

Vitamin D

Mother-child vitamin D deficiency: an international perspective

Adekunle Dawodu, Carol L Wagner

Perspective on the paper by Dijkstra *et al* (see page 750)

Rickets is often considered a 19th century disease. However, despite the availability of vitamin D and demonstration of its efficacy in preventing rickets, vitamin D deficiency rickets still exists as a public health problem with significant morbidity in the Middle East¹⁻⁵ and in many Asian countries,^{6,7} and has been reported with increasing prevalence in minority groups in North America⁸⁻¹⁰ and in immigrant populations in Europe, Australia and New Zealand.¹¹ In many countries, there are reports of a high prevalence of subclinical vitamin D deficiency in children and adolescents^{12,13} and rickets may merely represent the tip of the iceberg.

With more studies, there are reports from many countries of a high prevalence of vitamin D deficiency in women of child-bearing age¹⁴⁻²⁰ and during pregnancy²¹⁻²⁴ and in nursing mothers,²⁵⁻²⁷ with likely adverse consequences for women, the fetus and growing infants and children.²¹ What seemed to be a rare entity has become so common that by the end of 2006 a lot of literature had been published that linked vitamin D deficiency with long-latency diseases, with the implication that vitamin D affects all organ systems, not just calcium and bone.

In addition to rickets and other possible consequences of disturbed calcium homeostasis,¹² epidemiological evidence suggests that lack of vitamin D supplements in infancy and early childhood may increase the incidence of type 1 diabetes.^{28,29} In adults, new evidence³⁰ supports the role of vitamin D in maintaining innate immunity and in the prevention of certain disease states including autoimmune diseases, multiple sclerosis,^{31,32} systemic lupus erythematosus,³³ rheumatoid arthritis,³⁴ some forms of cancer (breast, ovarian, colon)³⁵ and type 2 diabetes.^{36,37} The questions then are: how did we become so nonchalant about vitamin D to the point that deficiency is a public health issue for many nations, and are we ignoring evidence that maternal vitamin D deficiency and childhood vitamin D deficiency and rickets are inter-related at least in populations where "sunshine deprivation" is very common? Further, are current recommended supplements for preventing

vitamin D deficiency in women and children adequate if sun exposure is insufficient?

INSUFFICIENT SUN EXPOSURE AND VITAMIN D DEFICIENCY

The story of deficiency begins with vitamin D itself and its primary mode of synthesis, which is from sunlight. This chemical moiety forms from epidermal 7-dehydrocholesterol when UV-B at 290–310 nm hits the skin creating pre-vitamin D₃ which is then transformed to vitamin D₃. Subsequently, vitamin D is transferred via blood to the liver to become 25-hydroxyvitamin D (25(OH)D), an important prehormone whose active metabolite 1,25(OH)₂D is involved in many metabolic processes beyond bone integrity and calcium homeostasis.³⁰

In comparison to sunlight, diet provides on average less than 10% of the body's vitamin D requirements in the best of circumstances.³⁸ However, a full body sunlight exposure during summer months for 10–15 min in a lighter pigmented adult individual will generate between 10 000 and 20 000 IU vitamin D₃ within 24 h; darker pigmented individuals require up to 10 times more exposure to generate similar levels of vitamin D₃.^{39,40} The amount of UV exposure available for the synthesis of vitamin D depends on many factors other than time spent outdoors, such as degree of skin pigmentation, body mass, latitude, season, the extent of air pollution blocking UV light, the amount of skin exposed and type of clothing, and the level of UV protection including sunscreens.^{40,41} In the Middle East and other Arab countries, time spent outdoors is severely limited and for cultural and religious reasons, the dress style of women outdoors prevents exposure of skin to sunlight.^{16,17} In many other parts of the world lifestyle changes are resulting in a decrease in time spent outdoors. In the US and other Western countries, there has been a shift from outdoor activities to time spent indoors. In the US alone, Americans were found to spend an average of 93% of their time indoors.⁴¹

Compounding the problem is the real concern that sunlight itself, the very entity that quickly creates vitamin D in our skin, has deleterious health effects when

exposure occurs in high concentrations or for sustained periods, especially in individuals with lighter pigmentation.^{42,43} In order to limit exposure to ultraviolet light, the US Centers for Disease Control and Prevention, with the support of many organisations including the American Academy of Pediatrics and the American Cancer Society, have launched a major public health campaign to increase public awareness about sunlight exposure and the risks of various skin cancers.⁴⁴ In many populations, there are conflicting concerns: on the one hand there are concerns about the hazards and consequences of excessive sun exposure and on the other there are concerns about current lifestyles with inadequate sun exposure increasing the risk of vitamin D deficiency.^{12,30}

