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REVIEW

Vitamin D nutrition in pregnancy: current opinion

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Abstract: There is increasing interest in vitamin D nutrition during pregnancy because of widespread reports of a high prevalence of low vitamin D status in pregnant women. While vitamin D is important for calcium and phosphorus homeostasis and for bone health, it also plays important roles in many other physiologic functions in the body. Consistent with the expanded role of vitamin D, recent observational studies have demonstrated that low vitamin D status in pregnancy is associated with multiple potential adverse maternal, fetal, and infant outcomes and contributes to low vitamin D status in infants at birth. Therefore, an overview of the current understanding of vitamin D nutrition in pregnancy and a review of the results of studies to optimize vitamin D status during pregnancy and in the offspring is of public health importance and timely.

Keywords: vitamin D, pregnancy, neonate

Introduction

Vitamin D deficiency in pregnancy is widespread in many parts of the world,[1] and there is an association between low vitamin D status and multiple potential adverse outcomes of pregnancy.[2–5] Therefore, vitamin D nutrition in pregnancy should be of global health interest. Although the synthesis and metabolism of vitamin D in the nonpregnant state is well known, its metabolism during pregnancy is less well understood.[3] The classical action of vitamin D is to maintain calcium homeostasis and bone health. In addition, it is now known to be involved in immunomodulation, cell proliferation, and cell differentiation, and in other physiologic functions in diverse tissues and organs, including the brain, pancreas, and heart.[6] Despite the reported high prevalence of vitamin D deficiency and its possible consequences, the criteria for defining an optimal level in the body, and hence the amount of vitamin D intake required to maintain adequate levels, is controversial.[3,7,8] This overview addresses the current information about vitamin D function, the global burden and potential consequences of low vitamin D status in pregnancy, and current strategies to optimize vitamin D status in pregnant mothers and their offspring.

Vitamin D sources and functions

The major source of vitamin D is endogenous synthesis from epidermal stores of 7-dehydrocholesterol following exposure of the skin to ultraviolet B radiation, resulting in formation of previtamin D_3 which is subsequently converted to vitamin D_3 (cholecalciferol).[9] Geographic location beyond latitude 35°, North or South, darker skin pigmentation due to melanin, winter season, and lifestyle factors, including avoidance of sun exposure, cloth-

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ing which covers most of the skin while outdoors, increased indoor activity, and the use of sunscreen, all reduce endogenous synthesis of vitamin D.[9,10] Endogenous synthesis accounts for about 90% of the body's vitamin D stores, while 10% is derived from dietary sources. Very few food items, including fatty fish, fortified dairy products, and egg yolk, contain vitamin D.[9,10] When exposure to sunlight is limited, individuals depend on dietary sources or vitamin D supplements to maintain adequate vitamin D status. Several reports in the literature have shown that inadequate or lack of sunlight exposure without appropriate corrective vitamin D intake or supplements accounts for the high prevalence of vitamin D deficiency in women.[11–18]

After synthesis in the skin, vitamin D attaches to vitamin D-binding protein and is transported to the liver, where it undergoes a process of hydroxylation to form 25-hydroxyvitamin D [25(OH)D].[9] The serum concentration of 25(OH)D is the most reliable marker of vitamin D nutritional status. A second hydroxylation takes place in the kidney, which converts 25(OH)D to the most biologically active metabolite, 1,25-dihydroxyvitamin D, the major classical physiologic function of which is to increase calcium and phosphorus absorption from the gut in order to maintain calcium homeostasis and promote mineralization of osteoid bone.[9]

Although the renal 1-alpha hydroxylase (cytochrome P450 [CYP]27B1) enzyme is a major determinant of synthesis of 1,25-dihydroxyvitamin D, it is known that CYP27B1 is expressed in nonrenal tissues to produce 1,25 dihydroxyvitamin D.[6,19] In addition, vitamin D receptors are also expressed in a variety of organs, tissues, and cells (see Figure 1).[20] The 1,25-dihydroxyvitamin D locally produced in extrarenal tissues, such as immune cells, pancreatic beta cells, the intestine, prostate, breast, and other organs, controls multiple vitamin D-responsive genes, and thus plays an important physiologic role in cardiovascular health,[21,22] the adaptive and innate immune responses,[23,24] insulin secretion,[25,26] regulation of cell proliferation, differentiation, and apoptosis, and inhibition of angiogenesis.[27]

Vitamin D homeostasis and functions during pregnancy

The classical function of vitamin D is to maintain calcium homeostasis. When serum vitamin D and calcium concentrations are low, there is increased synthesis of parathyroid hormone which further stimulates synthesis of 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] to correct calcium deficits through increased intestinal calcium absorption and mobilization of calcium from bone. Restoration of vitamin D status and calcium balance allows calcium accretion in the bones. However, sustained vitamin D deficiency results in rickets in children and osteomalacia in adults.[28] The commonly evaluated biomarkers of vitamin D nutrition include serum 25(OH)D concentrations, the inverse relationship

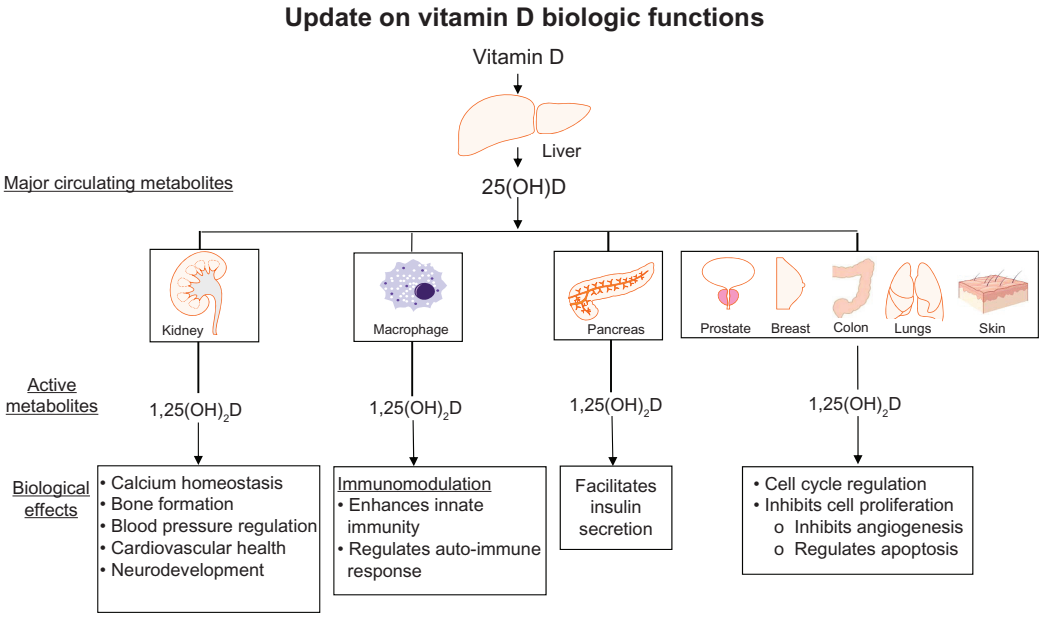

Figure 1 Biological functions of vitamin D. Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25(OH)$_2$D in the kidney and in several other organs and tissues, and the biological effects of 1,25(OH)$_2$D.

