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Prevention of vitamin D deficiency in mothers and infants worldwide — a paradigm shift

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Abstract

Vitamin D deficiency in mothers and infants is a global health disorder despite recognition that it is preventable. Recent data support the theory that vitamin D deficiency in adults and children may increase the risk of infections and auto-immune diseases. In most cases, vitamin D deficiency is caused by sunlight deprivation and inadequate corrective vitamin D intake. There is a strong mother/infant vitamin D relationship that affects vitamin D status both *in utero* and in infancy. Recognition that vitamin D deficiency is a worldwide mother/infant health problem is a basis on which to modify public health strategies to reduce the burden of disease and improve maternal and child vitamin D nutrition. This review provides an update on vitamin D function and the global scope and implications of vitamin D deficiency as it relates to pregnancy and infancy. It also addresses a combined strategy to prevent vitamin D deficiency during pregnancy, lactation and infancy.

Keywords

vitamin D; mother; infant; deficiency

Introduction

Vitamin D deficiency (VDD) and rickets in infancy and childhood are increasingly reported as public health problems in many parts of the world, especially Asia, the Middle East and North Africa, and among immigrant populations in Europe, Australia and New Zealand, as well as minority groups in the UK and US.[1–4] Many infants worldwide are born with low vitamin D stores because of the high prevalence of maternal VDD and, hence, are at risk of rickets.[5] This is despite recognition that vitamin D is effective in preventing VDD in adults and children.

In addition to its classical action of maintaining calcium homeostasis and bone health, vitamin D is involved in immune modulation, cell growth and cell metabolism.[6,7] A recent

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review discussed the association between VDD and the risk of multiple non-skeletal adverse health effects such as auto-immune diseases, cardiovascular diseases, diabetes and certain types of cancer.[6] In pregnancy, low vitamin D status or intake is detrimental to mother and fetus and predisposes to VDD in early infancy.[8] VDD in infancy and childhood has been linked to increased risk of lower respiratory tract infections[9,10] and low vitamin D levels in cord blood is associated with increased risk of acute respiratory infections and wheezing in childhood.[11] In addition, inadequate vitamin D intake in infancy has been associated with increased risk of type I diabetes mellitus.[12] A recent publication by the United States' Institute of Medicine (IOM), however, concluded that the association between vitamin D and non-skeletal outcomes does not prove causality and recommended more large-scale, randomised controlled trials to test the effects of vitamin D supplementation on non-skeletal conditions.[13]

There is growing concern that VDD during pregnancy and from birth through childhood is a global public health issue, but the magnitude is not well described. In view of new knowledge of possible multiple adverse health effects of low vitamin D status, it is appropriate and timely to review the scale of VDD in mothers and their infants and re-examine the strategies for prevention. The IOM's 2010 report recommends serum 25-hydroxyvitamin D [25(OH)D] concentrations <50 nmol/L as low vitamin D status in adults and children.[13]

This review addresses (i) new information on vitamin D functions; (ii) global magnitude and emerging consequences of VDD during pregnancy, lactation and infancy; and (iii) strategies to shift the focus of prevention to mothers as well as infants.

Vitamin D Synthesis and Functions

Vitamin D_3 is produced from epidermal 7-dehydrocholesterol after skin exposure to ultraviolet B (UVB) light with a wavelength of 290–310 nm, forming pre-vitamin D_3 which is then transformed into vitamin D_3 by thermal conversion through the skin. Subsequently, vitamin D, either made in the skin or ingested in the diet (either from animal sources as cholecalciferol or vitamin D_3 or from plant sources such as ergocalciferol or vitamin D_2), is bound to vitamin D protein and albumin and transferred via the bloodstream to the liver to be hydroxylated to form 25(OH)D.[14] The blood concentration of 25(OH)D is considered the best measure of vitamin D status in the body. Exposure to sunlight is the major source of vitamin D and, at best, only an average 10% of the body's vitamin D stores are provided by diet.[15] Full exposure to sunlight, causing slight pinkness to the skin in lighter-pigmented adults, would generate an equivalent of between 10,000 and 20,000 IU of vitamin D within 24 hours of exposure.[14] Individuals with darker pigmentation require about ten times more exposure to generate similar levels of vitamin D_3.[16,17]

In addition to skin pigmentation, the amount of vitamin D synthesis following UVB exposure depends on other factors which include amount of time spent outdoors and the degree of exposure, body mass index, latitude, season, the degree to which UV light is blocked by air pollution and the level of protection against UVB including use of sunscreens.[6,16] In many parts of the world, lifestyle changes are resulting in inadequate

endogenous vitamin D synthesis. In the Middle East and many Arab countries, for example, little time is spent outside and women's outdoor clothing prevents skin being exposed to sunlight.[18–20] In western countries, the amount of time spent indoors has increased significantly. In the US alone, an average 93% of time is spent indoors.[21] In addition, concern about the increased risk of cancer, especially in those with lighter skin exposed in high concentrations for a sustained amount of time, has led to recommendations to limit sun exposure.[22] Since sunlight is the major source of vitamin D, the current lifestyle of some populations, associated with inadequate sun exposure and endogenous vitamin D synthesis, contributes to the increasing risk and prevalence of VDD, especially among women of reproductive age.[1,5,23]