VITAMIN D DEFICIENCY IN WOMEN AND DURING PREGNANCY AND LACTATION

There are a growing number of reports on the high prevalence of low circulating serum 25(OH)D concentrations linked to restricted sunlight exposure and inadequate vitamin D intake in women of child-bearing age and in children in many countries. International comparison of the prevalence of vitamin D deficiency is difficult because of variation in the definition of vitamin D deficiency in reported studies. It is generally agreed that a serum 25(OH)D concentration <25 nmol/l is associated with rickets and osteomalacia. In adults, a serum 25(OH)D concentration <50–80 nmol/l is now considered insufficient for optimal bone health.⁴⁵ In the US, 45% of African American women have frank vitamin D deficiency as defined by a serum 25(OH)D concentration <37 nmol/l (15 ng/ml).¹⁴ In Turkey, women wearing traditional dress outdoors have a mean serum 25(OH)D concentration of 32 nmol/l compared with a mean of 9 nmol/l among those who are completely covered.⁴⁶ Reports indicate that upwards of 26–84% of women in Lebanon,¹⁷ Saudi Arabia,¹⁸ the United Arab Emirates (UAE),⁴⁷ Bangladesh,⁴⁸ Japan⁴⁹ and Finland⁵⁰ have serum 25(OH)D concentrations <25 nmol/l (10 ng/ml).

Maternal vitamin D deficiency during pregnancy also was documented in a number of studies two decades ago.^{21,51} In more recent reports, 18% of pregnant women in the UK,⁵² 25% in the UAE,⁵³ 80% in Iran,⁵⁴ 42% in northern India,⁵⁵ 61% in New Zealand⁵⁶ and 60–84% of pregnant non-Western women in the Netherlands²² have been shown to have serum 25(OH)D concentrations <25 nmol/l. These studies raise the concern that infants are entering the world with a vitamin D deficit that begins in utero.²¹ This concern is based on the strong relationship between maternal

and fetal (cord blood) circulating 25(OH)D levels,⁵⁷ and is supported by recent studies from many countries, including the UAE,⁵³ Iran,⁵⁴ India,⁵⁵ the United Kingdom,⁵⁸ Greece⁵⁹ and the US⁶⁰ that have demonstrated a high prevalence of vitamin D deficiency in mother-infant pairs at birth. Even infants born to vitamin D replete mothers become vitamin D deficient after 8 weeks if not supplemented with vitamin D,⁶¹ while an unsupplemented infant born to a vitamin D deficient mother will reach a state of deficiency more quickly than an infant whose mother was replete during pregnancy.²¹ The significance of maternal deficiency during pregnancy is that the fetus is developing in a state of hypovitaminosis D, which likely has significant effects on innate immune function and fetal and childhood bone development.^{52 62 63} With severe maternal vitamin D deficiency, the fetus may rarely develop rickets in utero and manifest this deficiency at birth.²¹

As one would predict, based on the physiology of vitamin D, the vitamin D content of human milk is related to the lactating mother's vitamin D status.^{21 64} In lactating mothers supplemented with 400 IU/day vitamin D, the vitamin D content of milk ranges from <25 up to 78 IU/l.^{64 65} Based on the concentration of vitamin D in the milk of mothers who have marginal vitamin D status or who are deficient, infants who are exclusively breastfed but who do not receive supplemental vitamin D or adequate sunlight exposure have a high prevalence of vitamin D deficiency based on serum 25(OH)D levels^{25 66} and are therefore at increased risk of developing vitamin D deficiency rickets.^{8-12 67} In many populations where sunshine exposure is severely limited and vitamin D supplementation is not generally practiced, there is also a high prevalence of vitamin D deficiency in nursing mothers.^{25 26 66} From the above data it is clear that severe vitamin D deficiency is a growing concern internationally in pregnant and non-pregnant women and nursing mothers.

CHILDHOOD VITAMIN D DEFICIENCY AND RICKETS AND INTER-RELATIONSHIP WITH MATERNAL VITAMIN D DEFICIENCY

Vitamin D deficiency is the major cause of rickets around the world.^{11 68} Recent reviews^{11 12 68} indicate that vitamin D deficiency in childhood and rickets are public health problems in the Middle East and North Africa, some parts of Asia, and among immigrant populations in the UK, Netherlands, Denmark, Norway, Spain, Australia and New Zealand^{11 12} and have re-emerged as an important public health issue in minority groups in the US.^{9 12} Studies examining the vitamin D status of

mothers of rachitic children have demonstrated a high prevalence of maternal vitamin D deficiency.^{4 69} Further, there is a higher prevalence of vitamin D deficiency in the mothers of rachitic than non-rachitic children⁷⁰; the authors of that study suggested that the vitamin D status of mothers of children with vitamin D deficiency rickets should be assessed.⁷⁰ Taken together, the data from these studies indicate a link between maternal vitamin D deficiency and childhood rickets. The connection may be a combined effect of the positive relationship between maternal vitamin D nutritional status and vitamin D status in early infancy^{61 65} and a similar pattern of maternal and childhood sun exposure.^{4 13 70} In some populations at least, it is reasonable to view rickets and maternal vitamin D deficiency as inter-related, with important implications for a shift in the strategy for comprehensive prevention of vitamin D deficiency in women and children.