between 25(OH)D and parathyroid hormone, intestinal calcium absorption, and assessment of skeletal integrity.[29] While there is an inverse relationship between serum parathyroid hormone and 25(OH)D in nonpregnant states, this relationship has been shown in recent studies to be weak during pregnancy,[6,18,30,31] indicating that serum parathyroid hormone may be a less reliable biomarker of maternal vitamin D status during pregnancy than serum 25(OH)D.[32] The maternal 25(OH)D level does not vary significantly during pregnancy unless there is a change in vitamin D intake or endogenous synthesis.[2,33,34] However, serum $1,25(OH)_2D$ levels increase by 100%–200% starting in the first trimester in both the mother and the fetus.[35–37] The increase in maternal $1,25(OH)_2D$, which originates mostly from the kidneys, accounts for increased intestinal calcium absorption during pregnancy.[38,39] The increase in fetal $1,25(OH)_2D$ level seems to be related to synthesis in placental and fetal tissues.[39,40]

An important aspect of vitamin D nutrition in pregnancy is that the vitamin D status of the infant at birth and in early infancy depends on the vitamin D status of the mother during pregnancy.[41] Vitamin D stores in the infant start with transplacental transfer of 25(OH)D in early pregnancy from mother to fetus. Physiologically active $1,25(OH)_2D$ does not readily cross the placenta.[41] Many studies have shown that the vitamin D status of infants at birth as measured by cord blood 25(OH)D correlates positively with maternal vitamin D status. In general, cord blood 25(OH)D concentrations are approximately 60%–89% of the maternal value.[11,17,35,41–47] Therefore, maintaining optimum vitamin D nutrition during pregnancy is essential for prevention of hypovitaminosis D in the fetus and vitamin D deficiency at birth and in early infancy.

High prevalence of low vitamin D intake in pregnancy

The vitamin D status in adults, including pregnant women, is based currently on measurement of serum 25(OH)D concentrations, but what constitutes the "normal" or "optimal" level is controversial. The Institute of Medicine in the US in its recent report recommends that a serum 25(OH)D concentration of 50 nmol/L (20 ng/mL) is adequate for calcium absorption and bone health in adults, including pregnant women, in the US and Canada.[7] However, new clinical guidelines from the Endocrine Society recommend maintaining a serum 25(OH)D concentration >75 nmol/L (30 ng/mL) in order to maximize calcium absorption and bone health, and for potential extraskeletal benefits noted in observational studies.[8] Many recent studies[13,15–17,48–57] that evaluated vitamin D nutrition during pregnancy in different geographic locations reported wide variation in vitamin D status depending on latitude, season, sunlight exposure behavior, and vitamin D intake (Table 1). The studies indicate that mean serum 25(OH)D concentrations during pregnancy or at delivery range from 12.8 nmol/L to 138.5 nmol/L. There is a high prevalence of vitamin D deficiency [serum 25(OH)D <50 nmol/L], and as shown in Table 1, most women studied (>80%) have serum 25(OH)D concentrations <75 nmol/L, which are considered "insufficient".[8] Mean serum 25(OH)D concentrations are highest and the prevalence of vitamin D deficiency is lowest in sun-enriched populations,[51,57] while the lowest mean serum 25(OH)D and the highest prevalence of vitamin D deficiency are reported in sunshine-deprived populations.[16,17,50,55,56] The high prevalence of low vitamin D associated with sunshine deprivation and inadequate corrective vitamin D intake should raise public health concern about the increased risk of adverse health effects of low vitamin D status for the mother and fetus and poor vitamin D nutrition in the infant at birth.

Implications of low vitamin D status during pregnancy

Skeletal and calcemic complications

It is generally accepted that maternal vitamin D deficiency can result in osteomalacia. A serum 25(OH)D concentration <25 nmol/L (10 ng/mL), which is associated with increased risk of osteomalacia in adults,[7] is common during pregnancy, as indicated by recent reports from many parts of the world.[1] For example, serum 25(OH)D < 25 nmol/L during pregnancy has been reported in 17%–18% of the Caucasian population in the UK,[48,49] 61% of a mixed population in New Zealand,[54] 32%–42% in the Indian population,[15,45] 59%–84% of a nonwestern population in The Netherlands,[14] 41% of the Kuwaiti population,[16] 80% of the Iranian population,[17] and 75% of the Arab population in the United Arab Emirates.[1] However, there are limited studies on the association between such low levels of vitamin D status and skeletal integrity in pregnant women. In a recent study from northern India,[45] 29 (14%) of 207 pregnant mothers showed biochemical evidence of osteomalacia (elevated heat-labile alkaline phosphatase, low phosphorus, and elevated parathyroid hormone), although none had demonstrable clinical evidence of the disease, ie, proximal muscle weakness, skeletal pain, or bone tenderness. Mothers with serum 25(OH)D < 25 nmol/L had elevated heat-labile alkaline phosphatase >125 IU/L and significantly lower phosphorus and higher parathyroid hormone levels than mothers with serum 25(OH)D > 25 nmol/L. Further, a recent study of the relationship between serum

Table 1 Vitamin D status during pregnancy or at delivery: international variations