After vitamin D synthesis, a second hydroxylation in the kidney leads to formation of the most important active metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D].[16,24] The major physiological function of 1,25$(OH)_2$D is to maintain serum calcium and phosphate at physiologically acceptable levels to maximize a wide variety of metabolic functions. This includes increasing the efficiency of intestinal calcium transport and dietary phosphate absorption, especially from the small intestine, and calcium reabsorption in the renal tubules. When calcium and phosphate products are maximized, the result is mineralisation of osteoid bone laid down by the osteoblast.[16]

It is now known that 1,25$(OH)_2$D is also locally produced in extra-renal tissues and directly or indirectly controls multiple genes including those responsible for the regulation of cellular proliferation and differentiation, apoptosis and angiogenesis.[6] 1,25$(OH)_2$D is also important in the regulation of innate and adaptive immune responses. When produced in monocytes and macrophages, 1,25$(OH)_2$D inhibits pro-inflammatory and auto-immune cytokine synthesis and promotes anti-inflammation.[25] In addition, activation of macrophages by mycobacteria or lipopolysaccharide enhances production of 1,25$(OH)_2$D, which stimulates the synthesis of cathelicidin, an antimicrobial peptide that enhances the killing of mycobacteria and other infectious agents.[26,27] These non-skeletal functions[28] are summarised in Fig. 1 and have been discussed in recent reviews.[6,7,27] VDD is now thought to be associated with increased risk of multiple adverse health effects, including malignancy, cardiovascular and auto-immune diseases in adults and lower respiratory infections and type 1 diabetes in children,[6] but intervention studies are needed to show the effect of vitamin D supplementation on the burden of these conditions.[13] While such investigations are awaited, the reported high prevalence of childhood rickets and VDD in mothers and their infants[5] worldwide is unacceptable and needs urgent preventive action.

Vitamin D Homeostasis During Pregnancy and Lactation

Early in pregnancy, 25(OH)D crosses the placenta from mother to fetus. Vitamin D stores in the fetus and infant at birth, as measured by serum 25(OH)D concentrations in cord blood, depend on maternal vitamin D status.[29] Hence, maternal vitamin D sufficiency will ensure adequate vitamin D status at birth. Many studies have reported that the umbilical cord blood 25(OH)D level is maintained at 60–85% of the maternal value.[29–33] Therefore, maternal VDD will expose the fetus to hypovitaminosis D and predispose infants to VDD at birth.

Vitamin D status in infancy depends on vitamin D stores at birth, dietary intake (human milk and formula), vitamin D supplementation and sunlight exposure. The anti-rachitic activities (vitamin D content) in human milk depend on mothers' vitamin D intake or UVB exposure.[29,34–36] Hence, mothers with low vitamin D status or intake will produce milk with low anti-rachitic activities and their breastfeeding infants will have low vitamin D status, unless supplemented by vitamin D or exposed to sunlight.[29,37,38] A study from The Netherlands showed that, even when serum 25(OH)D concentration was normal at birth, levels in breastfed infants became very low within 8 weeks because of inadequate vitamin D in breast-milk and limited sun exposure.[39] A study of 35 exclusively breastfed infants in Greece showed that mean maternal serum 25(OH)D concentration 1 week after delivery was low (32.3 nmol/L).[40] Subsequent mean serum 25(OH)D concentrations in the infants remained low, *viz* 25.3 nmol/L at 1 week, 24.5 nmol/L at 3 months and 33.3 nmol/L at 6 months.[40] In contrast, previous studies from New Zealand[41] and the US[42] demonstrated that, when a mother's vitamin D status is normal and there is no history of limited sun exposure, the vitamin D status of unsupplemented, exclusively breastfed infants is close to normal[43] in the 1st 6 months of life. In the New Zealand study,[41] mean maternal serum 25(OH)D concentrations at delivery, 3 months and 6 months were 86.9 nmol/L, 60.9 nmol/L and 64.9 nmol/L, respectively. Infants' mean serum 25(OH)D at birth (cord' blood), 3 months and 6 months was 74.3, 49.5 and 45.9 nmol/L, respectively. In the US study,[42] mean maternal serum 25(OH)D at 2 weeks, 4 months and 6 months after delivery was 60, 50 and 47.5 nmol/L, respectively, and mean serum 25(OH)D concentrations in unsupplemented, exclusively breastfed infants at 2 weeks, 4 months and 6 months after birth were 50, 42.5 and 47.5 nmol/L, respectively; bone mineral content was similar to that in breastfed infants who were supplemented with daily 400 IU vitamin D or were formula-fed. Taken together, these studies indicate that when mothers' vitamin D stores and infants' vitamin D status are normal at birth and sun exposure is not limited, exclusively breastfed infants can maintain normal vitamin D status adequate to support bone health[43] in the 1st 6 months of life. Studies in Nigeria and Gambia support this premise and have reported that when mothers' and infants' exposure to sunlight is unrestricted, VDD is rare in infants at birth[44] and in childhood.[45] However, calcium deficiency has been also implicated in rickets in Nigerian children.[46] Adequate maternal vitamin D stores in pregnancy and lactation combined with modest sun exposure after birth is the natural means to prevent VDD in infants. However, if a mother's vitamin D status is low and sunlight exposure is limited, vitamin D supplementation is essential to ensure vitamin D sufficiency in infants.[47]

