 1 or type 2 diabetes or existing chronic medical condition.

Methods

- At 12-15 weeks gestation:** body mass index (BMI); serum lipids; serum 25-hydroxyvitamin D3 (25(OH)D) (chemiluminescent assay); inflammatory markers: interleukin-6 (IL-6) and monocyte-chemoattractant protein-1 (MCP-1); and novel adipocytokines: omentin-1, visfatin, and high-molecular weight (HMW) adiponectin (ELISA).
- At 20-24 weeks gestation:** fasting, 1-hour, and 2-hour glucose (75g oral glucose tolerance test)
- At delivery:** gestation period and pregnancy outcomes
- Multivariable models were adjusted for maternal factors: age, BMI, parity, smoking, and birth country

Results

- 25(OH)D = 47.96 ± 16.04 nmol/L (mean ± SD)
- Age = 31.9 ± 4.5 yrs; BMI = 30.6 ± 6.7 kg/m² (mean ± SD)
- 25(OH)D levels were associated with:

Table 1. Univariable associations with 25(OH)D		
Variable	Coefficient (r) or odd ratio (95%CI)	p
Fasting glucose (mmol/L)	-0.32	0.002
1-hour glucose (mmol/L)	-0.21	0.049
Total cholesterol (mmol/L)	-0.22	0.03
Triglycerides (mmol/L)	-0.32	0.001
Interleukin-6 (pg/ml)	-0.20	0.049
HMW adiponectin (µg/ml)	0.26	0.008
Gestation (weeks)	0.27	0.006
GDM risk	0.97 (0.9-1.0)	0.04

25(OH)D is inversely related to fasting and 1-hour glucose (20-24 weeks gestation)

Table 2. Multiple Linear Regression					
Dependent Variable	Standardized β	R ²	t	p ¹	p ²
Gestation at birth (weeks)	0.30	0.11	2.71	0.008	0.02
Fasting glucose - OGTT ⁺ (mmol/L)	-0.32	0.17	-2.81	0.006	0.03
1-hour PC glucose - OGTT ⁺ (mmol/L)	-0.24	0.15	-2.04	0.045	0.3
Total cholesterol (mmol/L)	-0.26	0.21	-2.44	0.017	0.07
Triglycerides (mmol/L)	-0.28	0.15	-2.55	0.01	0.2
HMW adiponectin (µg/ml)	0.29	0.19	2.70	0.009	--

Table 3. Multiple Logistic Regression			
Dependent Variable	Model	OR (95% CI)	p
Gestational Diabetes Mellitus	+ maternal factors	0.97 (0.94 - 0.99)	0.04
	+ HMW adiponectin	0.98 (0.95 - 1.02)	0.3
Preterm birth (gestation <37 weeks)	+ maternal factors	0.93 (0.86 - 1.0)	0.06
	+ c-sections	0.89 (0.80 - 0.99)	0.04
	+ HMW adiponectin	0.89 (0.95 - 1.02)	0.09

All models adjusted for maternal factors: age, BMI, parity, smoking status and birth country. p¹= adjusted for maternal factors; p²= adjusted for maternal factors plus HMW adiponectin

Multivariable Analysis Results

- 25(OH)D remained associated with fasting glucose (p=0.006), 1-hour glucose (p=0.045), total cholesterol (p=0.02), triglycerides (p=0.01), HMW adiponectin (p=0.009), gestation (p=0.02), and GDM risk (0.04) after adjustment for maternal factors (Table 2 and Table 3).
- 25(OH)D was associated with reduced risk of preterm birth after additional adjustment for C-section (OR (95%CI)= 0.89 (0.80 - 0.99); p=0.04) (Table 3).
- Additional adjustment for HMW adiponectin in the models attenuated all associations except fasting glucose (p=0.03) and gestation (p=0.02) (Table 2 and 3).

Conclusions

- Consistent with previous studies, our data suggest a role for vitamin D in cardiometabolic risk factors in pregnancy and pregnancy outcomes.
- Most associations between vitamin D and cardiometabolic risk and pregnancy outcomes appear to be mediated by adiponectin.
- Interventional studies are needed to establish the effect of vitamin D supplementation on adiponectin and subsequent pregnancy risk factors and outcomes.

References

- Teh WT, Teede HJ, Paul E, Harrison CL, Wallace EM, Allan C. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. *Aust NZ J Obstet Gynaecol* 2011;51(1):26-30
- Flood-Nichols SK, Tinnemore D, Huang RR, et al. Vitamin D deficiency in early pregnancy. *PLoS ONE* 2015; 10(4):e0123763
- Yeow TP, Lim SL, Hor CP, et al. Impact of Vitamin D Replacement on Markers of Glucose Metabolism and Cardio-Metabolic Risk in Women with Former Gestational Diabetes – A Double-Blind, Randomized Controlled Trial. *PLoS ONE* 2015;10(6): e0129017