Reference	Country/race	n	Season	Latitude	Sun exposure/vitamin D intake	Serum 25(OH)D		
						Mean	% <50 nmol/L	% <75 nmol/L
Javaid et al[48]	UK/Caucasian	160	All	50°N	Low UV exposure/low rate of vitamin D supplementation in pregnancy	NSP	49	NSP
Holmes et al[49]	UK/Caucasian	99	Summer	54°–55°N	Low supplementation	NSP	75	98[++]
Viljakainen et al[50]	Finland/Caucasian	124	Winter	60°N	Low UV B exposure/ inadequate vitamin D intake	41.0	77	98
Hamilton et al[13]	US/mixed	559	All	32°N	Low sun exposure	54.3	48	85[++]
Ginde et al[51]	US/mixed	928	Summer/ winter	NSP	Low outdoor activity/low vitamin D intake	65.0	33	69
Newhook et al[52]	Canada/Caucasian	50	Winter Summer	46°N	Low UV exposure/low vitamin D supplementation	51.9 61.1	42	80
Bowyer et al[53]	Australia/mixed	971	All	34°S	Low sun exposure-sunscreen use/vitamin D intake NSP	52.0[+]	48	NSP
Judkins et al[54]	New Zealand/ mixed	90	All	41°S	Low sun exposure/low vitamin D intake	NSP	87	NSP
Jiang et al[55]	China/Chinese	152	Winter Summer	31°N	Low sun exposure/low vitamin D intake	22.7 31.8	96 95	NSP
Sahu et al[15]	India/Indian	139	All	24°N	Inadequate exposure/low vitamin D/Ca intake	31.8	74	NSP
Molla et al[16]	Kuwait/Kuwaiti	128	All	29°N	Low UV B exposure/low vitamin D/Ca intake	33.3	83	NSP
Bassir et al[17]	Iran/Iranian	50	All	36°N	Lack of sun exposure/low vitamin D intake	12.8	NSP[+++]	NSP
Dawodu et al[56]	United Arab Emirates/Arabs	192	All	32°N	Lack of sun exposure/low vitamin D intake	20.5	98	99.5[++]
Luxwolda et al[57]	Tanzania/traditional Tanzanians	138	All	3°S	Abundant sun exposure	138.5	1	2

Notes: [+]Median; [++](<80 nmol/L); [+++]80% <25 nmol/L; serum 25(OH)D, to convert to ng/mL divide by 2.5.
Abbreviations: Ca, calcium; NSP, not specified; UV, ultraviolet.

25(OH)D and bone turnover in pregnant women in Istanbul, Turkey, found a negative correlation between the second and third trimester and postpartum 25(OH)D concentrations and serum cross-linked C-terminal telopeptide of type 1 collagen, which is a marker of bone resorption.[58] These studies seem to indicate a link between very low vitamin D status and subclinical osteomalacia in the mothers.

There is controversy concerning the effect of maternal vitamin D deficiency on skeletal development of the fetus. From animal studies and some human data, it is suggested that mineralization of the fetal skeleton is independent of vitamin D and, therefore, maternal vitamin D deficiency has little effect on fetal skeletal development.[59] In contrast, some recent observational studies suggest that vitamin D nutrition during pregnancy may affect fetal bone development. High resolution three-dimensional ultrasound assessment in a study from the UK found greater splaying of the distal femoral metaphysis in the fetus when maternal serum 25(OH)D was <50 nmol/L,[60] and the authors suggested that this finding is similar to radiologic features in vitamin D-deficient rickets. In a Finnish study,[50] bone mineral content of the fetal tibia was higher and the cross-sectional area was larger when maternal serum 25(OH)D concentrations during the first trimester were above the median (54.4 nmol/L). There was no significant difference in bone mineral density. Maternal 25(OH)D concentrations during pregnancy was shown in one UK study[48] to affect childhood bone mass at nine years of age, but this was not confirmed in a larger more recent study from the UK.[61] In populations where vitamin D deficiency is very severe, maternal vitamin D deficiency during pregnancy has been associated with neonatal craniotabes[62] and congenital rickets.[63–65] Taken together, the results from observational studies suggest a possible effect of low maternal 25(OH)D during pregnancy on fetal bone development, but the association with lower childhood bone mass is unproven. Randomized controlled trials with large sample sizes are needed to assess the effect of maternal vitamin D supplementation on fetal bone development. Severe hypocalcemia occasionally presenting as neonatal seizures is a known complication of maternal vitamin D deficiency during pregnancy.[66,67]

Extraskeletal and noncalcemic complications of vitamin D deficiency during pregnancy

Several extraskeletal complications of vitamin D deficiency during pregnancy have been reported in the mother, fetus, and infant. These include potentially increased risk of fetal growth restriction, a higher rate of cesarean section, increased risk of pre-eclampsia, gestational diabetes, and bacteria vaginosis, and a higher risk of lower respiratory tract infection, wheezing, and eczema in infants.

Fetal growth

The association between birth weight and maternal vitamin D status or intake remains inconclusive.[5] While some observational[68–71] and interventional[53,72,73] studies found improvement in birth weight with maternal vitamin D supplementation or improved vitamin D status, several other observational studies[31,74–76] and some interventional studies[18,33,77,78] showed no improvement with higher vitamin D status or supplementation. A recent Cochrane review[79] of five small-sized intervention trials of vitamin D supplementation concluded that mothers who were supplemented tended to have fewer babies weighing <2500 g (relative risk 0.48; 95% confidence interval [CI] 0.23–1.01). Intervention trials and observational studies have also found an association between risk of small-for-gestational age infants and maternal vitamin D nutrition during pregnancy. In a study of 3730 women of variable ethnicity from Amsterdam in The Netherlands, those with serum 25(OH)D < 30 nmol/L had a higher risk of delivering a small-for-gestational age infant (odds ratio 2.4; CI 1.9–3.2) compared with those having a serum 25(OH)D ≥50 nmol/L.[68] Similarly, in another large study[80] of 1013 white and black mother-infant pairs from Boston, MA, second trimester serum 25(OH)D levels < 25 nmol/L were associated with an increased risk for delivery of a small-for-gestational age infant (odds ratio 3.93; CI 1.65–9.34). The relationship between maternal vitamin D status and small-for-gestational age infants was found to be U-shaped in a study from Pittsburgh in the US,[81] but this was not confirmed in the above studies.[68,80] The reasons for this difference are unclear. It is of note that the researchers from The Netherlands used a lower cutoff than the serum 25(OH)D value of <75 nmol/L used in the Pittsburgh study, while the proportions of white women with serum 25(OH)D > 75 nmol/L were lower in the Boston study than in the Pittsburgh study. Randomized controlled studies including larger sample sizes and repeated vitamin D measurements during pregnancy will be needed to confirm the relationship between vitamin D supplementation and fetal growth.[82]

Maternal complications

Observational studies reported an association between maternal vitamin D status during pregnancy and development of pre-eclampsia, which has both a genetic and an immunologic pathogenesis. A study from Pittsburgh showed an inverse relationship between vitamin D status and the risk of pre-eclampsia.[83] The authors found that the risk of pre-eclampsia was more than doubled (odds ratio 2.4; CI 1.1–5.4) for a 50 nmol/L decrease in maternal serum 25(OH)D concentration. Similarly, a study from North Carolina in the US[84] found a five-fold increased risk of pre-eclampsia in pregnant women with a serum 25(OH)D concentration <50 nmol/L compared with those with values >75 nmol/L (adjusted odds ratio 5.41; CI 2.02–14.52).

