

Invited Commentary

Further evidence that prevention of maternal vitamin D deficiency may benefit the health of the next generation

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Maternal nutritional status is an important determinant of fetal development, and potentially lifelong health. A considerable body of data underpins the important role of vitamin D and Ca in fetal skeletal development, and vitamin D deficiency during pregnancy is a recognised risk factor for nutritional rickets in infancy⁽¹⁾. In the context of research exploring the contribution of early nutrition to childhood and adult health, the role of vitamin D in extra-skeletal developmental outcomes including body composition, immunological function and neurological development is receiving increasing attention. Umbilical cord blood concentrations of 25-hydroxyvitamin D (25(OH)D), the most commonly used biomarker of vitamin D status, are highly correlated with maternal circulating 25(OH)D⁽²⁾. This has two obvious but crucial implications. The first is that neonatal vitamin D deficiency is always caused by maternal deficiency. This means that prevention of maternal vitamin D deficiency should be prioritised for the protection of both mother and baby⁽³⁾. Second, unlike many other nutrients, where validated biomarkers of exposure are unavailable, there is potential to explore the role of vitamin D status in health and disease throughout the life course.

Despite the undisputed observation that maternal circulating 25(OH)D determines neonatal vitamin D status, which Hollis & Pittard⁽⁴⁾ reported several decades ago, pregnancy and infancy are life stages during which the risk of vitamin D deficiency remains high. A recent systematic literature review aiming to provide a global summary of vitamin D status in pregnant women and newborns reported that 54% of pregnant women and 75% of newborns had 25(OH)D concentrations < 50 nmol/l, with 18% of pregnant women and 29% of newborns < 25 nmol/l, the threshold below which the risk of nutritional rickets and osteomalacia increases sharply⁽⁵⁾. These high levels of deficiency have serious implications for maternal and child health, and several studies have reported associations between low vitamin D status and adverse perinatal outcomes including preeclampsia, gestational diabetes, intra-uterine growth restriction and small-for-gestational age (SGA) birth^(6–8). However, for several reasons, including frequent reliance on retrospective data, sometimes with inadequate clinical phenotyping, and variability in 25(OH)D analysis, the data are inconsistent. In their updated Cochrane review of vitamin D (and/or Ca) intervention studies in pregnancy, De-Regil *et al.*⁽⁹⁾ found moderate evidence for a role of vitamin D supplementation in preventing preeclampsia, low birth-weight and preterm birth, all of which impact fetal and neonatal growth, but urged caution in the clinical interpretation of the data due to low quality, absent reporting of adverse

effects and a high risk of bias in most studies. Moreover, two recent high-profile systematic reviews of 25(OH)D and pregnancy outcomes in observational studies^(10,11) highlighted the limitations imposed by high levels of heterogeneity in the meta-analyses and decided that the evidence was insufficient to draw firm conclusions. Clearly, many gaps remain in the knowledge base about vitamin D and its impact on perinatal outcomes.

In 2010, the Institute of Medicine (IOM)⁽¹²⁾ found a profound lack of evidence on which to set dietary requirements for vitamin D during pregnancy. Thus, the IOM defined requirements on the basis of skeletal health outcomes and specified a minimum threshold for serum 25(OH)D of 30 nmol/l as the level below which the risk of vitamin D deficiency increases, 40 nmol/l as the adequacy threshold and vitamin D sufficiency at concentrations \geq 50 nmol/l. Shortly afterwards, the Endocrine Society Task Force⁽¹³⁾ defined vitamin D deficiency as a serum 25(OH)D concentration < 50 nmol/l and recommended an individual target of at least 75 nmol/l. Notwithstanding the ongoing debate about target cut-offs for 25(OH)D, which investigators are working to resolve by strengthening the evidence base, the lack of consensus around cut-offs for sufficient vitamin D status has hampered international comparisons of vitamin D deficiency prevalence for too long. It is high time that the international vitamin D community reported 25(OH)D data using a range of thresholds, thus providing insight into the distributions of 25(OH)D concentrations in epidemiological studies in particular and generating a sound basis for international comparison. Pregnancy-specific 25(OH)D concentration cut-offs may be required^(14,15), as comparing 25(OH)D concentrations in pregnant women with thresholds established in non-pregnant adults is questionable⁽²⁾. Neonatal reference ranges for 25(OH)D are also not available and vary depending on maternal values.

Saraf *et al.*⁽⁵⁾ emphasised the comparative paucity of 25(OH)D data among pregnant women and newborns in Southeast Asia, most African countries and the Eastern Mediterranean region. In this context, data from Ong *et al.*⁽¹⁶⁾ obtained from a large (n 910), well-characterised, mother–child cohort of Chinese, Malay and Indian ethnicity make a valuable addition to the literature. The Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study was established in 2009 with the primary aim of evaluating the role of early developmental influences and interactions with epigenetic factors on metabolic function and body composition in early life⁽¹⁷⁾. The current analysis was conducted to investigate associations between maternal vitamin D status during pregnancy and infant



birth outcomes, postnatal growth and adiposity up to 24 months of age. Women were sampled at 26–28 weeks of gestation, and 25(OH)D analysis was completed using tandem MS, although data were not provided on quality assurance or use of standard reference materials. Frequent paediatric follow-up, with comprehensive anthropometry shortly after delivery and at regular intervals until the 24-month measurement, provided excellent data on the growth trajectory of this cohort, referenced to the WHO 2006 growth standards⁽¹⁸⁾.