CURRENT RECOMMENDATIONS OF VITAMIN D REQUIREMENTS AND FUTURE STRATEGY

If sun exposure is insufficient, how adequate are the current recommendations to prevent vitamin D deficiency in mothers and children? Although vitamin D supplementation is effective in preventing vitamin D deficiency, the optimal vitamin D requirement in women and children is still unknown.^{12 21 71} In the past, studies by Delvin *et al*,⁷² Mallet *et al*⁷³ and Cockburn *et al*⁷⁴ showed that vitamin D supplements below 2000 IU/day did not effectively prevent deficiency. In pregnant women treated with 1000 IU vitamin D/day, maternal serum 25(OH)D levels ranged from a mean of 9.5 nmol/l at baseline to 25.3 nmol/l after receiving 1000 IU vitamin D/day during the last trimester.⁷³ The post-supplementation value is consistent with the definition of deficiency.²¹ In a more recent study,⁷⁵ supplementation of pregnant women belonging to minority groups in the UK with 800–1600 IU of vitamin D during pregnancy increased serum 25(OH)D levels from a mean of 14.5 nmol/l at baseline to only 28 nmol/l at term. In view of the complications of vitamin D deficiency, there is an urgent need to identify optimal vitamin D requirements in pregnancy. Recent studies indicate that vitamin D supplementation of >2000 IU/day is safe and effective in achieving vitamin D sufficiency in men and non-pregnant women.^{76 77} Studies are underway in the US to establish vitamin D requirements during pregnancy (<http://clinicaltrials.gov/#/R01HD043921>).

There also are attempts to evaluate vitamin D requirements in lactating women. In a pilot study, vitamin D supplementation of 4000 IU/day of vitamin D₂ was superior to

2000 IU/day in preventing hypovitaminosis D in lactating women.⁶⁴ In another recent study from the UAE, vitamin D₂ supplementation of 2000 IU/day or 60 000 IU/month in lactating women for 3 months was effective in achieving a serum 25(OH)D concentration >50 nmol/l in only 27% of the patients studied.⁷⁸ In these studies, there were no reports of vitamin D toxicity. Given the results of these recent studies, higher doses of supplemental vitamin D than currently recommended appear to be required to prevent vitamin D deficiency in lactating women, and should be investigated further.

The current accepted recommendation to prevent rickets in children includes supplementation of exclusively breastfeeding infants with 200–400 IU/day of vitamin D and ensuring adequate calcium intake.^{12 68 71} There are, however, not enough data to show that the recommendation is effective internationally.⁷¹ Although supplementation of the infant may prevent vitamin D deficiency in exclusively breastfeeding infants, it would not ensure the vitamin D sufficiency of the nursing mothers. Researchers, therefore, have begun to investigate the possibility of preventing vitamin D deficiency in lactating women and their breastfeeding infants through high-dose maternal vitamin D supplementation.

Studies in the 1980s showed that supplementation of nursing mothers with 2000 IU rather than 1000 IU of vitamin D had a significant effect on the breastfeeding infant's vitamin D status as measured by infant serum 25(OH)D levels.⁷⁹ Expanding on these findings, in two recent pilot studies involving lactating women supplemented with high-dose vitamin D of up to 6400 IU/day for 6 months, the vitamin D content of milk increased to levels as high as 873 IU/l without any evidence of maternal vitamin D toxicity.^{64 80} The serum 25(OH)D levels in the infants of mothers on 6400 IU/day increased from a mean of 32.5 nmol/l to 115 nmol/l and were similar to those of infants receiving 300–400 IU vitamin D/day whose 25(OH)D levels increased from a mean of 35 nmol/l to 108 nmol/l. Similarly, the vitamin D status of the mothers on high-dose supplementation increased from a mean serum 25(OH)D level of 85 nmol/l at baseline to 147 nmol/l after supplementation.⁸⁰ Although vitamin D levels can be increased in the milk of lactating women taking large vitamin D supplements, such high dose supplementation in lactating women must be validated and demonstrated to be safe in larger, more representative populations of lactating women.