Diabetes is a major health issue globally. With increasing interest in the role of vitamin D in glucose homeostasis, the association between maternal serum 25(OH)D concentration in early pregnancy and the risk of gestational diabetes mellitus was investigated in a study from the National Institutes of Health, Bethesda, MD.[85] The authors found that maternal vitamin D deficiency [serum 25(OH)D < 50 nmol/L] was associated with a higher risk of gestational diabetes mellitus (adjusted odds ratio 2.66; CI 1.01–7.02). Consistent with this report, a systematic review and meta-analysis of seven observational studies performed between 2008 and 2011 found serum 25(OH)D < 50 nmol/L to be associated with gestational diabetes but with an overall lower odds ratio of 1.61 (CI 1.19–2.17).[86] Another meta-analysis of maternal vitamin D status and pregnancy outcomes,[87] which included 24 studies up to 2012, found an overall increased risk of pre-eclampsia (odds ratio 2.09; CI 1.50–2.90) and gestational diabetes (odds ratio 1.38; CI 1.12–1.70). It is of note that not all the individual studies provided adjusted odds ratios.

Recent studies have indicated a role for vitamin D in the innate immune response. Vitamin D has been shown to upregulate endogenous synthesis of cathelicidin, a potent antimicrobial peptide, in response to microbial invasion, via activation of toll-like receptors on microphages and monocytes.[6,24] Given that antimicrobial peptides provide rapid defense against invading pathogens, it is plausible that vitamin D plays a role in host defense against infections in both mother and offspring. In support of this premise is the finding that vitamin D deficiency is an independent risk factor for bacterial vaginosis in pregnant women.[88] A study from Pittsburgh showed an inverse dose-response relationship between serum 25(OH)D concentrations and the prevalence of bacterial vaginosis.[88] Compared with a serum concentration of 75 nmol/L, the prevalence of bacterial

vaginosis increased 1.65-fold (CI 1.01–2.69) and 1.26-fold (CI 1.01–1.57) at serum concentrations of 20 nmol/L and 50 nmol/L, respectively. In another large study from New York in the US,[89] bacterial vaginosis was only associated with vitamin D deficiency (serum 25(OH)D < 75 nmol/L) in pregnant women (adjusted odds ratio 2.87; CI 1.13–7.28). Further, there is a suggestion of an association between vitamin D and periodontal disease,[90] and maternal serum 25(OH)D < 75 nmol/L during early pregnancy has been associated with a two-fold increased risk of periodontal disease.[91] In a recent randomized controlled trial of vitamin D supplementation from South Carolina, vitamin D supplementation of 4000 IU/day during pregnancy was associated with a reduction in the risk of combined morbidities, such as maternal infection, preterm labor, and preterm birth.[92]

In view of the possible association between maternal vitamin D status and the pattern of fetal growth, pre-eclampsia, gestational diabetes mellitus, and maternal infection, and the significant potential for perinatal morbidities associated with these conditions, evaluation of vitamin D nutrition in early pregnancy and the effect of appropriate supplementation seems warranted.

Impact on neonate and infant

Both in vitro and observational studies have demonstrated that vitamin D status during pregnancy impacts the immune response of the offspring. Vitamin D status in infant cord blood has been related to the innate immune response via toll-like receptor-mediated synthesis of antimicrobial peptides. Monocytes cultured in vitamin D-deficient plasma (serum 25(OH)D < 30 nmol/L) showed significantly decreased toll-like receptor-mediated expression of cathelicidin ($P < 0.05$) compared with those conditioned in vitamin D-sufficient plasma (serum 25(OH)D > 75 nmol/L).[93] Consistent with these in vitro findings, observational clinical data found an association between vitamin D status in cord blood and the risk of lower respiratory tract infection in the first year of life.[94] The risk of respiratory syncytial virus bronchiolitis in the first year of life is increased by six-fold (CI 1.6–24.9) in infants with cord blood 25(OH)D < 50 nmol/L compared with infants with 25(OH)D > 75 nmol/L. Cord blood 25(OH)D concentrations <75 nmol/L have also been linked to infantile wheezing[95] and eczema,[96] possibly due to adverse consequences on the early immune development of the fetus. In contrast, an observational study reported an increased risk of infantile eczema and pneumonia in association with maternal serum 25(OH)D > 75 nmol/L in the last trimester.[76] However, another recent study with a larger sample size from the same institution did not find an association between maternal 25(OH)D > 75 nmol/L in late pregnancy and eczema or asthma at 12 months and three and six years of age.[97] There was no report on the association between maternal vitamin D status and respiratory infections in the latter study. Regarding neurocognitive development, while one study found no association between maternal vitamin D status during pregnancy and neurocognitive function,[76] a recent larger-sized study linked maternal serum 25(OH)D levels during pregnancy with language development in the offspring.[98] The results of the above studies suggest that childhood infections, atopy, and neurocognitive development need to be included as outcomes of interest following vitamin D supplementation in pregnancy, and that clinical trials should include a relevant group of subjects considered to be replete for vitamin D.

Taken together, the high prevalence of vitamin D deficiency in pregnancy and the possible multiple potential adverse effects on mother and offspring identified in several epidemiologic studies underscore the urgent need for large randomized controlled trials to identify the amount of vitamin D supplementation that optimizes vitamin D status during pregnancy, and to determine the effect of supplementation on potential adverse conditions associated with vitamin D deficiency and any possible vitamin D excess.