This study describes a vitamin D-replete maternal population, with average 25(OH)D concentrations of approximately 80 nmol/l⁽¹⁶⁾. Only 13% of women had a 25(OH)D < 50 nmol/l and <2% had concentrations <30 nmol/l. Socio-demographic indicators interacted with vitamin D status in the cohort; women with comparatively lower circulating 25(OH)D were more likely to be younger, of Indian or Malay ethnicity, have a lower BMI and lower educational attainment. Most women consumed vitamin D supplements during pregnancy, but it is also important to note that at 1.4°N Singapore has abundant sunshine and little seasonal variation in UVB availability throughout the year. Limitations to sun exposure at this latitude are mainly determined by cultural and personal preferences, as opposed to the pronounced environmental deficit at high latitudes.

The GUSTO investigators reported no associations between maternal 25(OH)D at 26–28 weeks of gestation and preterm birth, SGA or any anthropometric variables or adiposity in the immediate postnatal period or during the first 2 years of life. The authors suggest that the absence of associations between vitamin D status and birth outcomes or postnatal growth and adiposity in this cohort may be due to the relatively high distribution of 25(OH)D concentrations in the sample. Recently, a Spanish cohort⁽¹⁹⁾ that reported a similar distribution of maternal 25(OH)D concentrations to GUSTO, with a median of 74 nmol/l and a prevalence of 20% < 50 nmol/l, noted only minor interactions between maternal vitamin D status and infant anthropometry, growth and adiposity at 2 years. On the other hand, Leffelaar *et al.*⁽²⁰⁾ observed strong associations between maternal vitamin D deficiency and risk of SGA as well as lower birth weight and accelerated growth in infancy. However, the distribution of 25(OH)D was much lower in the Dutch study, with 40% < 50 nmol/l and one-fifth < 30 nmol/l. These studies are comprehensively discussed by Ong *et al.*⁽¹⁶⁾ and interesting parallels are drawn with other studies expressing 25(OH)D data using various thresholds for deficiency. As in the GUSTO cohort, reported prevalence rates of vitamin D deficiency at higher and lower thresholds of 25(OH)D are likely to be driven by the distribution of 25(OH)D in the sample under investigation. Regardless of the distribution, it is imperative that all studies report data across all thresholds currently under debate.

These data, from a well-conducted and carefully described cohort study⁽¹⁶⁾, make a positive contribution to the evidence base for pregnancy-specific thresholds of 25(OH)D. The absence of an association between maternal 25(OH)D concentrations averaging approximately 80 nmol/l and an adverse effect on SGA, preterm birth, birth weight or infant growth is a significant indicator that, in this contemporary cohort of well-nourished women, vitamin D was not a limiting factor for fetal or neonatal physical development and did not have any adverse

effect on growth trajectory in the first 2 years. Of note is the low prevalence of infant vitamin D supplementation in the GUSTO cohort, as there may be a contrast between fetal and infant exposure to vitamin D, depending on customary infant sun exposure practices. Future research contrasting the data from GUSTO with similarly well-phenotyped cohorts displaying a higher prevalence of maternal vitamin D deficiency might be worthwhile to tease out some of the questions regarding the role of maternal vitamin D status in fetal and early infant growth.

In conclusion, these data are encouraging. No association between maternal vitamin D status during pregnancy and compromised fetal or infant growth in this vitamin D-replete cohort suggests that such adverse effects are only detectable in populations with a high prevalence of vitamin D deficiency. Aghajafari *et al.*⁽¹⁰⁾ noted that associations between vitamin D and metabolic abnormalities in pregnancy that impact fetal growth, including hypertension, are biologically plausible. In addition, Aghajafari *et al.*⁽¹⁰⁾ were persuaded that the relative consistency in the data increased the probability that low 25(OH)D preceded the adverse outcome, thus reducing the likelihood of reverse causation. Moreover, three recent systematic reviews^(9–11) concluded that intervention studies in pregnancy are warranted and should be implemented in populations with a high prevalence of deficiency and at doses sufficient to achieve pre-defined 25(OH)D targets and validated outcomes. Maternal vitamin D deficiency (at a minimum threshold of 30 nmol/l) is completely preventable and should be a public health priority⁽³⁾. Whether there is a detectable therapeutic window for additional benefit if every pregnancy is protected from deficiency is a critical ethical and methodological issue in terms of designing and implementing placebo-controlled vitamin D intervention studies in pregnant women.

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