European Journal of Clinical Nutrition (2013) **67**, 1010–1011

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EDITORIAL

Prevention of vitamin D deficiency during infancy is achieved by a combination of low-dose maternal and infant supplementation

European Journal of Clinical Nutrition (2013) **67,** 1010–1011; doi:10.1038/ejcn.2013.153

Owing to concerns about adequacy of nutritional status and implications of maternal deficiency for both skeletal and non-skeletal health outcomes in mothers and babies, vitamin D nutrition during pregnancy and early childhood is the focus of intense interest among practitioners, scientists and the public. Vitamin D deficiency during pregnancy and infancy appears to be relatively common at Northerly latitudes;[1] however, there is an absence of 25-hydroxyvitamin D (25OHD) reference data among sera collected from pregnant women at different gestational stages, from umbilical cords and from infants during the first 2 years.[2,3] Recent narrative and systematic reviews on the impact of vitamin D on pregnancy[2,4] and extra-skeletal health in children[5] concluded that there are unconfirmed effects of 25OHD on preventing pregnancy complications[4] and potentially serious adverse consequences of low maternal 25OHD during pregnancy on the risk of childhood infectious diseases, which require investigation.[5]

Although controversy persists in relation to optimal serum 25OHD concentrations for health promotion, most authoritative agencies now recommend maintenance of serum 25OHD concentrations $\geqslant$50 nmol/l on the basis of the evidence from systematic literature reviews to support normal skeletal growth and development during childhood and prevent aging-related bone demineralization during adulthood.[1,6,7] The evidence basis for establishing target serum 25OHD concentrations on the basis of perinatal outcomes is inconclusive and largely based on observational studies;[1,2,4,6] therefore, authorities have tended to extend recommendations for vitamin D requirements among non-pregnant adults to pregnancy and lactation. Tracking target 25OHD concentrations back to dietary recommendations for vitamin D is particularly challenging, and one of the issues highlighted by the US Institutes of Medicine (IOM),[6] and other regulatory authorities, is the almost total lack of experimental data from studies designed to provide an estimate of the dietary intakes of vitamin D required to maintain serum 25OHD above specified thresholds in pregnancy and early childhood. Thus, the current US Dietary Reference Interval (DRI) for pregnant and lactating women, at 15 μg per day (600 IU), is the same as for non-pregnant women, on the basis that there were no data to presume otherwise. Similarly, scant data were available to set serum 25OHD targets during infancy, and for this reason the IOM established an Adequate Intake (AI) value, designated as an individual target in the absence of sufficient data to establish a DRI. The target value was based on evidence that maintaining serum 25OHD around 40–50 nmol/l was desirable, coupled with observational data suggesting that 10 μg per day (400 IU) was adequate to maintain this level.[6] ESPGHAN Committee on Nutrition[1] has recently endorsed the pragmatic use of a serum 25OHD $>$50 nmol/l to indicate sufficiency and a serum concentration $<$25 nmol/l to indicate severe deficiency and recommend that all infants should receive an oral supplementation of 10 μg per day of vitamin D.

Despite fundamental knowledge gaps in relation to the dose–response of vitamin D during pregnancy and infancy, increased transparency and widespread reliance on the systematic evaluation of the evidence basis among international agencies has increased harmonization with respect to authoritative vitamin D recommendations. One implication of this increased harmonization is that Clinical Research Ethics Boards would now be unlikely to approve implementation of a placebo-controlled dose–response vitamin D intervention study in infancy, and it appears that the window on a true placebo-controlled trial in babies has closed. Carefully conducted prospective observational studies, which include comprehensive data on the factors that determine the variability in circulating 25OHD among women and infants and the impact of habitual supplementation during pregnancy on maternal and infant 25OHD concentrations, such as the one described by vid Streym and colleagues[8] in the current issue, are rare and make a valuable contribution to knowledge in this field.

The Aarhus-based study (latitude 56°N) included 107 women and their 108 infants, who were followed up from delivery through to 9 months of age.[8] Maternal and infant plasma 25OHD data are reported for three time points, at birth, 4 months and 9 months, and determinants of 25OHD concentrations are quantified. The effect sizes of season, maternal 25OHD, maternal and infant supplement use and dose and maternal and infant BMI on plasma 25OHD are reported, in addition to relevant biochemical data (parathyroid hormone (PTH), ionized calcium and creatinine). Meticulous reporting, sample handling and LC-MS/MS analysis of 25OHD all contribute to quality evidence for the evaluation of the efficacy of low-dose supplementation in preventing maternal and infant vitamin D deficiency in Caucasian women and infants resident at Northerly latitude.