Vitamin D Functions *In Utero*

The human fetus accumulates 30 g of calcium, mostly in the 3rd trimester,[48,49] the result of active transplacental transfer from mother to fetus. Fetal calcium demand is met by increased maternal intestinal calcium absorption and resorption from bone. There is considerable debate about the role of vitamin D in fetal bone development.[48,49] Data mostly from animal studies indicate that fetal calcium homeostasis and skeletal development are not related to maternal vitamin D status.[49]

There are no published randomised controlled trials (RCTs) on the effect of prenatal vitamin D supplementation and maternal vitamin D status during pregnancy on fetal skeletal

development. However, observational studies link maternal vitamin D status to fetal bone development and childhood bone health. A UK study[50] found that low maternal vitamin D status (serum 25(OH)D <27 nmol/L) compared with serum 25(OH)D >50 nmol/L during late pregnancy is associated with lower bone mass in their children at 9 years of age. The authors suggested that intra-uterine vitamin D status may determine bone health in childhood. A study from Cincinnati, USA[51] found an association between season of birth and infant bone mass, indicating a relationship between fetal bone health and seasonal variation in maternal vitamin D status. A recent study of 125 pregnant Finnish women who participated in a cross-sectional study at 8–10 weeks gestation with postnatal follow-up found an association between maternal vitamin D status and infants' bone health after birth.[52] The tibia bone mineral content after birth was significantly greater and the cross-sectional area was larger in infants whose mothers' serum 25(OH)D levels were above the median (54.4 nmol/L) than in those whose mothers' serum was below the median (35.6 nmol/L). This significant relationship was maintained after adjustment for newborn Z-score birthweight, maternal height and newborn age at the time of measurement. No differences were detected in bone mineral density.

In the first study of fetal skeletal morphology related to maternal vitamin D status, Mahon *et al.*[53] performed high resolution 3-D ultrasound analysis in pregnant women and showed that inadequate vitamin D status (serum 25(OH)D <50 nmol/L) is associated with increased fetal femur metaphyseal cross-sectional area and femur splaying index at 19 and 34 weeks of gestation, while femur lengths showed no variability. These changes are similar to radiological findings in rickets. Taken together, observational studies indicate that maternal vitamin D status during pregnancy may enhance fetal bone development.

The Magnitude and Emerging Implications of Worldwide Vitamin D Deficiency During Pregnancy and Infancy

Different stages of vitamin D status in adults have been categorised in the current literature as deficiency, insufficiency and sufficiency and are based on physiological and functional outcome measures.[6] More specifically, categorisation is based on the serum 25(OH)D level's negative correlation with serum parathyroid hormone concentration and positive correlation with maximum calcium absorption, optimal bone mineral density and prevention of fractures in the elderly. Using this categorisation, serum 25(OH)D >75 nmol/L is considered to be vitamin D sufficiency. Values of 50–75 nmol/L are considered insufficient, and values <50 nmol/L are considered deficient.[6,54] On the basis of this classification, it is estimated that one billion people worldwide have VDD or insufficiency.[6] However, the recent IOM report questions this categorisation and considers that serum 25(OH)D >50 nmol/L meets the needs of 97.5% of the North American population and that using current classification in the literature might lead to over-estimation of the burden of low vitamin D status.[43] It is generally accepted that serum 25(OH)D <25 nmol/L is associated with increased risk of rickets and osteomalacia.[13] In view of the relationship between maternal vitamin D status and infant vitamin D status at birth and in early infancy, a review of the magnitude of low vitamin D status as measured by serum 25(OH)D concentrations of <25 nmol/L and <50 nmol/L in pregnancy and infancy would be appropriate.

Vitamin D deficiency in pregnancy

There are now many reports worldwide of the high prevalence of low circulating serum 25(OH)D concentrations in pregnant women which increase the risk of adverse health consequences for the mother and fetus (see Table 1). Low vitamin D status is linked to a lack of exposure to sunlight and inadequate intake of corrective vitamin D supplements.[5] In most recent reports,[50,52,55–66] 15–84% of pregnant women worldwide have very low vitamin D status (serum 25(OH)D <25 nmol/L) which in mothers is associated with an increased risk of osteomalacia. In many of these reports, 40–98% of the women have serum 25(OH)D <50 nmol/L, thus exposing the infants to low vitamin D stores *in utero* and at birth and the risk of VDD and rickets in early infancy. This level of global VDD in pregnancy is of major concern and needs to be addressed urgently as part of the strategy to improve the health of mothers and prevent VDD in infants.

Vitamin D deficiency in infants and lactating mothers

In view of reports of a high prevalence of VDD in pregnancy, it is not surprising that it is also of growing concern for both nursing mothers and their infants. Studies of vitamin D status of exclusively breastfed infants are few and recent studies[33,40,67–71] report a high prevalence of VDD in mothers and their infants (Table 2). In a recent study in a predominantly white population in Iowa, USA, 70% of unsupplemented breastfed infants had serum 25(OH)D <27.5 nmol/L at 4 months of age.[69] The prevalence of the low vitamin D levels was 50% in summer and 79% in winter. Twenty (57%) of 35 infants who were followed longitudinally still had VDD at 6 months. In another study from Cincinnati, USA, 18% of exclusively breastfed infants aged 1 month had vitamin D levels <25 nmol/L; 76% of the infants and 17% of their mothers had serum 25(OH)D <50 nmol/L. The prevalence of serum 25(OH)D <50 nmol/L was five times higher in infants born to African American mothers than to non-Hispanic white mothers.[68] A study from Greece (mentioned above) found that 27% of exclusively breastfed infants had serum 25(OH)D <25 nmol/L.[40] Seasonal variation in the prevalence of VDD were documented in all three studies, supporting the contribution of sunlight and endogenous vitamin D synthesis to vitamin D status.