In summary, the shift from vitamin D sufficiency to deficiency has occurred in many populations as a result of insufficient

sun exposure and inadequate corrective vitamin D supplementation. Published data indicate that vitamin D deficiency may be an unrecognised public health problem in women, nursing mothers and children in many populations. At least in populations where sun exposure in women and children is severely limited, there is an inter-relationship between maternal vitamin D deficiency and childhood rickets. There is an urgent need to determine the optimal dose of vitamin D to ensure vitamin D sufficiency⁴⁵ in pregnant and lactating women when sun exposure is inadequate. A strategy to prevent vitamin D deficiency in infants through maternal supplementation which would achieve the double effect of preventing vitamin D deficiency in both mothers and children may be a way forward and needs further study.

Strategies to prevent vitamin D deficiency and achieve adequate intake of vitamin D and calcium in women and throughout childhood would not only prevent rickets but may also reduce the risk of osteoporosis as well as other long-latency disease processes that have been associated with vitamin D deficient states in adults. This may be one of the more important preventive public health initiatives. The time for action is now.

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Authors' affiliations

Adekunle Dawodu, Center for Global Child Health, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH, USA

Carol L Wagner, Division of Neonatology, Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

Correspondence to: Dr Adekunle Dawodu, Center for Global Child Health, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 5041, Cincinnati, OH 45229-3039, USA; adekunle.dawodu@cchmc.org

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Vitamin D

Vitamin D in pregnancy: an old problem still to be solved?

A F Williams

Perspective on the paper by Dijkstra *et al* (see page 750)

In this issue Dijkstra *et al* describe the high incidence of hypovitaminosis D (serum 25-hydroxyvitamin D <25 nmol/l) amongst infants born in Rotterdam, the Netherlands (latitude 52°N). Babies born to veiled or dark-skinned mothers were significantly more likely than those of white mothers to have a low 25-hydroxyvitamin D (25OHD) concentration in umbilical cord blood. Similarly, a recent study of pregnant women in the Hague found that 56–66% of women of Moroccan and Turkish descent had 25OHD levels <25 nmol/l, compared with 8% of women of Western origin.¹ Given that mainland United Kingdom lies at a latitude of 50°–58°N and the populations of its large cities show similar ethnic and cultural diversity, these findings are very relevant to Britain. Indeed amongst Cardiff women from ethnic minority groups attending their first antenatal appointment, half showed a serum 25OHD concentration <20 nmol/l.² Those of Indian or African origin were most likely to be affected, especially women who had arrived in the UK within the last 3 years. Interestingly these problems are not confined to northerly latitudes but occur in sunnier climes as well.³

We have known for over 30 years that hypovitaminosis D is common amongst pregnant women in ethnic minority groups, particularly those of Asian origin.⁴ Intervention studies, including a randomised placebo-controlled trial (amongst women of south Asian origin living in South London) showed that infants of vitamin D supplemented mothers were less likely to be small for gestational age, less likely to develop neonatal hypocalcaemia, and had better tooth enamel mineralisation.^{5,6} Recent epidemiological data have added another perspective to maternal vitamin D status in pregnancy and challenge the widely held assumption that suboptimal vitamin D status in pregnancy is a problem confined to at risk ethnic groups. Amongst white women living in Southampton (at one of the most southerly latitudes of the United Kingdom) maternal 25OHD concentrations in the third trimester of pregnancy correlated significantly with the child's whole body and lumbar spine bone mineral content at the age of 9. Eighteen per cent of these mothers showed a 25OHD concentration <28 nmol/l at parturition. Although no national data exist for pregnant women, the low status of UK women of childbearing age

is borne out by the National Diet and Nutrition Survey of British adults: 28% of women aged 19–24 and 13% of those aged 25–34 had plasma 25OHD concentrations <25 nmol/l. These findings suggest that infants who present clinically with vitamin D deficiency, either in the neonatal period or later with clinical rickets, represent only a small proportion of those with suboptimal vitamin D status.

How can the risk of vitamin D deficiency in pregnancy, and by implication in infancy, be reduced? In 1991 the Committee on Medical Aspects of Food and Nutrition Policy (COMA) set a reference nutrient intake (RNI) of 10 µg/day (400 IU/day) vitamin D for women who are pregnant or breast feeding.⁷ This amount was chosen as sufficient to maintain plasma 25OHD >20 nmol/l during the winter months in Scotland and was endorsed by COMA as recently as 1998.⁸ Whilst sunlight exposure is generally of greater importance than diet in the maintenance of vitamin D status, there is no ambient ultraviolet light of the appropriate wavelength at UK latitudes during the winter months. For this reason maintenance of adequate vitamin D status in pregnancy is best achieved through dietary means. However, the average dietary vitamin D intake of young women in the UK approximates 3 µg/day and fewer than 1% consume more than the 10 µg RNI.⁹ Achieving the RNI therefore necessitates supplementation. The advice applies to all women and not merely those in ethnic minority groups, yet very few women take a vitamin D supplement during pregnancy and an individual woman's risk of deficiency in pregnancy seems rarely to be assessed.

Unfortunately there have been many barriers to policy implementation. These