Vitamin D requirement during pregnancy

In order to determine the vitamin D requirement during pregnancy, one needs to define the target serum 25(OH)D concentration considered as "normal" or "optimal". As noted previously, the recent Institute of Medicine report recommends that a circulating serum 25(OH)D concentration of 50 nmol/L is adequate to meet the needs for calcium homeostasis and bone health in adults.[7] The recommended dietary allowance of 600 IU/day for both pregnant and lactating women in the US and Canada would theoretically meet the daily requirement in 97.5% of the population for achieving the recommended target serum 25(OH)D concentration of 50 nmol/L. However, a committee of vitamin D experts[99] and the Endocrine Society[8] recommend a target serum concentration >75 nmol/L based on the available evidence in order to achieve optimal benefits for skeletal health as well as potential nonskeletal benefits. A target concentration of 75 nmol/L is consistent with the cord blood 25(OH)D level reported in some studies as being protective against lower respiratory infection, wheezing, and eczema in infants.[94–96] To achieve a target serum concentration >75 nmol/L, the society

recommends a daily vitamin D intake of 1500–2000 IU. These recommendations are based mostly on studies from the US and may not be applicable worldwide due to differences in baseline vitamin D status,[100] particularly in populations where severe vitamin D deficiency is prevalent.

A review of the few previous randomized controlled trials of vitamin D supplementation during pregnancy indicates that doses of 400–1600 IU/day were insufficient in achieving a mean serum 25(OH)D concentration ≥50 nmol/L in most of the studies.[41] In a recent vitamin D supplementation trial from the UK, a multiethnic group of 180 pregnant women were randomized at 27 weeks' gestation to receive a single oral dose of 200,000 IU of vitamin D, daily supplementation of 800 IU, or no treatment.[33] The median serum 25(OH)D concentration in the 800 IU/day group at study entry was 26 nmol/L (interquartile range 22–37), and the median 25(OH)D concentration at delivery following supplementation was 42 nmol/L (interquartile range 31–76). Only 30% of the women treated with 800 IU/day of vitamin D achieved a serum 25(OH)D concentration >50 nmol/L. In another study from the UK,[101] the investigators recruited 80 consecutive pregnant women from minority ethnic backgrounds whose serum 25(OH)D concentrations at the first antenatal visit were <20 nmol/L. These subjects with very low vitamin D status were started on 800 IU/day of vitamin D, increased to 1600 IU/day at 36 weeks' gestation if serum 25(OH)D was still low. The mean serum 25(OH)D concentration increased from 14.4 ± 2.3 nmol/L at enrollment to only 28.5 ± 15.8 nmol/L at delivery despite supplementation of 800–1600 IU/day. These two studies and older research[41] indicate that, in populations with a high prevalence of severe vitamin D sufficiency, supplementation up to 1600 IU/day may be inadequate to achieve the recommended target serum 25(OH)D concentration of 50 nmol/L.[7] In two recent studies from India, which used large single-dose supplementation of 120,000 IU at the fifth and seventh month of gestation[15] or at the second and third trimester,[69] only 25% and 62%, respectively, achieved a serum 25(OH)D concentration >50 nmol/L. The recent Cochrane review of vitamin D supplementation alone during pregnancy[79] considered five trials that compared the effects of supplementation with placebo or no supplementation.[33,73,77,78,102] The review concluded that vitamin D supplementation increases serum 25(OH)D concentrations during pregnancy. Of note, in two of the five studies, the mean concentration of 25(OH)D after supplementation was <50 nmol/L,[33,78] and serum 25(OH)D was not measured in one study.[73] All these studies underscore the uncertainty about the amount of vitamin D supplementation required to optimize vitamin D status in pregnancy and which would be generalizable worldwide.

As mentioned earlier, the criteria for defining what constitutes "normal" vitamin D status are controversial. The Institute of Medicine[7] considers a serum 25(OH)D concentration >50 nmol/L as acceptable, while the Endocrine Society and vitamin D experts recommend >75 nmol/L.[8,99] A recent study among traditional populations in Tanzania with type VI (dark) skin color living in a sun-abundant environment recommended a mean serum 25(OH)D concentration of 115 nmol/L in nonpregnant adults and 139 nmol/L in pregnant women.[57] The question then is: what serum concentration of 25(OH)D is "normal" in adults, including during pregnancy? While the debate and studies to identify optimal serum 25(OH)D concentration continue, it is prudent to monitor vitamin D status and develop strategies to ensure at least a minimum serum 25(OH)D concentration of 50 nmol/L in pregnant women, especially in an environment where vitamin D deficiency is endemic.

In studies of adults and nonpregnant women, a vitamin D intake of up to 10,000 IU/day is associated with achievement of a serum 25(OH)D concentration ≥80 nmol/L without vitamin D toxicity.[103,104] From a review of previous studies, an additional daily intake of 100 IU of vitamin D increases the serum 25(OH)D concentration by 1–2 nmol/L.[7,105] Therefore, knowing the population baseline serum 25(OH)D concentration, it is possible to estimate the vitamin D intake required to replete body stores and achieve an expected target serum 25(OH)D concentration. Because of controversy surrounding vitamin D requirements during pregnancy, investigators from South Carolina performed a comprehensive, large, randomized controlled study of vitamin D supplementation in pregnancy to achieve optimal vitamin D status, defined as a serum 25(OH)D concentration ≥80 nmol/L at delivery.[18] Based on the pharmacokinetics of vitamin D, the authors investigated the safety and effectiveness of high-dose vitamin D supplementation. They hypothesized that daily vitamin D_3 supplementation of 4000 IU/day would be more effective than 2000 IU and a standard dosing regimen of 400 IU in achieving a serum 25(OH)D concentration of >80 nmol/L without any safety issues referable to vitamin D supplementation. In this study, women of varied ethnicity were randomized at <16 weeks' gestation into 4000 IU, 2000 IU, or 400 IU daily treatment groups, which were continued through to delivery. Subjects with an initial baseline 25(OH)D >100 nmol/L were allocated to vitamin D_3 2000 IU/day or 400 IU/day. Vitamin D status was monitored in the mother during pregnancy and in cord blood as

a surrogate marker of infant vitamin D status at birth. The safety outcome measures monitored were serum 25(OH)D concentration, hypercalcemia, and hypercalciuria.