Studies from India and United Arab Emirates (UAE) indicate that serum 25(OH)D <25 nmol/L is of epidemic proportions in mothers and infants.[67,70] In a study of 180 breastfeeding mother–infant pairs in New Delhi, almost half of the infants and their mothers had serum 25(OH)D <25 nmol/L.[70] The mean (SD) PTH level in mothers with serum 25(OH)D <25 nmol/L was 78.7 (65.5) pg/ml compared with 28.6 (13.6) pg/ml in mothers with serum 25(OH)D ≥25 nmol/L ($P = 0.001$). A significant negative correlation was found between serum 25(OH)D and serum alkaline phosphatase (ALP) in the infants ($r = 0.24$, $P = 0.001$). The findings support the expected inverse relationship between low vitamin D status and PTH and ALP levels.

In the UAE study, the median baseline serum 25(OH)D concentration at a median age of 6 weeks was 21.5 nmol/L (IQR 14.8–34.1) in mothers and 11.5 nmol/L (IQR 6.3–19.8) in their infants.[67] Mothers with low serum 25(OH)D concentrations (<25 nmol/L) had higher median PTH levels (40.8 pg/ml, IQR 26.8–56.7) than those with serum 25(OH)D >25

nmol/L (29.4 pg/mL, IQR 19–39.1) (P = 0.02). Infants with serum 25(OH)D >25 nmol/L also had higher median ALP levels (323 IU/L, IQR 253–425) compared with those with serum 25(OH)D <25 nmol/L (260 IU/L, IQR 229–303) (P = 0.02). In addition, 12 (19%) of 64 infants with serum 25(OH)D <25 nmol/L had ALP above the 75th percentile compared with none of the infants with serum 25(OH)D ≥25 nmol/L. These studies in populations at risk of very low vitamin D status indicate that a large proportion of unsupplemented, breastfed infants have biochemical markers of rickets. If low vitamin D status is sustained, the risk of ALRTI is increased[9,10] and some infants could later develop clinical evidence of VDD rickets. For example, a recent longitudinal study from India found that 55% of exclusively breastfed infants had serum 25(OH)D <27.5 nmol/L at 10 weeks of age and at 6 months 43% still had serum 25(OH)D <27.5 nmol/L and 16% had developed clinical and radiological evidence of rickets.[72] Knowledge of baseline vitamin D status and the high prevalence of VDD and rickets is important in determining the extent of the public health issue of vitamin D requirements in high-risk populations.

Implications of the High Prevalence of Low Vitamin D Status in Pregnancy, Infancy and Childhood

VDD in pregnancy is detrimental to the health of the mother and the developing fetus. In many countries, a serum 25(OH)D concentration <25 nmol/L, which is known to be associated with an increased risk of osteomalacia,[13] is widely reported in pregnant women (Table 1). In addition, large studies from the USA[73] and Norway[74] link low vitamin D intake or status in pregnancy with an increased risk of pre-eclampsia, which is an important cause of perinatal morbidity and mortality. Therefore, urgent action is required worldwide to prevent epidemics of VDD in pregnancy.

Although the role of maternal vitamin D status in fetal skeletal development, as mentioned earlier, has generated considerable controversy,[48,49,51,52] studies in humans suggest that maternal VDD during pregnancy is associated with a risk of reduced fetal bone mineral content[52,53] and occasionally presents with rickets at birth or in early infancy in populations in which severe VDD is common.[75–78]

Severe hypocalcaemia with or without seizures is a common complication of VDD in the neonatal period or in early infancy owing to maternal VDD during pregnancy, coupled with inadequate vitamin D intake from human milk or supplements.[79,80] It generally responds to vitamin D and calcium supplementation.[79,81,82] This life-threatening condition can be prevented by ensuring that maternal vitamin D status is adequate during pregnancy.

Rickets, the end-stage of VDD, is a public health problem in many countries and has re-emerged in minority groups in industrialised countries because of inadequate exposure to sunlight and a lack of appropriate vitamin D supplementation.[1,2,83,84] VDD is also common in mothers of children with VDD rickets, suggesting a common major risk factor, probably sunshine deprivation.[23] Other serious complications such as cardiomyopathy and heart failure secondary to hypocalcaemia can complicate severe VDD.[1,85,86]

More recent data mostly from observational studies indicate that low maternal vitamin D intake during pregnancy and VDD in infants at birth and in early childhood are associated with an increased risk of extra-skeletal disorders. Case-control studies from Ethiopia,[87] India,[9] Turkey[88] and Bangladesh[10] have linked subclinical VDD in childhood to ALRTI. Other studies indicate an inverse relationship between vitamin D intake during pregnancy and cord blood vitamin D status and the risk of recurrent wheezing and respiratory infections in the offspring in the 1st 5 years of life.[11,89] A recent RCT in school children in Japan reported that daily supplementation with 1200 IU vitamin D is associated with a 42% reduction in the incidence of seasonal influenza A.[90] In a birth cohort study from Finland, daily vitamin D intake of 2000 IU during the 1st year of life was associated with an 80% reduction in the incidence of type 1 diabetes during a follow-up period of 30 years.[12]

These findings support the premise that maintaining adequate vitamin D status in fetal life, early infancy and childhood has the potential not only to prevent rickets and calcium biochemical disorders but also to reduce the burden of respiratory illness in childhood, and even auto-immune disease such as type 1 diabetes.