The close association between maternal and umbilical cord plasma 25OHD levels, with maternal sampling close to delivery, confirmed previously described correlations. However, the prevalence of 25OHD $<$50 and 25 nmol/l in mothers and cords reported in this study showed that among mothers with 25OHD $<$50 nmol/l the prevalence of cord plasma $<$25 nmol/l was 66%. Only one infant born to a mother with 25OHD $>$50 nmol/l had a cord plasma concentration below 25 nmol/l. Therefore, to prevent vitamin D deficiency (defined as 25OHD $\leqslant$25 nmol/l) in neonates in the Aarhus sample, the maternal 25OHD requirement at delivery was $\geqslant$50 nmol/l. This observation has direct and profound implications for maternal 25OHD requirements during pregnancy. Specification of 25OHD requirements during gestation on the basis of maintaining fetal circulating 25OHD at delivery at a minimum of 25 nmol/l would stipulate the attainment of serum 25OHD $\geqslant$50 nmol/l in every pregnant woman. As an individual target, this is a completely different benchmark to recommending the achievement of a population average of 50 nmol/l, or indeed the achievement of a low prevalence of 25OHD below the average requirement of 40 nmol/l, and has direct consequences for vitamin D intake recommendations during pregnancy. A further consideration is that calcium intakes in the Aarhus cohort were likely to be high (measured but not reported), which may have had a 25OHD sparing effect, and thus the individual target of 50 nmol/l implied by these data is based on adequate calcium nutrition.

A high proportion of women in the Aarhus cohort used vitamin D supplements at a dose of 10 μg/day during pregnancy, in line with Nordic recommendations for pregnant women to maintain intakes at or above 10 μg/day,[7] and there was a 25 nmol/l difference in 25OHD concentrations between mothers who reported using supplements and those who did not. The influence of maternal supplementation during pregnancy was apparent at delivery, with a difference of 10 nmol/l between cord 25OHD levels in users versus non-users. More than 90% of infants also received a dose of 10 μg/day, and this was associated with increasing 25OHD concentrations at 4 and 9 months compared with delivery. Daily supplementation at a dose of 10 μg maintained plasma 25OHD levels above 50 nmol/l in 85–90% of infants up to 9 months, with up to 10% >125 nmol/l. A surprising finding was the persistence of the influence of maternal 25OHD concentrations on infant 25OHD concentrations at 4 months, despite almost universal supplementation. Seasonal variability among infants was only apparent at 9 months of age.[8]

Data from the Aarhus cohort should be considered in the light of a recently reported randomized controlled trial by Gallo *et al.*[9] in Montreal, as both have substantial implications for vitamin D requirements and recommendations during infancy. Briefly, Gallo *et al.*[9] implemented a dose–response study in 132 1-month-old infants[9] to test the efficacy of vitamin D, at doses of 10, 20, 30 and 40 μg/day, in maintaining 25OHD concentrations at 75 and 50 nmol/l. Infants were followed up for 11 months. By 3 months, 55% of infants in the 10 μg group and 80–100% of those in the higher doses had a 25OHD level ⩾75 nmol/l, although these concentrations were not sustained over time. Almost all (97%) infants in each of the four treatment groups achieved 50 nmol/l or higher at 3 months and almost everyone sustained this to 12 months. Growth and bone mineral content did not differ by dosage. The authors discontinued the 40 μg/day dose prematurely because almost all infants on this dose had serum 25OHD concentrations ⩾250 nmol/l by 3 months of age, although these concentrations were not associated with any adverse effects.[9]

The observational data reported in the current issue by the Aarhus group[8] and the intervention data from the Montreal group[9] complement each other and provide additional evidence to support the recent recommendations for vitamin D in infancy from authoritative agencies.[1,6,7] It currently appears that 10 μg/day of vitamin D among healthy infants is safe and effective in achieving a circulating 25OHD ⩾50 nmol/l. Although further studies are required in toddlers and older children to better define vitamin D requirements among these age groups,[3] these data should help increase harmonization among national and international agencies with respect to vitamin D recommendations for deficiency prevention in infancy. The Aarhus data show that maintenance of 25OHD ⩾50 nmol/l during pregnancy (in a well-nourished and calcium-replete population) prevents neonatal deficiency, defined as 25OHD <25 nmol/l, and this has direct consequences for 25OHD requirements and vitamin D recommendations during pregnancy. Dose–response intervention studies among pregnant women, of variable ethnic backgrounds and calcium intakes, including quality bio-banking of umbilical cord serum and, ideally, post-natal follow-up, are urgently required.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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