Of the 494 women enrolled in the study, 350 continued participation until delivery. The mean serum 25(OH)D concentrations at entry to the study were not significantly different between the groups. However, mean serum 25(OH)D concentrations at delivery were significantly different, with the highest level achieved by the group on 4000 IU/day. The mean serum 25(OH)D concentrations at delivery in the 4000 IU, 2000 IU, and 400 IU daily groups were 110 ± 40.4, 98.3 ± 34.2, and 78.9 ± 36.5 nmol/L respectively, ($P = 0.0001$). Similarly, 82%, 71%, and 50%, respectively, of the mothers on 4000 IU, 2000 IU, and 400 IU of vitamin D daily achieved a serum 25(OH)D concentration >80 nmol/L ($P = 0.0001$). The authors also found that supplementation with 4000 IU/day was associated with maximal $1,25(OH)_2D$ production. Although the implications of this finding are unclear, they require exploration in future studies because of the possible role of $1,25(OH)_2D$ in control of multiple gene expression. Neonatal serum 25(OH)D concentrations correlated significantly with maternal serum 25(OH)D at delivery and were significantly different by dosing group. If the Institute of Medicine's target of a serum 25(OH)D concentration ≥50 nmol/L[7] was adopted for neonatal vitamin D status, 79%, 58%, and 40%, respectively, of the infants of mothers on 4000, 2000, and 400 IU per day achieved adequate vitamin D status ($P = 0.0001$). There were no adverse events related to vitamin D supplementation during the study. Based on this protocol, the authors concluded that 4000 IU/day of vitamin D_3 supplementation is safe and most effective in achieving vitamin D sufficiency in mothers and adequate vitamin D status in their offspring, irrespective of ethnicity. The authors also found that maternal vitamin D supplementation with 4000 IU/day decreased the risk of combined comorbidities, including infection, preterm birth, gestational diabetes, and pre-eclampsia,[82] and suggested that additional studies with adequate power for assessment of other endpoints were needed. Another recent study from the United Arab Emirates among pregnant Arab women with a high prevalence of vitamin D deficiency also confirmed that 4000 IU/day of vitamin D supplementation was safe and more effective than 2000 IU/day and 400 IU/day in optimizing vitamin D status during pregnancy and in achieving vitamin D sufficiency at birth in mothers and offspring.[106] In the United Arab Emirates study, the increment from baseline to delivery was about four-fold higher than expected based on previous pharmacokinetic studies, possibly related to low baseline vitamin D status.[100] This indicates that baseline vitamin D status should be taken into consideration when evaluating vitamin D supplementation.[100,107]

The findings of these recent intervention studies indicate an urgent need for more randomized controlled trials in diverse geographic locations with large sample sizes to identify the vitamin D intake required to optimize vitamin D status, and to assess the effect on pregnancy-related and infant-related complications. Based on biomarkers affected by vitamin D status, and findings from observational studies and recent randomized trials, future studies should include trial arms to achieve serum 25(OH)D concentrations that have been associated with potential extraskeletal benefits[8,82,84,94–96] of vitamin D to understand better both the benefits and risks of vitamin D supplementation to mother and offspring.

Conclusion

The criteria for defining optimal vitamin D intake during pregnancy remain controversial. In view of the high prevalence of low vitamin D status in pregnancy worldwide, intervention trials to identify optimal vitamin D status and the required safe vitamin D intake could be an important part of public health strategy to improve the health of mothers, and the short-term and long-term outcomes for their offspring.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Dawodu A, Wagner CL. Prevention of vitamin D deficiency in mothers and infants worldwide – a paradigm shift. *Paediatr Int Child Health*. 2012;32(1):3–13.
2. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. *Am J Obstet Gynecol*. 2009;202(5):e421–e429.
3. Wagner CL, Taylor SN, Dawodu A, Johnson DD, Hollis BW. Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus. *Nutrients*. 2012;4(3):208–230.
4. Lucas RM, Ponsonby AL, Pasco JA, Morley R. Future health implications of prenatal and early-life vitamin D status. *Nutr Rev*. 2008;66(12):710–720.
5. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. *Paediatr Perinat Epidemiol*. 2012;26 Suppl 1:75–90.
6. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–281.
7. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011.
8. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911–1930.
9. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004;80(Suppl 6):1678S–1688S.