Strategies to Prevent Vitamin D Deficiency in Mothers and Their Infants

The inter-relationship between maternal vitamin D nutrition and vitamin D nutrition *in utero* and in breastfeeding infants is illustrated in Fig. 2.[91] This could form the basis of a combined mother–infant strategy to prevent VDD in infants. The strategy, which should commence in pregnancy, is based on the principle of a continuum of vitamin D sufficiency through fetal life, infancy and childhood. Current recommendations for preventing VDD in infants and children focus on supplementing with 400 IU/day formula-fed and exclusively breastfed infants whose vitamin D intake is likely to be inadequate.[47] In view of the high prevalence of VDD at birth, prevention in infancy should start by ensuring maternal vitamin D sufficiency during pregnancy and lactation. This would reduce intra-uterine exposure to hypovitaminosis D and improve vitamin D status at birth and in early infancy.

Ensure vitamin D sufficiency in pregnant and lactating women

When exposure to sunlight is insufficient,[1,13,18,84] how much vitamin D supplementation is required to prevent maternal VDD? In November 2010, the IOM, assuming minimal exposure to sunlight, recommended 600 IU/day as a dietary reference intake for pregnant and lactating women in the USA and Canada.[13,43] This intake is considered to correspond with a serum 25(OH)D concentration of at least 50 nmol/L in 97.5% of the North American population. The tolerable upper intake level was set at 4000 IU/day for adults including pregnant and lactating women.[43] The response to vitamin D supplementation depends on baseline vitamin D status[92,93] and the recommendation is based on studies in which the baseline vitamin D level is generally higher[5,71] than in populations with a high prevalence of severe VDD.

A study of vitamin D supplementation was recently undertaken in 180 women of multi-ethnicity in the UK who were at risk of VDD.[32] The subjects were randomised at 27 weeks gestation to three treatment groups of 60 subjects per group: (i) a single oral dose of 200,000 IU vitamin D, (ii) daily supplementation of 800 IU vitamin D, and (iii) no treatment. In the

daily 800 IU group, the median 25(OH)D concentration at 27 weeks gestation was 26 nmol/L (IQR 20– 37) and serum 25(OH)D was <25 nmol/L in 27 (45%). After supplementation with 800 IU/day from 27 weeks to delivery, median serum 25(OH)D concentrations at delivery had risen to 42 nmol/L (IQR 31–76) but in 7 of the 60 (12%) it remained at <25 nmol/L.[32] Only 30% of the women treated with 800 IU daily achieved serum 25(OH)D >50 nmol/L. In an earlier UK study, 80 consecutive pregnant women from ethnic minority groups whose serum 25 (OH)D was <20 nmol/L were started on vitamin D supplementation at the first antenatal visit. The serum 25(OH)D concentrations increased from 14.4 nmol/L at the first antenatal visit to 28.5 nmol/L at delivery with supplementation of 800–1600 IU vitamin D/day.[94] Twenty-three (40%) of 58 mothers tested at delivery still had serum 25(OH)D levels <20 nmol/L. It seems, therefore, that 800–1600 IU/day vitamin D is insufficient to prevent VDD in these high-risk populations.

A study of vitamin D supplementation was undertaken in 90 healthy lactating and 88 nulliparous women in UAE where VDD from lack of exposure to sunshine is common.[95] The study compared the efficacy of 2000 IU/day vitamin D_2 with 60,000 IU/month vitamin D_2 in women with vitamin D deficiency. Vitamin D_2 was given because it was the only high-dose oral vitamin D available. Mean (SD) baseline serum 25(OH)D concentration in the lactating women was 27.3 (10.4) nmol/L. All had serum 25(OH)D levels <50 nmol/L and 33% had serum 25(OH)D levels <20 nmol/L. After 3 months of supplementation, mean (SD) serum 25 (OH)D concentrations in the group who received 2000 IU/day had increased to 42.2 (13.9) nmol/L. Only 35% of the lactating women achieved serum 25(OH)D levels >50 nmol/L, which is considered acceptable by the IOM[43] but not by some other groups.[6,54] It is clear that the amount of vitamin D supplementation necessary to prevent VDD in pregnant and lactating women in populations with a high prevalence of vitamin D deficiency is not known and needs to be investigated using higher doses of vitamin D_3 than currently recommended by the IOM.[43]

