

Routine screening for vitamin D deficiency in early pregnancy: past its due date?

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Screening plus equitable provision of vitamin D supplements could mitigate many adverse outcomes

For nothing worthy proving can be proven,
Nor yet disproven: wherefore thou be wise,
Cleave ever to the sunnier side of doubt.

Alfred, Lord Tennyson, *The ancient sage*

Tennyson may not have been alluding to the need for high-level evidence from randomised controlled trials (RCTs) to alter clinical practice, but he would have been aware of children with rickets. Evidence has accumulated linking vitamin D deficiency to adverse outcomes in pregnancy, such as pre-eclampsia, hypertension, higher rates of caesarean section and preterm delivery. Lau and colleagues (*page 334*) contribute to this evidence by demonstrating that, in women with gestational diabetes mellitus (GDM), a lower serum 25-hydroxyvitamin D (25[OH]D) concentration was independently associated with poorer glycaemic control.¹

Of 147 women who were studied late in pregnancy (at a mean of 35 weeks' gestation), about 40% had vitamin D insufficiency or deficiency (serum 25[OH]D concentrations ≤ 50 nmol/L). Most of the women in this study were not white, and ethnicity, occupational status and season, not surprisingly, all influenced 25(OH)D concentrations, while body mass index did not. Perhaps more surprisingly, however, 25(OH)D concentrations were inversely associated with fasting and 2-hour glucose levels measured during an oral glucose tolerance test and with the marker of glycaemic control, glycated haemoglobin. Most importantly, serum 25(OH)D was an independent predictor of glycaemic control.



In adults, a number of large cross-sectional studies have shown a consistent, independent and positive relationship between serum 25(OH)D and insulin sensitivity, and an inverse relationship with risk of diabetes.²⁻⁵ Serum 25(OH)D levels have been shown to account for 42% of the variation in insulin sensitivity assessed by hyperglycaemic clamp.³ Consistent with Lau et al's findings, fasting and 2-hour levels of glucose and insulin have

been shown to be independently and inversely associated with serum 25(OH)D levels.³⁻⁵ In a United States study, the odds ratio for diabetes was 0.25 (95% CI, 0.11–0.60) for non-Hispanic white participants in the highest versus the lowest serum 25(OH)D quartile.² The highest-level evidence to date comes from a large prospective study with a 17-year follow-up that showed people in the highest quartile of serum 25(OH)D had a 40% decreased risk of type 2 diabetes compared with those in the lowest quartile.⁶ Based on these data, RCTs of vitamin D supplementation in adults to improve insulin sensitivity and reduce diabetes risk are underway.

GDM is becoming increasingly more common, affecting up to 10% of pregnancies. The presence of GDM is not trivial and has long-term implications for the health of mothers and their children. The former have an increased risk of developing type 2 diabetes, while their offspring have an increased risk of obesity and diabetes later in life. Vitamin D deficiency is also very common in

pregnancy. The prevalence of inadequate levels of vitamin D in Lau et al's study is comparable with rates of vitamin D insufficiency of 47.1% and 83.5% in white and black pregnant women, respectively, in the northern US (defined as 25[OH]D <80 nmol/L)⁷ and 65.3% in pregnant women in rural Victoria (defined as 25[OH]D <75 nmol/L).⁸ RCTs of vitamin D supplementation, initiated early in pregnancy, are now required to demonstrate whether vitamin D supplementation might reduce the incidence or severity of GDM.

International debate is currently focused on the optimal level of serum 25(OH)D. Based on meta-analyses using musculoskeletal end points in older individuals, cut points of 60 nmol/L and 75 nmol/L seem appropriate to prevent falls and fractures, respectively.⁹ However, a recent Institute of Medicine report recommended at least 50 nmol/L,¹⁰ which appears overly conservative and does not take season into account.

The public health implications of vitamin D deficiency in pregnancy are far broader than glycaemic control. In Australia, there has been a resurgence of rickets — partly owing to an increased refugee population comprising dark-skinned and veiled women with vitamin D deficiency, and also because of decreased exposure of babies to sunlight, lack of supplementation of infant feeds with vitamin D and weaning of infants onto non-milk liquids.

Milder forms of bone disease may also occur with vitamin D deficiency. Recently, a study that used three-dimensional ultrasonography in pregnant women showed that vitamin D deficiency was associated with increased femur metaphyseal cross-sectional area and increased femur splaying (the ratio of femoral metaphyseal cross-sectional area to femoral length) at as early as 19 weeks' gestation.¹¹ In addition, it was previously shown that children born to mothers with vitamin D deficiency (<50 nmol/L) during pregnancy exhibit deficits in total body bone mineral content as great as 11% at 9 years of age.¹² This could lead to an increased risk of osteoporotic fracture later in adult life, but this is unlikely to be evaluated in long-term studies.

In addition, maternal or early life vitamin D deficiency has been linked to an increased risk of several other disorders, including neonatal craniofacial, prematurity, type 1 diabetes mellitus, schizophrenia, and childhood respiratory infections and wheeze.^{13,14}

Current evidence strongly supports routine screening for vitamin D deficiency early in pregnancy. Furthermore, vitamin D supplementation to correct deficiency should be initiated early in pregnancy as it might reduce the incidence or severity of GDM and because changes in skeletal morphology of the fetus associated with deficiency are seen as early as 19 weeks' gestation. The most common recommended daily doses of cholecalciferol are 1000 IU–2000 IU, however, daily doses of up to 4000 IU have recently been shown to be safe in pregnancy (Bruce W Hollis, Professor, Department of Paediatrics, Medical University of South Carolina, USA, personal communication).

What is problematic is the equitable provision of vitamin D supplements to pregnant Australian women with deficiency. Pregnant and breastfeeding women who are most at risk of vitamin D deficiency are often the least likely to be able to afford supplements. In the United Kingdom, vitamin D supplements are provided free of charge to such women through the Healthy Start program.¹⁵ There is evidence to support more widespread use of

vitamin D supplements during pregnancy in Australia, although more research is required. One way to increase access might be to alter the scheduling of higher-dose, lower-cost vitamin D supplements.

Competing interests

I have received two research grants, one from sanofi-aventis, who market cholecalciferol in Australia, and one from DiaSorin in the US, who manufacture an assay for measurement of serum 25(OH)D. In addition, I am speaking at meetings for sanofi-aventis and DiaSorin later this year.

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