10. Holick MF. McCollum Award Lecture, 1994: vitamin D – new horizons for the 21st century. *Am J Clin Nutr*. 1994;60(4):619–630.
11. Dawodu A, Wagner CL. Mother-child vitamin D deficiency: an international perspective. *Arch Dis Child*. 2007;92(9):737–740.
12. Dawodu A, Agarwal M, Sankarankutty M, Hardy D, Kochiyil J, Badrinath P. Higher prevalence of vitamin D deficiency in mothers of rachitic than nonrachitic children. *J Pediatr*. 2005;147(1):109–111.
13. Hamilton SA, McNeil R, Hollis BW, et al. Profound vitamin D deficiency in a diverse group of women during pregnancy living in a sun-rich environment at latitude 32 degrees N. *Int J Endocrinol*. 2010;2010:917428.
14. van der Meer IM, Karamali NS, Boeke AJ, et al. High prevalence of vitamin D deficiency in pregnant non-Western women in The Hague, Netherlands. *Am J Clin Nutr*. 2006;84(2):350–353.
15. Sahu M, Bhatia V, Aggarwal A, et al. Vitamin D deficiency in rural girls and pregnant women despite abundant sunshine in northern India. *Clin Endocrinol (Oxf)*. 2009;70(5):680–684.
16. Molla AM, Al Badawi M, Hammoud MS, et al. Vitamin D status of mothers and their neonates in Kuwait. *Pediatr Int*. 2005;47(6):649–652.
17. Bassir M, Laborie S, Lapillonne A, Claris O, Chappuis MC, Salle BL. Vitamin D deficiency in Iranian mothers and their neonates: a pilot study. *Acta Paediatr*. 2001;90(5):577–579.
18. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res*. 2011;26(10):2341–2357.
19. Bikle D. Nonclassic actions of vitamin D. *J Clin Endocrinol Metab*. 2009;94(1):26–34.
20. Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern. *CMAJ*. 2006;174(9):1287–1290.
21. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. *Am J Med Sci*. 2009;338(1):40–44.
22. Ullah MI, Uwaifo GI, Nicholas WC, Koch CA. Does vitamin D deficiency cause hypertension? Current evidence from clinical studies and potential mechanisms. *Int J Endocrinol*. 2010;2010:579640.
23. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol*. 2007;179(3):1634–1647.
24. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*. 2006;311(5768):1770–1773.
25. Kadowaki S, Norman AW. Demonstration that the vitamin D metabolite 1,25(OH)2-vitamin D3 and not 24R,25(OH)2-vitamin D3 is essential for normal insulin secretion in the perfused rat pancreas. *Diabetes*. 1985;34(4):315–320.
26. Lee S, Clark SA, Gill RK, Christakos S. 1,25-Dihydroxyvitamin D3 and pancreatic beta-cell function: vitamin D receptors, gene expression, and insulin secretion. *Endocrinology*. 1994;134(4):1602–1610.
27. Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin*. 2008;24(1):139–149.
28. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest*. 2006;116(8):2062–2072.
29. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr*. 2005;135(2):317–322.
30. Haddow JE, Neveux LM, Palomaki GE, et al. The relationship between PTH and 25-hydroxy vitamin D early in pregnancy. *Clin Endocrinol (Oxf)*. 2011;75(3):309–314.
31. Morley R, Carlin JB, Pasco JA, Wark JD. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *J Clin Endocrinol Metab*. 2006;91(3):906–912.
32. Wagner CL, Hollis BW. Beyond PTH: assessing vitamin D status during early pregnancy. *Clin Endocrinol (Oxf)*. 2011;75(3):285–286.
33. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clin Endocrinol (Oxf)*. 2009;70(5):685–690.
34. Ardawi MS, Nasrat HA, BA'Aqueel HS. Calcium-regulating hormones and parathyroid hormone-related peptide in normal human pregnancy and postpartum: a longitudinal study. *Eur J Endocrinol*. 1997;137(4):402–409.
35. Kaludjerovic J, Vieth R. Relationship between vitamin D during perinatal development and health. *J Midwifery Womens Health*. 2010;55(6):550–560.
36. Bikle DD, Gee E, Halloran B, Haddad JG. Free 1,25-dihydroxyvitamin D levels in serum from normal subjects, pregnant subjects, and subjects with liver disease. *J Clin Invest*. 1984;74(6):1966–1971.
37. Wilson SG, Retallack RW, Kent JC, Worth GK, Gutteridge DH. Serum free 1,25-dihydroxyvitamin D and the free 1,25-dihydroxyvitamin D index during a longitudinal study of human pregnancy and lactation. *Clin Endocrinol (Oxf)*. 1990;32(5):613–622.
38. Specker B. Vitamin D requirements during pregnancy. *Am J Clin Nutr*. 2004;80(Suppl 6):1740S–1747S.
39. Perez-Lopez FR. Vitamin D: the secosteroid hormone and human reproduction. *Gynecol Endocrinol*. 2007;23(1):13–24.
40. Salle BL, Delvin EE, Lapillonne A, Bishop NJ, Glorieux FH. Perinatal metabolism of vitamin D. *Am J Clin Nutr*. 2000;71(Suppl 5):1317S–1324S.
41. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr*. 2004;79(5):717–726.
42. Bouillon R, Van Baelen H, De Moor P. 25-hydroxyvitamin D and its binding protein in maternal and cord serum. *J Clin Endocrinol Metab*. 1977;45(4):679–684.
43. Dawodu A, Agarwal A, Patel M, Ezimokhai M. Serum 25-hydroxyvitamin D and calcium homeostasis in the United Arab Emirates mothers and neonates: a preliminary report. *Middle E Paediatr*. 1997;2:9–12.
44. Markestad T, Aksnes L, Ulstein M, Aarskog D. 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D of D2 and D3 origin in maternal and umbilical cord serum after vitamin D2 supplementation in human pregnancy. *Am J Clin Nutr*. 1984;40(5):1057–1063.
45. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr*. 2005;81(5):1060–1064.
46. Nicolaidou P, Hatzistamatiou Z, Papadopoulou A, et al. Low vitamin D status in mother-newborn pairs in Greece. *Calcif Tissue Int*. 2006;78(6):337–342.
47. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr*. 2007;137(2):447–452.
48. Javaid MK, Crozier SR, Harvey NC, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet*. 2006;367(9504):36–43.
49. Holmes VA, Barnes MS, Alexander HD, McFaul P, Wallace JM. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. *Br J Nutr*. 2009;102(6):876–881.
50. Viljakainen HT, Saarnio E, Hytinantti T, et al. Maternal vitamin D status determines bone variables in the newborn. *J Clin Endocrinol Metab*. 2010;95(4):1749–1757.
51. Ginde AA, Sullivan AF, Mansbach JM, Camargo CA Jr. Vitamin D insufficiency in pregnant and nonpregnant women of childbearing age in the United States. *Am J Obstet Gynecol*. 2010;202(5):e431–e438.
52. Newhook LA, Sloka S, Grant M, Randell E, Kovacs CS, Twells LK. Vitamin D insufficiency common in newborns, children and pregnant women living in Newfoundland and Labrador, Canada. *Matern Child Nutr*. 2009;5(2):186–191.
53. Bowyer L, Catling-Paull C, Diamond T, Homer C, Davis G, Craig ME. Vitamin D, PTH and calcium levels in pregnant women and their neonates. *Clin Endocrinol (Oxf)*. 2009;70(3):372–377.
54. Judkins A, Eagleton C. Vitamin D deficiency in pregnant New Zealand women. *N Z Med J*. 2006;119(1241):U2144.
55. Jiang L, Xu J, Pan S, Xie E, Hu Z, Shen H. High prevalence of hypovitaminosis D among pregnant women in southeast China. *Acta Paediatr*. 2012;101(4):e192–e194.