Some have advocated a daily intake for adults of ≥1000 IU vitamin D to achieve optimal vitamin D status associated with improved BMD and reduction in the risk of fractures and colorectal cancer.[6,54] Critical review of published studies suggests that an additional intake of 100 IU/day would increase serum 25(OH)D concentration by 1–2 nmol/L.[13,96,97] Therefore, in a population with a mean baseline 25(OH)D concentration of approximately 25 nmol/L, daily vitamin D_3 intake of 1250–2500 IU may be expected to build the body stores and achieve a mean serum 25(OH)D concentration of 50 nmol/L to prevent VDD. In high-risk populations in whom severe VDD is prevalent and adequate exposure to sunlight cannot be assured, a dose of at least 2000 IU/day might well be required in pregnancy and during lactation to prevent maternal VDD and enhance fetal and infant vitamin D status.[98] Meanwhile, it is important to alert paediatricians, other healthcare providers and the public at large to the need for adequate maternal vitamin D intake during pregnancy and lactation as part of a strategy to ensure vitamin D sufficiency in mothers and breastfeeding infants,

Improve vitamin D status of breastfeeding infants

There is a positive correlation between maternal vitamin D intake, vitamin D status and breast-milk vitamin D anti-rachitic activities, which reflect vitamin D intake by

unsupplemented breastfed infants.[29,34,36] When the vitamin D content of breast-milk is low, vitamin D status correlates with childhood exposure to sunlight.[38,99] In view of the recommendation to restrict exposure of infants aged <6 months to direct sunlight[22] and the high prevalence of VDD in lactating women, vitamin D supplementation of lactating mothers and their exclusively breastfed infants is necessary to prevent VDD. The American Academy of Pediatrics currently recommends a minimum of 400 IU/day vitamin D for all breastfeeding infants and for non-breastfed infants who ingest less than 1 litre of fortified formula per day.[47] In the UK, vitamin D supplementation of 400 IU/day is recommended for all breastfeeding infants.[100] The most recent IOM report recommends 400 IU/day for infants <1 year and 600 IU/day for children aged 1–8 years.[13] In populations at risk of very low baseline vitamin D status, it is not known whether such doses would achieve a serum 25(OH)D level of 50 nmol/L in the majority of breastfed infants.

In a study of the effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants in the UAE, 90 healthy breastfeeding mothers were randomly assigned to 2000 IU/day or 60,000 IU/month vitamin D_2 and all their infants received 400 IU/day vitamin D_2 for 3 months.[37] In 45 mothers assigned to daily 2000 IU vitamin D, mean (SD) baseline serum 25(OH)D concentration at a mean (SD) postnatal age of 19 days was 27.3 (10.4) nmol/L in the mothers and 13.1 (7.3) nmol/L in their infants. At 19 days post-partum, 89% of mothers and 98% of infants were considered vitamin D-deficient as defined by serum 25(OH)D concentration <37.5 nmol/L. After 3 months of combined maternal and infant supplementation, mean (SD) serum 25(OH)D in 22 infants who completed the 3-month study was 49.6 (18.5) nmol/L. Despite the substantial increase in serum 25(OH)D levels, 23% still had serum 25(OH)D <37.5 nmol/L. Based on the IOM guidelines for low vitamin D status, 50% of the infants still had serum 25(OH)D <50 nmol/L. A dose of 400 IU vitamin D_2 to the infants combined with daily maternal supplementation of 2000 IU was therefore insufficient to elevate serum 25(OH)D to 50 nmol/L in the majority of infants. In contrast, in a North American study of exclusively breastfed infants, 400 IU vitamin D_3/day was sufficient to elevate mean serum 25(OH)D from 40.0 (23.3) at 1 month of age to 109.0 (35.3) nmol/L at 4 months, and only 5% had serum 25(OH)D <50 nmol/L after 3 months supplementation.[71] Where VDD is highly prevalent because of low maternal vitamin D status and a lack of infant exposure to sunlight, supplementation of 600–800 IU/day vitamin D_3 for breastfeeding infants and 2000 IU/day for their mothers might be appropriate.[98]

Maternal supplementation alone for prevention of vitamin D deficiency in breastfeeding mothers and their infants

Studies in the 1980s found that supplementing lactating mothers with 2000 IU/day vitamin D had a substantial effect on the vitamin D status of their breastfeeding infants as measured by serum 25(OH)D levels.[101] Two recent small pilot studies of high-dose vitamin D supplementation in nursing mothers given 2000 and 4000 IU/day vitamin D_2 demonstrated that the mean (SD) milk anti-rachitic activity during 3 months of treatment increased from 35.5 (3.5) to 69.7 (3.0) IU/L in the 2000 IU group while the milk anti-rachitic activity in the 4000 IU/day group increased from 40.4 (3.7) to 134.6 (48.3) IU/L. The mean (SD) infant serum 25(OH)D level increased from 19.8 (2.8) to 69.5 (7.3) nmol/L in the 2000 group and

from 33.5 (8.3) to 77.0 (12.5) nmol/L in the 4000 group.[102] In another study by the same group, maternal supplementation with 6400 IU/day vitamin D_3 for a period of 6 months increased the mean anti-rachitic activity in breast-milk from 82 to 873 IU/L; the serum 25 (OH)D concentrations in the infants (32.5–115 nmol/L) were similar to those (35–108 nmol/L) in infants supplemented with 300 IU/day vitamin D_3.[103] Serum and urinary calcium to creatinine ratios remained in the normal range for mothers and infants during the study period. Therefore, vitamin D concentration can be raised to adequate levels in breast-milk by high-dose vitamin D supplementation. Such high doses, however, must be validated and demonstrated to be safe in larger sample-size studies and in diverse geographical areas. If maternal supplementation alone is proven to be a safe and effective method to prevent VDD, it would achieve the double effect of preventing VDD in mothers and their breastfeeding infants. It would also support the view that ensuring adequate maternal vitamin D nutrition provides adequate vitamin D for her breastfeeding infant and combat the notion that human milk is deficient in vitamin D.