56. Dawodu A, Saadi HF, Bekdache G, Altaye M, Hollis BW. Randomized controlled trial of prenatal vitamin D supplementation in a population with endemic vitamin D deficiency: effectiveness and safety results. Presented at the Pediatric Academic Societies Annual Meeting, April 27, 2012 to May 1, 2012, Boston, MA.
57. Luxwolda MF, Kuipers RS, Kema IP, van der Veer E, Dijck-Brouwer DA, Muskiet FA. Vitamin D status indicators in indigenous populations in East Africa. *Eur J Nutr*. 2013;52(3):1115–1125.
58. Haliloglu B, Ilter E, Aksungar FB, et al. Bone turnover and maternal 25(OH) vitamin D3 levels during pregnancy and the postpartum period: should routine vitamin D supplementation be increased in pregnant women? *Eur J Obstet Gynecol Reprod Biol*. 2011;158(1):24–27.
59. Kovacs CS. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. *Am J Clin Nutr*. 2008;88(2):520S–528S.
60. Mahon P, Harvey N, Crozier S, et al. Low maternal vitamin D status and fetal bone development: cohort study. *J Bone Miner Res*. 2010;25(1): 14–19.
61. Lawlor DA, Wills AK, Fraser A, Sayers A, Fraser WD, Tobias JH. Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study. *Lancet*. March 18, 2013. [Epub ahead of print.]
62. Yorifuji J, Yorifuji T, Tachibana K, et al. Craniotabes in normal newborns: the earliest sign of subclinical vitamin D deficiency. *J Clin Endocrinol Metab*. 2008;93(5):1784–1788.
63. Anatoliotaki M, Tsilimigaki A, Tsekoura T, Schinaki A, Stefanaki S, Nicolaidou P. Congenital rickets due to maternal vitamin D deficiency in a sunny island of Greece. *Acta Paediatr*. 2003;92(3):389–391.
64. Maiyegun SO, Malek AH, Devarajan LV, Dahniya MH. Severe congenital rickets secondary to maternal hypovitaminosis D: a case report. *Ann Trop Paediatr*. 2002;22(2):191–195.
65. Mohapatra A, Sankaranarayanan K, Kadam SS, Binoy S, Kanbur WA, Mondkar JA. Congenital rickets. *J Trop Pediatr*. 2003;49(2): 126–127.
66. Camadoo L, Tibbott R, Isaza F. Maternal vitamin D deficiency associated with neonatal hypocalcaemic convulsions. *Nutr J*. 2007;6:23.
67. Teaema FH, Al Ansari K. Nineteen cases of symptomatic neonatal hypocalcemia secondary to vitamin D deficiency: a 2-year study. *J Trop Pediatr*. 2010;56(2):108–110.
68. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. *Br J Nutr*. 2010;104(1):108–117.
69. Kalra P, Das V, Agarwal A, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *Br J Nutr*. 2012;108(6):1052–1058.
70. Scholl TO, Chen X. Vitamin D intake during pregnancy: association with maternal characteristics and infant birth weight. *Early Hum Dev*. 2009;85(4):231–234.
71. Watson PE, McDonald BW. The association of maternal diet and dietary supplement intake in pregnant New Zealand women with infant birthweight. *Eur J Clin Nutr*. 2010;64(2):184–193.
72. Marya RK, Rathee S, Lata V, Mudgil S. Effects of vitamin D supplementation in pregnancy. *Gynecol Obstet Invest*. 1981;12(3): 155–161.
73. Marya RK, Rathee S, Dua V, Sangwan K. Effect of vitamin D supplementation during pregnancy on foetal growth. *Indian J Med Res*. 1988;88:488–492.
74. Farrant HJ, Krishnaveni GV, Hill JC, et al. Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. *Eur J Clin Nutr*. 2009;63(5):646–652.
75. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr*. 2007;85(3):788–795.
76. Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008;62(1): 68–77.
77. Brooke OG, Brown IR, Bone CD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *BMJ*. 1980;280(6216):751–754.
78. Mallet E, Gugi B, Brunelle P, Henocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstet Gynecol*. 1986;68(3):300–304.
79. De-Regil LM, Palacios C, Ansary A, Kulier R, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2012;2:CD008873.
80. Burris HH, Rifas-Shiman SL, Camargo CA Jr, et al. Plasma 25--hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. *Ann Epidemiol*. 2012;22(8):581–586.
81. Bodnar LM, Catov JM, Zmuda JM, et al. Maternal serum 25--hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *J Nutr*. 2010;140(5):999–1006.
82. Hollis BW, Wagner CL. Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. *Calcif Tissue Int*. 2013;92(2): 128–139.
83. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab*. 2007;92(9):3517–3522.
84. Baker AM, Haeri S, Camargo CA Jr, Espinola JA, Stuebe AM. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *J Clin Endocrinol Metab*. 2010;95(11):5105–5109.
85. Zhang C, Qiu C, Hu FB, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. *PLoS One*. 2008;3(11):e3753.
86. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: a systematic review and meta-analysis. *Eur J Intern Med*. 2012;23(5):465–469.
87. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. February 11, 2013. [Epub ahead of print.]
88. Bodnar LM, Krohn MA, Simhan HN. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J Nutr*. 2009;139(6):1157–1161.
89. Hensel KJ, Randis TM, Gelber SE, Ratner AJ. Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. *Am J Obstet Gynecol*. 2011;204(1):e41–e49.
90. Grant WB, Boucher BJ. Are Hill's criteria for causality satisfied for vitamin D and periodontal disease? *Dermatoendocrinology*. 2010;2(1):30–36.
91. Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S, Camargo CA Jr. Vitamin D status and periodontal disease among pregnant women. *J Periodontol*. 2011;82(2):195–200.
92. Wagner CL, McNeil R, Hamilton SA, et al. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. *Am J Obstet Gynecol*. 2013;208(2):137. e1–e13.
93. Walker VP, Zhang X, Rastegar I, et al. Cord blood vitamin D status impacts innate immune responses. *J Clin Endocrinol Metab*. 2011;96(6):1835–1843.
94. Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics*. 2011;127(6):e1513–e1520.
95. Camargo CA Jr, Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics*. 2011;127(1):e180–e187.
96. Jones AP, Palmer D, Zhang G, Prescott SL. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. *Pediatrics*. 2012;130(5):e1128–e1135.
97. Pike KC, Inskip HM, Robinson S, et al. Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. *Thorax*. 2012;67(11):950–956.
98. Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*. 2012;129(3):485–493.

99. Souberbielle JC, Body JJ, Lappe JM, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev*. 2010;9(11):709–715.
100. Heaney RP. Vitamin D – baseline status and effective dose. *N Engl J Med*. 2012;367(1):77–78.
101. Datta S, Alfaham M, Davies DP, et al. Vitamin D deficiency in pregnant women from a non-European ethnic minority population – an interventional study. *BJOG*. 2002;109(8):905–908.
102. Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *J Pediatr*. 1986;109(2):328–334.
103. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr*. 2001;73(2):288–294.
104. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003;77(1):204–210.
105. Cranney A, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *Am J Clin Nutr*. 2008;88(2):513S–519S.
106. Dawodu A, Saadi HF, Bekdache G, Javed Y, Altaye M, Hollis BW. Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin d deficiency. *J Clin Endocrinol Metab*. April 4, 2013. [Epub ahead of print.]
107. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. *Anticancer Res*. 2011;31(2):607–611.