Conclusion

VDD in mothers and their infants appears to be a major public health problem with potentially serious adverse health consequences worldwide. The strategy for prevention must ensure vitamin D sufficiency in women during pregnancy and lactation. If maternal supplementation alone is safe and effective in preventing VDD in breastfeeding mothers and their infants, this will be a step forward. Areas for future research include RCTs to determine (i) optimal vitamin D requirements in women and breastfeeding infants in high-risk populations in whom adequate exposure to sunlight cannot be assured; (ii) whether ensuring vitamin D sufficiency will improve fetal skeletal development and reduce pregnancy-induced hypertension; and (iii) the effect of vitamin D supplementation on other non-skeletal conditions such as respiratory infections, wheezing and type 1 diabetes associated with low vitamin D in mothers and infants.[13]

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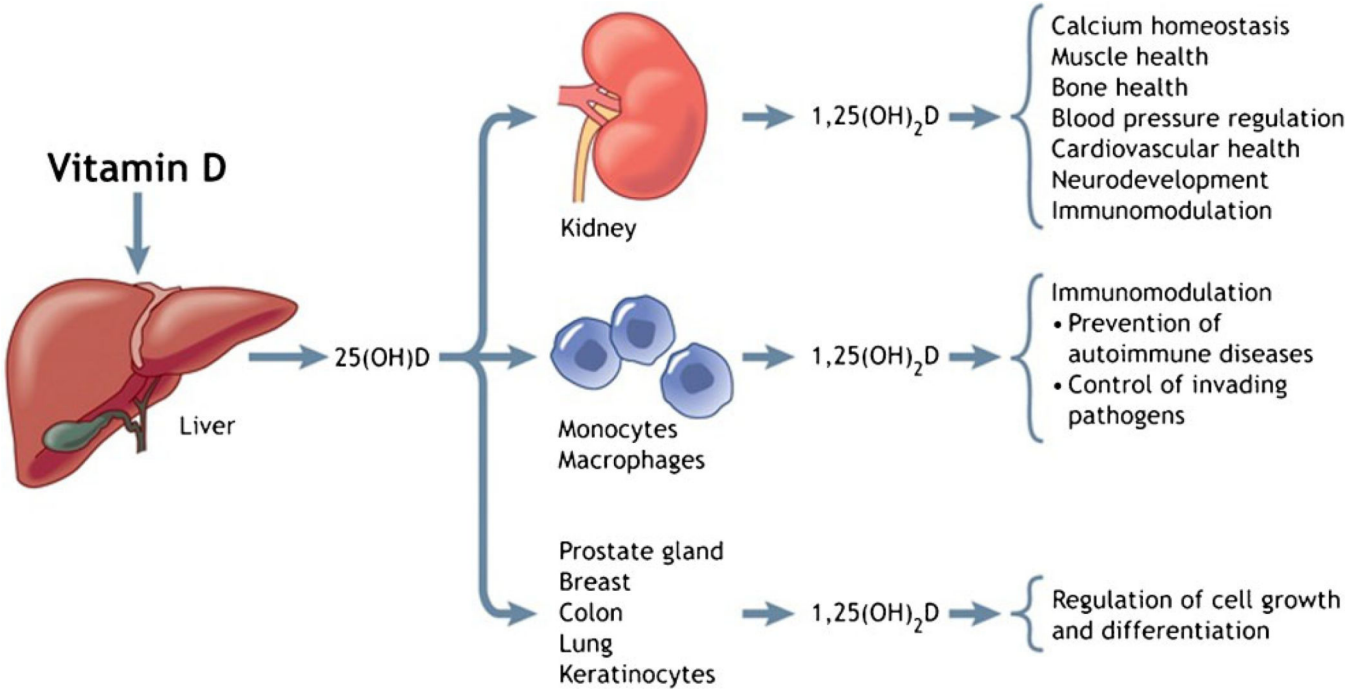

Figure 1.

Biological functions of vitamin D. Metabolism of 25-hydroxyvitamin D [25(OH)D] to $1,25(OH)_2D$ in the kidney and a variety of other organs and tissues and the biological functions of $1,25(OH)_2D$. (Reproduced from Hollis and Wagner[28] with permission from the *Canadian Medical Association Journal*.)

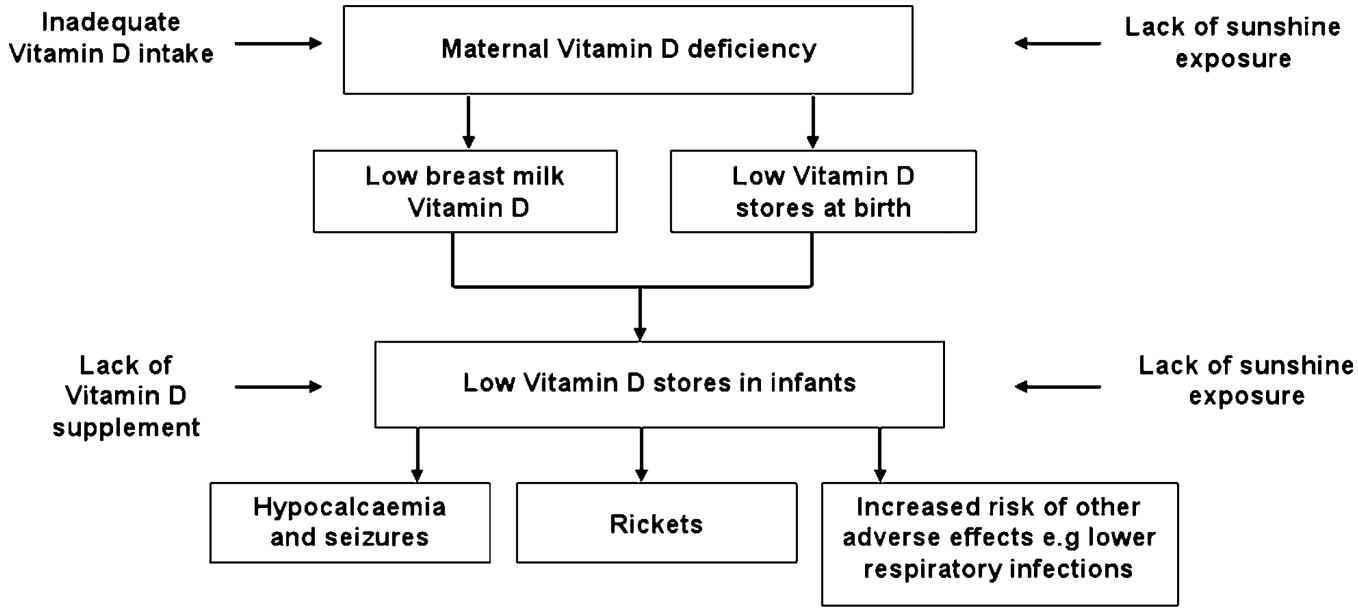

Figure 2.

Maternal and infant vitamin D inter-relationship during breastfeeding. Maternal vitamin D deficiency from lack of sunshine exposure and inadequate vitamin D intake results in low infant vitamin D stores at birth and intake from breast-milk, resulting in low vitamin D status in the infant. Lack of infant vitamin D supplementation and sun exposure further lowers infant vitamin D status and results in vitamin D deficiency and complications such as hypocalcaemia, rickets and increased risk of other adverse effects including lower respiratory tract infections. (Adapted from Dawodu and Tsang[91].)

Table 1

Recent studies of vitamin D deficiency in women during pregnancy or at delivery: international comparison.

		Population				% Serum 25(OH)D, nmol/L	
Author	**Country/Yr**	**No. studied**	**Race/ ethnicity**	**Gestation, wks**	**Season**	**<25**	**<50**
Javaid[50]	UK/2006	596	Caucasian	34	All	18	49
Holmes[55]	UK/2009	99	Caucasian	35	All	17	75
Newhook[56]	Canada/2009	50	Caucasian	NR	All	2	42
Hamilton[57]	USA/2010	559	Mixed	18	All	15.8*	48
Ginde[58]	USA/2010	928	Mixed	NR	All	7	33
Judkins[59]	New Zealand/2006	90	Mixed	13	All	61	85
Bowyer[60]	Australia/2009	971	Mixed	28	All	15†	48
Viljakainen[52]	Finland/2010	124	Caucasian	8–10	Winter	NR	77
Van der	The Netherlands/2006	79	Turkish	12	All	84	NR
Meer[61]		69	Moroccan	12	All	81	NR
		105	Other non-Western	12	All	59	NR
		105	Western	12	All	8	NR
Sahu[62]	India/2009	139	Indian	28	All	32	74
Molla[63]	Kuwait/2005	128	Kuwaiti	Term	All	41	83
Bassir[64]	Iran/2001	50	Iranian	38–41	All	80	NR
Dawodu[65]	UAE/2010	105	Arab	12	All	75	98
Narchi[66]	UAE/2010	75	Multi-ethnic	10	Warm‡	26	69

*<30 nmol/L;

†≤25 nmol/L;

‡warm but sunny – September to November; NR, not reported.

Table 2

Vitamin D deficiency in unsupplemented breastfed infants and mothers

					Infants		Mothers	
Author/Yr	**Location**	**No. studied**	**Infants' ages**	**Season**	**Prevalence of deficiency, %**	**Cut-off for 25(OH)D concentration, nmol/L**	**Prevalence of deficiency, %**	**Cut-off for 25(OH)D concentration, nmol/L**
Challa/2005[40]	Greece (Ioannina)	66	6 m	All	27	<25	NR	NR
Bhalala/2007[33]	India (Mumbai)	35	3 m	NA	51	<37.5	NR	NR
Dawodu/2003[67]	UAE (Al Ain)	78	1–4 m	All	82	<25	61	<25
Dawodu/2010[68]	USA (Cincinnati)	87	1 m	All	18	<25	17	<50
					76	<50		
Ziegler/2006[69]	USA (Iowa)	35	4 m	All	70	<27.5	NR	NR
Seth/2009[70]	India (New Delhi)	180	2–24 w	All	43	<25	48	<25
Wagner/2010[71]	USA (SC – Rochester)	33	1 m	All	72	<50	NR	NR